# The American Psychiatric Association Practice Guideline for the Prevention and Treatment of Delirium

## Appendices

### Table of Contents

# Appendix A. Clinical Questions

The following Key Questions (KQs) were developed by the Pacific Northwest Evidence-based Practice Center (EPC) in conjunction with APA practice guidelines staff and were registered in PROSPERO (ID CRD42020172961).

KQ 1. What is the evidence on benefits and harms of interventions to prevent delirium, including:

KQ 1a. Drug interventions compared with placebo?

KQ 1b. Drug interventions compared with each other?

KQ 1c. Non-drug interventions (e.g., environmental, pain management) compared with no intervention (e.g., usual care)?

KQ 1d. Non-drug interventions compared with each other?

KQ 1e. Drug and non-drug interventions compared with each other?

KQ 2. What is the evidence on benefits and harms of interventions to treat delirium, including:

KQ 2a. Drug interventions compared with placebo?

KQ 2b. Drug interventions compared with each other?

KQ 2c. Non-drug interventions (e.g., environmental, pain management) compared with no intervention (e.g., usual care)?

KQ 2d. Non-drug interventions compared with each other?

KQ 2e. Drug and non-drug interventions compared with each other?

KQ 3. Are there patient-level or setting factors that modify the effects (benefits or harms) of these interventions?

KQ 3a. Demographics

KQ 3b. Co-morbidities and severity of underlying illness, such as dementia, traumatic brain injuries, cancer, or patients who have undergone major surgery (factors include type of surgery and duration of anesthesia); co-interventions (e.g., propofol, polypharmacy); hypoactive vs. hyperactive delirium?

KQ 3c. Type of setting (e.g., acute care, hospice care, long-term care)

# Appendix B. Search Strategies, Study Selection, and Search Results

## General Methods

This guideline is based on a systematic search of available research evidence conducted by the EPC. The methods for this systematic review followed the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (available at https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview).

## Search Strategies

Table B-1. MEDLINE literature search strategy with explanation of key search elements

| **Search term** | Explanation |
|---|---|
| 1 exp Confusion/ (13473) | Population |
| 2 (confusion or confuse* or delirium or delirious or disorient*).ti,ab,kf. (63424) | |
| 3 "altered consciousness".ti,ab,kf. (1033) | |
| 4 ((emergence or emergent or emerging or emerge or postanesthe* or postanaesthe* or anesthe* or anaesthe*) adj3 (agitat* or excite*)).ti,ab,kf. (540) | |
| 5 ("Memorial Delirium Assessment Scale" or "MDAS").ti,ab,kf. (530) | |
| 6 (prevent* or avoid* or treat* or intervention* or drug or medication* or pharmacologic* or nonpharmacologic* or psychosocial).ti,ab,kf. (7773407) | Intervention |
| 7 (dt or pc or th).fs. (4889066) | |
| 8 or/1-5 (68737) | Population terms combined |
| 9 6 or 7 (9874700) | Intervention terms combined |
| 10 8 and 9 (34202) | Population terms + Intervention terms |
| 11 (pediatric* or preschool* or toddler* or infan* or child* or adolescent*).ti. (1161267) | |
| 12 10 not 11 (32487) | |
| 13 (animal* or mouse or mice or rat* or dog* or canine or cow* or horse* or mare* or rabbit*).ti. (2055970) | |
| 14 12 not 13 (31967) | Population + Intervention, limited to adult humans |
| 15 (random* or control* or placebo or sham or trial or blind*).ti,ab,kw. (4661795) | |
| 16 exp clinical trial/ (849614) | |
| 17 14 and (15 or 16) (6289) | Line 14, limited to trials |
| 18 observational study/ or comparative study/ (1917972) | |
| 19 exp cohort studies/ (1947912) | |
| 20 exp case-control studies/ (1050058) | |
| 21 (cohort* or case* or prospective or retrospective or observational).ti,ab,kw. (4494584) | |
| 22 or/18-21 (6816722) | |
| 23 case reports.pt. (2070898) | |
| 24 "case series".ti,ab,kf. (70549) | |
| 25 "case report".ti,ab,kf. (302812) | |
| 26 22 not (or/23-25) (5652367) | |
| 27 14 and 26 (8555) | Line 14, limited to controlled observational studies |
| 28 meta-analysis/ or "systematic review"/ (180810) | |
| 29 (systematic or "meta analysis" or metaanalysis or medline or cochrane).ti,ab,kf. (472488) | |
| 30 14 and (28 or 29) (1491) | Line 14, limited to systematic reviews |
| 31 17 or 27 or 30 (13069) | |
| 32 limit 31 to english language (11680) | Total, no date limit |

| | |
|---|---|
| 33 limit 32 to yr="2000 - 2020" (9094) | Total, limited by date |

Table B-2. PsycINFO literature search strategy

Dates of search 1806 to January Week 3 2020

1 Delirium/ (3250)
2 (confusion or confuse* or delirium or delirious or disorient* or agitat*).ti,ab. (39619)
3 "altered consciousness".tw. (350)
4 ((emergence or emergent or emerging or emerge or postanesthe* or postanaesthe* or anesthe* or anaesthe*) adj3 excite*).tw. (9)
5 ("Memorial Delirium Assessment Scale" or "MDAS").tw. (106)
6 ("Confusion Assessment Method for the Intensive Care Unit" or "CAM ICU").tw. (84)
7 ("Intensive Care Delirium Screening Checklist" or "ICDSC").tw. (13)
8 ("Delirium Rating Scale" or "DRS R 98").tw. (198)
9 "Neecham Confusion Scale".tw. (23)
10 "Nursing Delirium Screening Scale".tw. (16)
11 or/1-10 (40056)
12 exp Schizophrenia/ (89432)
13 schizophreni*.ti,ab. (117908)
14 12 or 13 (122418)
15 11 not 14 (37692)
16 (pediatric* or preschool* or toddler* or infan* or child* or adolescent*).ti. (472850)
17 15 not 16 (35290)
18 (animal* or mouse or mice or rat* or rodent* or dog* or canine or cow* or horse* or mare* or rabbit*).ti,sh. (399469)
19 17 not 18 (33893)
20 Treatment Outcome/ (33020)
21 Drug Therapy/ (134452)
22 (prevent* or avoid* or treat* or intervention* or drug or medication* or pharmacologic* or nonpharmacologic* or psychosocial).tw. (1319300)
23 or/20-22 (1335276)
24 19 and 23 (13679)
25 (random* or controlled or placebo or sham or trial or blind*).ti,ab. (362222)
26 (cohort* or "case control" or prospective or retrospective or observational or longitudinal).ti,ab. (259602)
27 ("meta analysis" or "systematic review" or medline or cochrane).ti,ab. (53759)
28 or/25-27 (626757)
29 24 and 28 (2833)

Table B-3. EBM reviews - Cochrane Central Register of Controlled Trials literature search strategy

Date of search December 2019

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1 exp Confusion/ (676)
2 (confusion or confuse* or delirium or delirious or disorient* or agitat*).ti,ab,hw. (9881)
3 "altered consciousness".ti,ab,hw. (39)
4 ((emergence or emergent or emerging or emerge or postanesthe* or postanaesthe* or anesthe* or anaesthe*) adj3 excite*).ti,ab,hw. (18)
5 ("Memorial Delirium Assessment Scale" or "MDAS").ti,ab,hw. (82)
6 ("Confusion Assessment Method for the Intensive Care Unit" or "CAM ICU").ti,ab,hw. (190)
7 ("Intensive Care Delirium Screening Checklist" or "ICDSC").ti,ab,hw. (50)
8 ("Delirium Rating Scale" or "DRS R 98").ti,ab,hw. (92)
9 "Neecham Confusion Scale".ti,ab,hw. (11)
10 "Nursing Delirium Screening Scale".ti,ab,hw. (26)
11 or/1-10 (9966)
12 exp Schizophrenia/ (6816)
13 schizophreni*.ti,ab,hw. (16967)
14 12 or 13 (16969)
15 11 not 14 (9382)
16 (pediatric* or preschool* or toddler* or infan* or child* or adolescent*).ti. (107273)
17 15 not 16 (8335)

| | | |
|---|---|---|
| 18 | (animal* or mouse or mice or rat* or rodent* or dog* or canine or cow* or horse* or mare* or rabbit*).ti,sh. (39514) |
| 19 | 17 not 18 (8198) |
| 20 | Treatment Outcome/ (127605) |
| 21 | Drug Therapy/ (343) |
| 22 | (prevent* or avoid* or treat* or intervention* or drug or medication* or pharmacologic* or nonpharmacologic* or psychosocial).ti,ab,hw. (1151550) |
| 23 | (dt or pc or th).fs. (337157) |
| 24 | or/20-23 (1193845) |
| 25 | 19 and 24 (6979) |
| 26 | conference abstract.pt. (16743) |
| 27 | "journal: conference abstract".pt. (147924) |
| 28 | "journal: conference review".pt. (756) |
| 29 | "http://.www.who.int/trialsearch*".so. (126720) |
| 30 | "https://clinicaltrials.gov*".so. (142443) |
| 31 | 26 or 27 or 28 or 29 or 30 (434586) |
| 32 | 25 not 31 (4672) |
| 33 | limit 32 to medline records (2281) |
| 34 | 32 not 33 (2391) |
| 35 | limit 34 to english language (1766) |

Table B-4. EBM Reviews - Cochrane Database of Systematic Reviews literature search strategy

Dates of search 2005 to January 21, 2020

| | |
|---|---|
| 1 | (confusion or confuse* or delirium or delirious or disorient* or agitat*).ti,ab. (85) |
| 2 | schizophreni*.ti,ab. (323) |
| 3 | (pediatric* or preschool* or toddler* or infan* or child* or adolescent*).ti. (1298) |
| 4 | (prevent* or avoid* or treat* or intervention* or drug or medication* or pharmacologic* or nonpharmacologic* or psychosocial).ti,ab. (9151) |
| 5 | 1 not (2 or 3) (65) |
| 6 | 4 and 5 (60) |
| 7 | limit 6 to full systematic reviews (51) |

Table B-5. EMBASE literature search strategy

| | |
|---|---|
| 1. | Confusion/exp |
| 2. | (delirium OR delirious ):ti,ab,kw |
| 3. | 'altered consciousness':ti,ab,kw |
| 4. | ((Emergence OR Emergent OR Emerging OR Emerge OR postanesthe* OR postanaesthe* OR anesthe* OR anaesthe*) NEAR/3 (agitat* OR excite*)):ti,ab,kw |
| 5. | ('Memorial Delirium Assessment Scale' OR MDAS):ti,ab,kw |
| 6. | ('Confusion Assessment Method for the Intensive Care Unit' OR 'CAM ICU' ):ti,ab,kw |
| 7. | ('Intensive Care Delirium Screening Checklist' OR ICDSC ):ti,ab,kw |
| 8. | ('Delirium Rating Scale' OR 'DRS R 98' ):ti,ab,kw |
| 9. | 'Neecham Confusion Scale':ti,ab,kw |
| 10. | 'Nursing Delirium Screening Scale':ti,ab,kw |
| 11. | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 |
| 12. | Schizophrenia/exp |
| 13. | schizophreni*:ti,ab,kw |
| 14. | #12 OR #13 |
| 15. | #11 NOT #14 |
| 16. | (pediatric* OR preschool* OR toddler* OR infan* OR child* OR adolescent* ):ti |
| 17. | #15 NOT #16 |
| 18. | (animal* OR mouse OR mice OR rat* OR rodent* OR dog* OR canine OR cow* OR horse* OR mare* OR rabbit* ):ti ,sh. |
| 19. | #17 NOT #18 |
| 20. | 'Treatment Outcome'/de |
| 21. | 'Drug Therapy'/de |

22. (prevent* OR avoid* OR treat* OR intervention* OR drug OR medication* OR pharmacologic* OR nonpharmacologic* OR psychosocial ):ti,ab,kw
23. :lnk
24. #20 OR #21 OR #22 OR #23
25. #19 AND #24
26. (random* OR controlled OR placebo OR sham OR trial OR blind* ):ti,ab ,kw.
27. 'Clinical Trial'/exp
28. #26 OR #27
29. #25 AND #28
30. 'limit 29 to english language'
31. 'observational study'/de OR 'comparative study'/de
32. 'cohort studies'/exp
33. 'case-control studies'/exp
34. (cohort* OR 'case control' OR prospective OR retrospective OR observational OR longitudinal ):ti,ab ,kw.
35. #31 OR #32 OR #33 OR #34
36. term:it
37. ('case series' OR 'case report*' ):ti,ab,kw
38. #35 NOT (#36 OR #37)
39. #25 AND #38
40. 'limit 39 to english language'
41. meta-analysis/de
42. 'systematic review'/de
43. (systematic OR 'meta analysis' OR metaanalysis OR medline OR cochrane ):ti,ab,kw
44. #41 OR #42 OR #43
45. #25 AND #44
46. 'limit 45 to yr="2010 - 2020"'
47. 'limit 46 to english language'
48. #30 OR #40 OR #47

Table B-6. CINAHL literature search strategy

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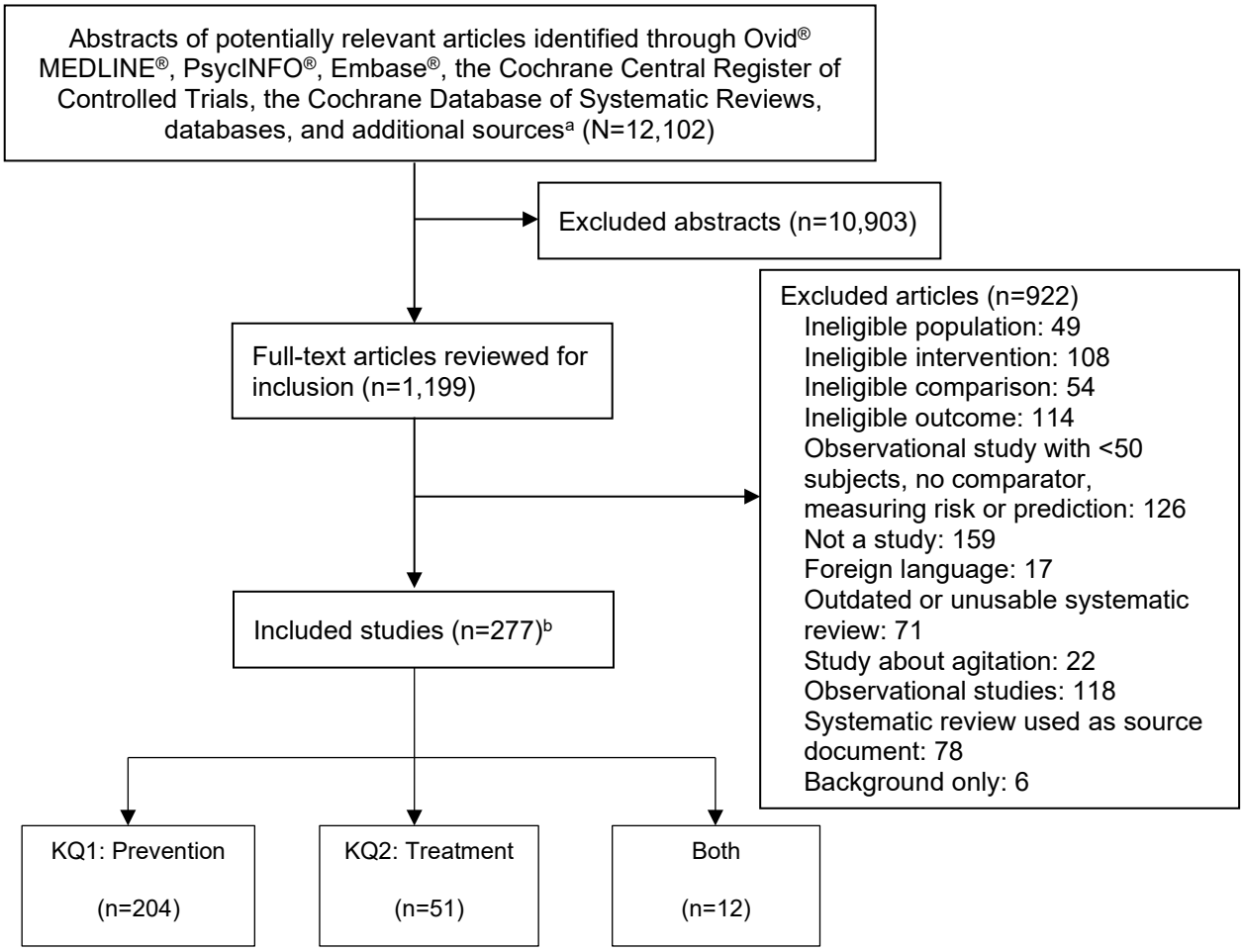
1. (MH Confusion+)
2. ((TI delirium OR AB delirium OR SU delirium) OR (TI delirious OR AB delirious OR SU delirious))
3. (TI "altered consciousness" OR AB "altered consciousness" OR SU "altered consciousness")
4. (((TI emergence OR AB emergence OR SU emergence) OR (TI emergent OR AB emergent OR SU emergent) OR (TI emerging OR AB emerging OR SU emerging) OR (TI emerge OR AB emerge OR SU emerge) OR (TI postanesthe* OR AB postanesthe* OR SU postanesthe*) OR (TI postanaesthe* OR AB postanaesthe* OR SU postanaesthe*) OR (TI anesthe* OR AB anesthe* OR SU anesthe*) OR (TI anaesthe* OR AB anaesthe* OR SU anaesthe*)) N3 ((TI agitat* OR AB agitat* OR SU agitat*) OR (TI excite* OR AB excite* OR SU excite*)))
5. ((TI "Memorial Delirium Assessment Scale" OR AB "Memorial Delirium Assessment Scale" OR SU "Memorial Delirium Assessment Scale") OR (TI MDAS OR AB MDAS OR SU MDAS)) (439 )
6. ((TI "Confusion Assessment Method for the Intensive Care Unit" OR AB "Confusion Assessment Method for the Intensive Care Unit" OR SU "Confusion Assessment Method for the Intensive Care Unit") OR (TI "CAM ICU" OR AB "CAM ICU" OR SU "CAM ICU")) (349 )
7. ((TI "Intensive Care Delirium Screening Checklist" OR AB "Intensive Care Delirium Screening Checklist" OR SU "Intensive Care Delirium Screening Checklist") OR (TI ICDSC OR AB ICDSC OR SU ICDSC)) (109 )
8. ((TI "Delirium Rating Scale" OR AB "Delirium Rating Scale" OR SU "Delirium Rating Scale") OR (TI "DRS R 98" OR AB "DRS R 98" OR SU "DRS R 98")) (247 )
9. (TI "Neecham Confusion Scale" OR AB "Neecham Confusion Scale" OR SU "Neecham Confusion Scale") (36 )
10. (TI "Nursing Delirium Screening Scale" OR AB "Nursing Delirium Screening Scale" OR SU "Nursing Delirium Screening Scale") (42 )
11. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 (20165 )
12. (MH Schizophrenia+) (102926 )
13. (TI schizophreni* OR AB schizophreni* OR SU schizophreni*) (110310 )
14. S12 OR S13 (130102 )
15. S11 NOT S14 (19394 )
16. (TI pediatric* OR TI preschool* OR TI toddler* OR TI infan* OR TI child* OR TI adolescent*) (1044684 )
17. S15 NOT S16 (18544 )

18. (TI animal* OR TI mouse OR TI mice OR TI rat* OR TI rodent* OR TI dog* OR TI canine OR TI cow* OR TI horse* OR TI mare* OR TI rabbit*) ,sh. (6801219 )
19. S17 NOT S18 (17860 )
20. (MH "Treatment Outcome") (945755 )
21. (MH "Drug Therapy") (30310 )
22. ((TI prevent* OR AB prevent* OR SU prevent*) OR (TI avoid* OR AB avoid* OR SU avoid*) OR (TI treat* OR AB treat* OR SU treat*) OR (TI intervention* OR AB intervention* OR SU intervention*) OR (TI drug OR AB drug OR SU drug) OR (TI medication* OR AB medication* OR SU medication*) OR (TI pharmacologic* OR AB pharmacologic* OR SU pharmacologic*) OR (TI nonpharmacologic* OR AB nonpharmacologic* OR SU nonpharmacologic*) OR (TI psychosocial OR AB psychosocial OR SU psychosocial)) (6784727 )
23. ((MW dt) OR (MW pc) OR (MW th) OR (MW nu)) (4983222 )
24. S20 OR S21 OR S22 OR S23 (9135995 )
25. S19 AND S24 (11120 )
26. ((TI random* OR AB random*) OR (TI controlled OR AB controlled) OR (TI placebo OR AB placebo) OR (TI sham OR AB sham) OR (TI trial OR AB trial) OR (TI blind* OR AB blind*)) ,kw. (1683803 )
27. (MH "Clinical Trial"+) (849102 )
28. S26 OR S27 (2017548 )
29. S25 AND S28 (1595 )
30. "limit 29 to english language" (1448 )
31. (MH "observational study") OR (MH "comparative study") (1917741 )
32. (MH "cohort studies"+) (1947656 )
33. (MH "case-control studies"+) (1049859 )
34. ((TI cohort* OR AB cohort*) OR (TI "case control" OR AB "case control") OR (TI prospective OR AB prospective) OR (TI retrospective OR AB retrospective) OR (TI observational OR AB observational) OR (TI longitudinal OR AB longitudinal)) ,kw. (1453878 )
35. S31 OR S32 OR S33 OR S34 (4096950 )
36. PT "case reports" (1971444 )
37. ((TI "case series" OR AB "case series" OR SU "case series") OR (TI "case report*" OR AB "case report*" OR SU "case report*")) (364960 )
38. S35 NOT (S36 OR S37) (3932204 )
39. S25 AND S38
40. "limit 39 to english language"
41. (MH meta-analysis)
42. (MH "systematic review")
43. ((TI systematic OR AB systematic OR SU systematic) OR (TI "meta analysis" OR AB "meta analysis" OR SU "meta analysis") OR (TI metaanalysis OR AB metaanalysis OR SU metaanalysis) OR (TI medline OR AB medline OR SU medline) OR (TI cochrane OR AB cochrane OR SU cochrane))
44. S41 OR S42 OR S43
45. S25 AND S44
46. "limit 45 to yr="2010 - 2020""
47. "limit 46 to english language"
48. S30 OR S40 OR S47

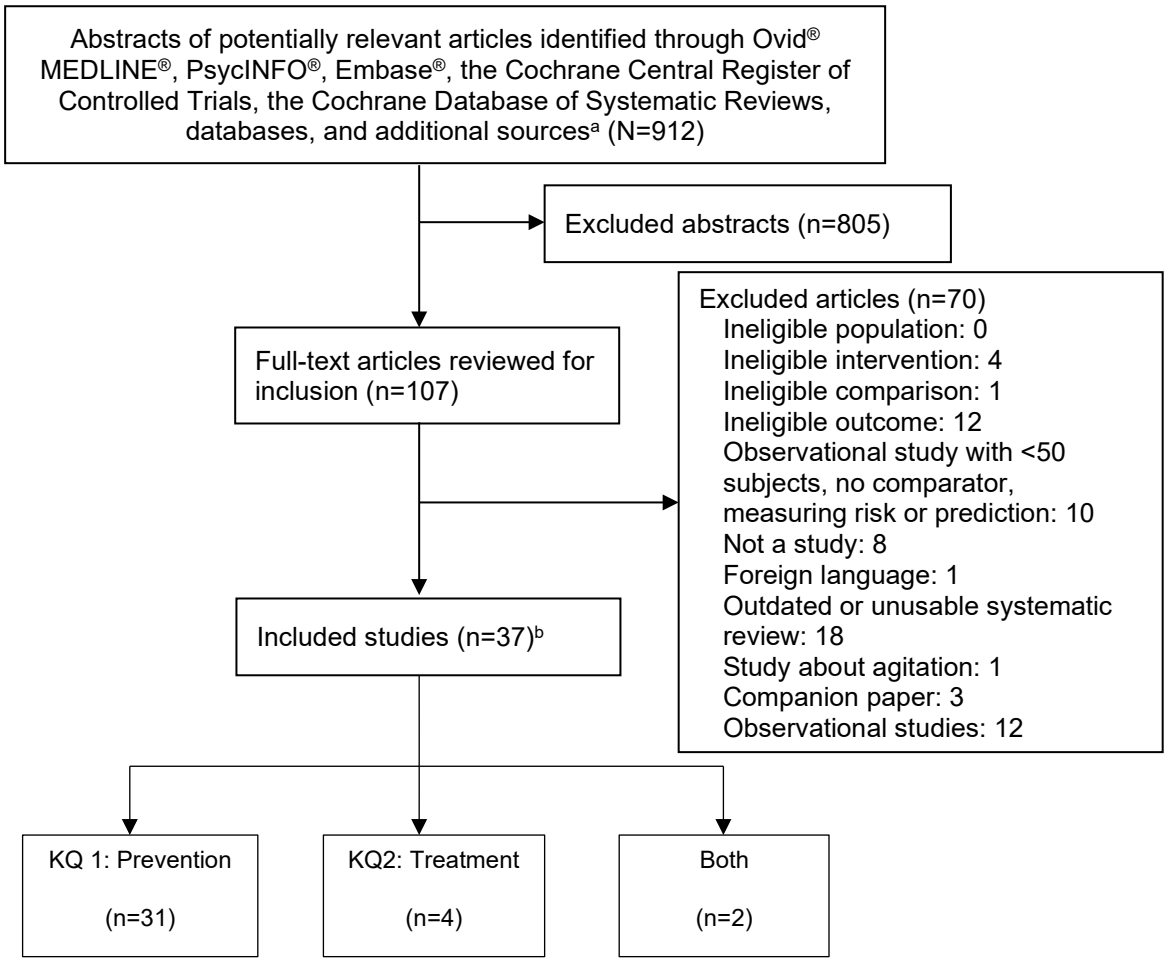
## Literature Flow Diagrams

Figure B-1. Literature flow diagram for initial literature search.




[a] Additional sources include suggested references, reference lists, etc.
[b] 267 studies in 277 publications

Figure B-2. Literature flow diagram for updated literature search.




[a] Additional sources include suggested references, reference lists, etc.
[b] 34 new trials and 3 cohort studies

## Study Selection

Initial searches were conducted in Ovid® MEDLINE®, PsycINFO®, Embase®, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews from database inception through October 2020 to identify studies eligible for this review, according to the criteria listed in Table B-7. An updated search was conducted using the same search strategies to identify studies through July 9, 2021.

Studies were selected for inclusion using pre-established criteria based on the KQs (see Appendix A) and PICOTs (see Table B-7), which focused on the benefits and harms of interventions to prevent and treat delirium. Studies with mixed populations, where interventions addressed both prevention and treatment of delirium, were included and classified separately. A third KQ assessed patient-level or setting factors that modify the effects (benefits or harms) of the interventions, which included demographics, comorbidities and severity of underlying illness, and type of setting.

The population was restricted to adults (≥18 years old) at risk for delirium or with delirium. Studies that used Diagnostic and Statistical Manual (DSM) criteria were considered for inclusion, as well as studies that used a clinical diagnosis of delirium. Studies that assessed agitation, including post-operative agitation, were excluded if there was no DSM or clinical diagnosis of delirium. Inclusion was restricted to English-language articles and interventions that were available in the United States.

A hierarchy-of-evidence approach was used in which observational studies with at least 50 participants were included only if inadequate evidence was found in randomized controlled trials (RCTs) for primary outcomes on any KQ. Given the substantial number of RCTs that were identified, observational studies were only included to fill in gaps in the review.

For both the initial and updated searches, title and abstract were screened by an initial reviewer with excluded articles screened by a second reviewer. Full text review was conducted in duplicate. Any discrepant determinations in title/abstract or full text review were resolved by consensus with input included from a third individual if consensus could not be reached.

Table B-7. Inclusion criteria by PICOTS element

| PICOTS Element | Include | Exclude |
|---|---|---|
| Populations | Adults (≥18 years old) at risk for delirium or with delirium, including those on palliative care and at end of life | Children and adolescents (<18 years old), delirium tremens |
| Interventions | Drug interventions (e.g., antipsychotics, cholinesterase inhibitors, sedatives, hypnotics, analgesics, melatonin, over-the-counter medications, complementary and alternative medicine) and nondrug interventions (e.g., environmental, light therapy, pain management, psychosocial interventions, reduction of unnecessary medications) | No intervention |

| PICOTS Element | Include | Exclude |
|---|---|---|
| Comparisons | Placebo, no intervention (usual care), other drug interventions, other non-drug interventions, different doses, frequencies, or intensities of interventions | No comparison |
| Outcomes | **Incidence and severity of delirium**, frequency of delirium episodes, **duration of delirium**, agitation, re-admission or admission to hospital, quality of life (including PTSD, cognitive decline, etc.), caregiver burden, rescue medication use, length of stay in hospital or ICU, mortality, **adverse events**[a] | None |
| Duration | Any duration | None |
| Settings | Any setting, including inpatient, hospice, and nursing homes | None |
| Study designs | RCTs, observational studies with N≥50, non-randomized clinical studies with a comparator | Uncontrolled, observational study with no comparator |

[a]Outcomes for which Strength of Research Evidence was assessed are shown in **bold**.
*Abbreviations*. ICU=intensive care unit; N=number; PTSD=post-traumatic stress disorder; RCT=randomized controlled trial.

## Data Extraction

Data were abstracted from included studies into evidence tables, including study and patient characteristics and study results, with data verified for accuracy and completeness by a second team member. Study and patient characteristics abstracted were: setting, eligibility criteria, age, percent female, race, other population characteristics (baseline delirium, function, dementia, cancer, and admission for surgery), number of participants randomized and analyzed, whether the intervention was for prevention or treatment, intervention characteristics, timing and duration of the intervention, duration of follow-up, and funding source. Data abstracted for results were incidence, severity, and duration of delirium, length of intensive care unit (ICU) and hospital stay, mortality, treatment-related adverse events, and additional outcomes identified in our PICOTS. Where trials reported more than one delirium measurement over the study period, a cumulative measure was reported if available. Otherwise, a time point was used that either matched that reported in other similar studies or was the latest one reported. All study data were verified for accuracy and completeness by a second team member.

## Risk of Bias Assessment

Risk of bias ratings are included in evidence tables (see Appendix D) with specific factors contributing to the risk of bias for each study shown in Appendix E. Predefined criteria were used to assess the risk of bias of included trials. RCTs were assessed based on criteria established in the Cochrane Handbook for Systematic Reviews of Interventions (Furlan et al. 2015; Higgins et al. 2023) with observational studies assessed using criteria developed by the U.S. Preventive Services Task Force (Harris et al. 2001). Two team members independently assessed risk of bias and assigned an overall rating of low, moderate, or high risk of bias, with disagreements were resolved by consensus.

Studies rated low are considered to have the least risk of bias, and their results are generally considered valid. Low risk of bias intervention studies include a valid method for allocating patients to treatment, and similar patient characteristics across groups at baseline; blinding of patients, caregivers, and outcome assessors to treatment received; low and non-differential dropout rates and clear reporting of dropouts; and use of intention-to-treat analysis.

Studies rated moderate are susceptible to some bias, though not enough to invalidate the results. These studies may not meet all the criteria for a rating of low risk of bias, but no flaw or combination of flaws is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The moderate risk of bias category is broad, and studies with this rating vary in their strengths and weaknesses. The results of some moderate studies are likely to be valid, while others may be only possibly valid.

Studies rated high have significant flaws that imply biases of various types that may invalidate the results. They have a serious or "fatal" flaw (or combination of flaws) in design, analysis, or reporting; large amounts of missing information or very high attrition; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of these studies are at least as likely to reflect flaws in the study design as to show true difference between the compared interventions. We did not exclude studies rated high risk of bias a priori, but high risk of bias studies were considered less reliable and given less weight than lower risk of bias studies when synthesizing the evidence, particularly when discrepancies between studies were present.

### Data Synthesis and Analysis

Evidence was analyzed according to KQs, using both qualitative (narrative) and where possible quantitative (meta-analysis) methods. In both approaches, drug studies were grouped by setting (e.g., surgical, ICU, general inpatient), and non-drug studies by intervention type (single-component vs. multi-component). For drug studies, within each setting, drugs of the same general class were assessed together.

To determine whether meta-analysis could be meaningfully performed, we considered the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes. Meta-analyses were conducted on outcomes of delirium incidence, severity, and duration, ICU and hospital length of stay, and mortality, when there were at least two studies reporting the same outcome.

DerSimonian and Laird random effects models were used for meta-analyses (Hardy and Thompson 1996), with heterogeneity assessed using both the $\chi^2$ test and the I-squared ($I^2$) statistic (Higgins and Thompson 2002). Small study effects (including potential publication bias) were analyzed using funnel plots and the Egger and Harbord tests, where there were at least 10 studies combined in meta-analyses. For dichotomous outcomes, relative risks (RRs) and 95% confidence intervals (CIs) were calculated and presented with the incidence in each group. RRs were calculated rather than absolute risk differences to account for variation in the underlying risk for the outcome in different study populations. For continuous outcomes, mean differences (MDs) were calculated (or standardized mean differences

[SMDs] when outcome measures differed) as well as 95% CIs. When necessary, standard error was estimated from other measures of variance that trials reported. All analyses were performed using STATA® 14.2 (StataCorp, College Station, TX). Selected forest plots for meta-analyses are included in the text, and additional forest plots for additional outcomes are available upon request.

The *a priori* plan for subgroup analysis included the population characteristics specified in KQ 3 in Appendix A. For studies that could be combined, meta-analyses were stratified by factors such as setting, type of surgery, or comparator. Meta-regression was used to calculate p-values for the interaction between these factors and treatment in their effects on outcomes. Where individual trials analyzed subgroups within their study populations, these are reported as well.

### Rating the Strength of Guideline Statements and the Body of Research Evidence

Each guideline statement is separately rated to indicate strength of recommendation and strength of supporting research evidence as described in the Introduction and Guideline Development Process.

The Pacific Northwest EPC evaluated the strength of research evidence (SRE) of primary outcome-intervention pairs using AHRQ methods (Berkman et al. 2015). Primary outcomes assessed were delirium incidence, severity, and duration, and adverse events.

Outcomes assessed for SRE were prioritized based on input from the American Psychiatric Association (APA); these are footnoted and listed in bold in the Table B-7. PICOTS element. Based on this prioritized list, the SRE for comparison-outcome pairs within each KQ was initially assessed by one researcher for each clinical outcome by using the approach described in the AHRQ *Methods Guide for Comparative Effectiveness Review* (Berkman et al. 2015). To ensure consistency and validity of the evaluation, the ratings for SRE were dual reviewed for:

- Study limitations (low, medium, or high)

  Rated as the degree to which studies for a given outcome are likely to reduce bias based on study design and study conduct (reflected in risk of bias assessments).

- Consistency (consistent, inconsistent, or unknown/not applicable)

  Rated by degree to which studies find similar magnitude of effect (i.e., range sizes are similar) or same direction (i.e., effect sizes have the same sign). When available, measures of statistical heterogeneity in meta-analyses also contributed to assessments of consistency.

- Measures of statistical heterogeneity in meta-analyses

  Rated as unknown (rather than not applicable) with downgrading of the SRE if only one study was available. This evidence was not automatically assessed as “insufficient,” but instead, the SRE considered the sample size or number of events available for analysis.

- Directness (direct or indirect)

Rated by degree to which evidence assesses a) comparison of interest, with studies that directly compare included interventions b) in the population of interest, and c) measures a clinically important outcome of interest.

- Precision (precise or imprecise)

  Rated based on the degree of certainty surrounding an effect estimate as it relates to a specific outcome. This may be based on sufficiency of sample size and number of events, and if these are adequate, the interpretation of the confidence interval. Thresholds of 400 analyzed patients were used for continuous outcomes, and 300 events were used for dichotomous outcomes to determine whether the Optimal Information Size (OIS) had been met. If the OIS was met, the 95% CI was evaluated according to the criteria in the AHRQ *Methods Guide for Comparative Effectiveness Review* (Berkman et al. 2015). The SRE was downgraded if either assessment indicated imprecision.

- Publication bias (suspected or undetected)

  Rated based on whether funnel plots or statistical methods showed evidence of selective publishing of research findings based on favorable direction or magnitude of effects. If fewer than 10 studies were available to conduct such analyses, this domain was rated as "unknown".

By evaluating and weighing the combined results of the above domains, the bodies of research evidence (specific outcome and intervention comparisons) were assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale that reflected the confidence or certainty in the findings (Table B-8).

Table B-8. Definitions of the grades of overall strength of research evidence (Berkman et al. 2015)

| Grade | Definition |
|---|---|
| High | We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable (i.e., another study would not change the conclusions). |
| Moderate | We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains. |
| Low | We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect. |

| | |
|---|---|
| Insufficient | We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available, or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion. |

The APA uses these same definitions for the overall strength of research evidence with the modification that the *low* rating is used when evidence is insufficient because there is low confidence in the conclusion and further research, if conducted, would likely change the estimated effect or confidence in the estimated effect.

In addition to assessing the SRE, the magnitude of effects were summarized according to thresholds of little to no difference, small, moderate, or large effects (Table B-9). These were applied regardless of the statistical significance of the differences.

Table B-9. Categories of magnitude of difference or effect

| Magnitude | Absolute Difference | RR (or OR) | MD (days) | SMD (severity) |
|---|---|---|---|---|
| Little/no difference: | <5% | >0.81 to <1.2 | <1.0 | <0.2 |
| Small | 5% to 10% | 1.2 to 1.4 | >1 to 2.0 | 0.2 to 0.5 |
| Moderate | 11% to 20% | 1.5 to 1.9 | >2.0 to 3.0 | >0.5 to 0.8 |
| Large | >20% | ≥2.0 | > 3.0 | >0.8 |

*Abbreviations*. MD=mean difference; OR=odds ratio; RR=relative risk; SMD=standardized mean difference.

In reporting the results of studies on treatment of delirium, the word “response” is used to indicate that the study reported the proportion of patients who either had no symptoms of delirium or did not meet the threshold for delirium on the scales used, at study endpoint. Note that, in this report, the term “significant” is used to describe statistically significant differences in the results, and the categories above are used to describe the magnitudes of difference in findings.

# Appendix C. Review of Research Evidence Supporting Guideline Statements

## Assessment and Treatment Planning

### *Statement 1 – Structured Assessments for Delirium*

APA recommends **(1C)** that patients with delirium or who are at risk for delirium undergo regular structured assessments for the presence or persistence of delirium using valid and reliable measures.

Support for this statement comes from the literature on delirium prevention and management, general principles of assessment, and clinical care in psychiatric practice, from epidemiologic data on the prevalence of delirium in non-community populations (e.g., hospitalized general medical patients, critical care patients), and from data on the validation of delirium screening tools. Together, the strength of research evidence is rated as low.

A detailed systematic review to support this statement is outside the scope of this guideline; however, a less comprehensive search of the literature identified multiple studies and reviews advising clinicians to engage in routine assessment and screening for delirium (Bush et al. 2017; Devlin et al. 2018; Kotfis et al. 2018; Mart et al. 2021). In addition, delirium is under-detected, even by highly trained health care professionals in acute care settings, unless screening is implemented using tools as used in validation studies and including deliberate cognitive assessment (Bush et al. 2017; Carpenter et al. 2021; Devlin et al. 2007; Geriatric Medicine Research Collaborative 2019; Grossmann et al. 2014; Kotfis et al. 2018; Spronk et al. 2009). These findings also support this guideline recommendation.

### Grading of the Overall Supporting Body of Research Evidence for Structured Assessments for Delirium

In the absence of a detailed systematic review on the topic of structured assessments for delirium, no grading of the body of research evidence is possible.

### *Statement 2 – Determination of Baseline Neurocognitive Status*

APA recommends **(1C)** that a patient's baseline neurocognitive status be determined to permit accurate interpretation of delirium assessments.

Support for this statement comes from the literature on delirium diagnosis and assessment and from the definition of delirium itself, which states that delirium represents an acute departure from a person's baseline attention and awareness (American Psychiatric Association 2022). Additionally, many delirium assessments, such as the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), include instructions or assessment items that state outright that the patient's symptoms must represent a change from baseline cognitive functioning.

A detailed systematic review to support this statement is outside the scope of this guideline; however, a less comprehensive search of the literature identified multiple studies and reviews that emphasized the importance of baseline cognitive status for determining whether cognitive changes are present and reflective of delirium or some other pathology (Duggan et al. 2021; Fong and Inouye 2022; Grover and Kate 2012; Kotfis et al 2018; Maldonado 2017; Meagher and Leonard 2008; Oh et al. 2017; Ospina et al. 2018). Without information on the patient's baseline cognitive status, the diagnosis of delirium can be missed, as the clinician would be unable to tell whether the presenting symptoms represent an acute

change from normal (Oh et al. 2017). This is particularly true in patients who have some pre-existing cognitive impairment. Baseline cognitive status upon hospital admission also may help determine the risk of incident delirium and duration during a hospital stay (Tsui et al. 2022), because patients with pre-existing cognitive impairment are more likely to develop delirium and for delirium to persist. Similarly, knowledge of a patient's baseline cognitive status is important for differentiating between delirium and dementia, as acute changes from baseline are more indicative of the former whereas slower, more subtle changes reflect the latter (Fong and Inouye 2022).

### Grading of the Overall Supporting Body of Research Evidence for Determination of Baseline Cognitive Status

In the absence of a detailed systematic review on the topic of baseline cognitive status determination, no grading of the body of research evidence is possible.

### *Statement 3 – Review for Predisposing or Contributing Factors*

APA recommends **(1C)** that patients with delirium or who are at risk for delirium undergo a detailed review of possible predisposing or contributing factors.

Support for this statement comes from the literature on delirium management, which underscores the importance of resolving delirium precipitants as the primary intervention. Although not all contributing factors to delirium will be modifiable, review of possible precipitants can help clinicians identify factors amenable to change and implement interventions in a timely manner. Early intervention in delirium can help reduce the risk of serious complications, such as dehydration, pneumonia, and falls, among others (O'Hanlon et al. 2014). In some studies, timely intervention has also been associated with a reduction in delirium duration (O'Hanlon et al. 2014).

A detailed systematic review to support this statement is outside the scope of this guideline; however, a less comprehensive search of the literature on the management of delirium found numerous studies and reviews that emphasize the importance of identifying and reversing underlying causes and contributors to delirium as a cornerstone of delirium treatment (Z. Jin et al. 2020; Maldonado 2017; Mart et al. 2021; Mattison et al. 2020; Oh and Park 2019; Ospina et al. 2018; Wilson et al. 2020; see also Statement 3, Implementation). This is especially important given that some underlying causes may be life-threatening, such as intracranial hemorrhage, hypertensive crisis, electrolyte imbalance, hypoxemia, and infection (Ospina et al. 2018).

### Grading of the Overall Supporting Body of Research Evidence for Review of Predisposing or Contributing Factors

In the absence of a detailed systematic review on the topic of predisposing or contributing factors to delirium, no grading of the body of research evidence is possible.

### *Statement 4 – Review of Medications*

APA recommends **(1C)** that a detailed medication review be conducted in patients with delirium or who are at risk for delirium, especially those with pre-existing cognitive impairment.

Support for this statement comes from the literature on delirium risk, management, and prevention, which underscores the importance of assessing medication use as a potential contributor to or exacerbator of delirium.

A detailed systematic review to support this statement is outside the scope of this guideline; however, a less comprehensive search of the literature on the risks, management, and prevention of delirium highlights the importance of medication review. It has been estimated that as many as 39% of all cases of delirium may be due to medication use (Adeola et al. 2018). Research on medication-related risk factors for delirium has found a higher odds of delirium in patients treated with antipsychotics, benzodiazepines, anticholinergics, opioids (especially when combined with benzodiazepines), and polypharmacy (Aloisi et al. 2019; Duprey et al. 2021, 2022; Featherstone et al. 2022; Kang et al. 2019; Kassie et al. 2017; Lee et al. 2022; Marquetand et al 2022; Reisinger et al. 2023; Rigor et al. 2020; Saljuqi et al. 2020; Shi et al 2022; Silva et al. 2021; Softy et al. 2023; Vacas et al. 2022; H. Zhang et al. 2021); however, some of these associations may result from the use of these medications in patients with early signs of delirium to address neuropsychiatric symptoms. In addition, medications such as antipsychotics and benzodiazepines can increase the risk of adverse effects, including cardiac disturbances, falls, cognitive impairment, cerebrovascular events, infection, and mortality (Johnson et al. 2017; Markota et al. 2016). Although antipsychotic medications do not appear to decrease the incidence or duration of delirium (Neufeld et al. 2016; Nikooie et al. 2019; see also Statement 8), they are sometimes used in an effort to reduce behavioral symptoms of delirium. Once prescribed, these medications are often continued after transfer of care and hospital discharge (Boncyk et al. 2021; Dixit et al. 2021; Flurie et al. 2015; Johnson et al. 2017; Lambert et al. 2021; see also Statements 14 and 15).

Deliriogenic medication use is even more concerning in patients with preexisting cognitive impairment because some of these medications can exacerbate cognitive dysfunction and lead to poorer outcomes for patients. For instance, anticholinergics are associated with increased memory and learning impairment, with a greater magnitude of effect observed in people with preexisting cognitive dysfunction versus cognitively normal individuals (Taylor-Rowan et al. 2023). Benzodiazepines similarly are associated with an increased risk of impairments in memory, learning, attention, and visuospatial abilities especially with prolonged exposure in older adults (Markota et al. 2016; Picton et al. 2018). Furthermore, patients with premorbid cognitive dysfunction are already at a greater risk of delirium than cognitively healthy adults, likely due in part to the neurodegeneration and neuroinflammation associated with cognitive decline (Davis et al. 2015; Prendergast et al. 2022). Exposure to potentially deliriogenic medication in these patients further increases their vulnerability to delirium and could make them more susceptible to poor outcomes associated with delirium, such as further cognitive deterioration and dementia (Wilson et al. 2020).

Medication review is a necessary precursor to medication cessation or dose reduction. It can also be an effective non-pharmacologic strategy to reduce unnecessary exposure to high-risk medication. Although many studies of medication review and deprescribing have been conducted in ambulatory or long-term care settings (Evrard et al. 2022), some studies have examined hospital settings or patients with delirium or at risk for delirium. For example, in a large study of ICU patients (N=281), physician and nurse education, medication review, and an antipsychotic discontinuation algorithm were associated with

reduced rates of antipsychotic continuation at transfer of care (*P*=0.014) and at hospital discharge (*P*=0.024) (D'Angelo et al. 2019). Similarly, a pharmacist-led intervention (e.g., pharmacy surveillance alerts and discontinuation/dose reduction plans) effectively reduced unnecessary exposure to high-risk medications in hospitalized patients with delirium (Adeola et al. 2018). In contrast, in a study of 200 adults age 18 or older who were admitted to an ICU with delirium, there was no impact of a deprescribing initiative that used electronic alerts and pharmacist support to reduce use of anticholinergic medications and benzodiazepines (Campbell et al. 2019).

Medication review is often a component of multi-component non-pharmacologic interventions for patients at risk for delirium (Burton et al. 2021), and much of the literature on its effects in preventing incident delirium come from studies of multi-component interventions. A pilot study of a nurse intervention to prevent delirium in hospitalized older adults (N=50; Avendano-Cespedes et al. 2016) found that a multifactorial intervention, which included medication review, was associated with a significantly lower incidence of delirium versus controls (3% vs. 12%, *P*=0.039), as well as lower delirium severity (*P*=0.04). In a study of older adults with severe pancreatic encephalopathy, use of the Hospital Elderly Life Program intervention—which included medication review and management—was associated with significantly lower incidence of delirium versus controls (4% vs. 17%, *P*=0.033 [Dong et al. 2020]). A multicenter RCT of a geriatric-focused multi-component intervention that included medication review also reported a reduced incidence of delirium with the intervention versus usual care (N=260; 9.4% vs. 14.3%, OR 0.63, 95% CI 0.29–1.35 [Hempenius et al. 2013]).

Fewer studies have examined medication review as an intervention in isolation, but existing evidence suggests it could help reduce delirium prevalence, duration, and length of episodes. In a trial conducted in the Netherlands (N=93) that assessed the effects of medication review on length of delirium, length of stay, mortality, and discharge destination (van Velthuijsen et al 2018), delirium duration was shorter in intervention patients versus controls (8.56 days vs. 15.47 days). Additionally, among intervention patients who were taking up to six medications, episodes of delirium were significantly shorter than in controls taking up to six medications (MD 15.46 days, *P*<0.001).

### Grading of the Overall Supporting Body of Research Evidence for Detailed Medication Review

In the absence of a detailed systematic review on the topic of detailed medication review for patients with delirium or who are at risk for delirium, no grading of the body of research evidence is possible.

### *Statement 5 – Use of Restraints*

APA recommends **(1C)** that physical restraints not be used in patients with delirium, except in situations where injury to self or others is imminent and only:

- after review of factors that can contribute to racial/ethnic and other biases in decisions about restraint;
- with frequent monitoring; and
- with repeated reassessment of the continued risks and benefits of restraint use as compared to less restrictive interventions.

This recommendation is based on a focused review of the literature on the use of physical restraints in patients with or at risk for delirium as well as the literature on precipitating and predisposing factors of delirium.

Physical restraints are often used to enhance patient safety, prevent self-extubation or tube dislodgment, reduce the risk of falls, and protect staff from patient combativeness (Devlin et al. 2018). However, there are no data from RCTs that support these benefits. Paradoxically, one post-hoc study found greater rates of device removal or need for reintubation in patients who were physically restrained (Rose et al. 2016). Several additional studies also reported rates of self-extubation of at least 80% despite the presence of physical restraints (Perez et al. 2019). Data on falls and restraint use is also limited and likely dependent on the type of restraint used, with some studies including bedrails or bed/chair alarms as forms of restraint (Abraham et al. 2022). Studies of falls and restraint use have also been confounded by factors that could increase both types of events. For example, one study found injurious falls occurred in individuals who had a mental status change in the prior 24 hours and that such falls were associated with a greater length of stay in those who were physically restrained after the mental status change (Francis-Coad et al. 2020). Another study found that patients with an order for physical restraint fell more often than patients without such an order; however, many patients with an order were not actually found to be restrained and the order for restraint may have been placed due to a perceived increase in fall risk (Shorr et al. 2002).

In patients with delirium, use of physical restraints is generally not recommended because delirium can be caused by easily identifiable and correctable factors that can be avoided by thoroughly assessing for contributing factors to the delirium (Smithard and Randhawa 2022). Use of restraints can also exacerbate agitation, heighten confusion, and lead to injury (Sharifi et al. 2021; Teece et al. 2020). Many physical consequences of restraints have been reported and can include pressure ulcers, fractures, cardiac arrythmias, musculoskeletal injuries, incontinence, asphyxiation, and potentially death from strangulation (Sharifi et al. 2021). Rates of such events have not been well studied, but one prospective study found that neurovascular effects (e.g., redness, edema, color changes, reduced pulse strength) were greater in restrained limbs after 4 days of restraint than on the initial day of restraint (Ertuğrul and Özden 2020).

Emotional harms of restraint have also been described. In one qualitative study of patients who had been physically restrained in an emergency department, the experience was viewed as frightening and dehumanizing, prompting a sense of helplessness, anxiety, and mistrust of health care as well as some long-term psychological effects (Wong et al. 2020). A systematic review of PTSD in ICU settings identified three studies that examined the association of PTSD and restraint use (Franks et al. 2021). One of these studies (N=98) found that one-third of ICU survivors had symptoms of PTSD and that risk of PTSD symptoms was greater in those who recalled being physically restrained during the admission (OR 6.04, 95% CI 2.21–16.33, $P<0.001$ [Hatchett et al. 2010]). Another study (N=114) also found use of physical restraint to be associated with a greater risk of meeting criteria for PTSD when assessed 3 months after ICU discharge (OR 6.27, 95% CI 1.66–23.67, $P=0.007$ [Zghidi et al. 2019]). A larger study (N=238) used structural equation modeling to investigate relationships between PTSD and possible contributors; it

found that individuals who were physically restrained without being concomitantly sedated were predisposed to develop PTSD symptoms (Jones et al. 2007).

A number of observational studies have suggested that use of physical restraints is associated with an increase in the likelihood of incident delirium (Maldonado 2017; McPherson et al. 2013; Mehta et al. 2015; Pan et al. 2018). However, this does not imply a causal relationship. Rather, underlying factors or unreported clinical observations may contribute both to a greater likelihood of restraint use as well as to a greater likelihood of delirium being recognized. Future clinical trials could help establish whether restraint-free approaches to care are feasible and could improve delirium outcomes (Flaherty and Little 2011).

When the potential benefits of using physical restraints appear to outweigh the harms, it is important to consider whether any biases have been introduced into the clinical decision-making. Evidence suggests racial/ethnic bias may be present in the use of physical restraints among hospitalized or emergency department patients (Wong et al. 2021). For example, a retrospective chart analysis of more than 195,000 patients with emergency department visits found a significant increase in the use of restraints among Asian patients (RR 0.71, 95% CI 0.55–0.92, *P*=0.009) and Black patients (RR 1.22, 95% CI 1.05–1.40, *P*=0.007) compared to White patients (Schnitzer et al. 2020). Another large retrospective study (Wong et al. 2021) examined use of restraints among 726,417 emergency department visits of which 1% included an episode of physical restraint. Black individuals were more likely to be restrained than White individuals (adjusted OR 1.13, 95% CI 1.08–1.21), whereas Hispanic or Latino individuals (adjusted OR 0.78, 95% CI 0.70–0.88) had lower odds of being restrained compared with non-Hispanic individuals (Wong et al. 2021). Female patients also had lower odds of being restrained (adjusted OR 0.75, 95% CI 0.71–0.79 as compared to male patients [Wong et al. 2021]). Differences in the likelihood of restraint use were also noted based on housing (patients who were homeless had adjusted OR 1.35, 95% CI 1.14–1.16 as compared to those with housing) and insurance status (as compared to patients with private insurance, patients with Medicaid had adjusted OR 1.55, 95% CI 1.45–1.67 and those with Medicare had adjusted OR 1.67, 95% CI 1.54–1.82) (Wong et al. 2021). A retrospective study of 4,410,816 encounters in Northern California included 6,369 encounters (5,554 unique patients) in which physical restraint was used (Walia et al. 2023). Black patients and patients with other or unknown race/ethnicity had higher odds of restraint (adjusted OR 1.11, 95% CI 1.02–1.21 and adjusted OR 1.52, 95% CI 1.34–1.72, respectively) whereas Asian patients had lower odds (adjusted OR 0.75, 95% CI 0.66–0.85) as compares to White patients (Walia et al. 2023). Another analysis of 12,229 emergency department patient visits focused on patients 16 and older with diagnoses of aggression or agitation who received either chemical or physical restraints used (Conteh et al. 2023). This study found Hispanic patients, as compared to White patients, were less likely to receive physical restraints (*P*=0.044, 95% CI 0.467–0.989) or a dose of a chemical restraints (*P*=0.008, 95% CI -0.359 to -0.053) (Conteh et al. 2023). However, this study differed from the other emergency department samples in noting no statistically significant differences when comparing Black patients to White patients on the likelihood of restraint use.

In studies that focused on restraint use during psychiatric emergency encounters, one study of more than 32,000 emergency department encounters reported significantly higher odds of restraint use among Black (adjusted OR 1.22, 95% CI 1.01–1.48, *P*<0.001) and Hispanic patients (adjusted OR 1.45,

95% CI 1.22–1.73, *P*<0.01) compared with White patients (Carreras Tartak et al. 2021). Another retrospective study of 12,977 emergency psychiatric evaluations observed that Black patients were more likely to be physically (adjusted OR 1.35, 95% CI 1.07–1.72) or chemically (adjusted OR=1.33, 95% CI 1.15–1.55) restrained than White patients (Smith et al. 2022).

Limited research has examined potential bias in the restraint of patients with delirium, but existing studies are consistent with this pattern. In the National Inpatient Sample, a de-identified all-payors database of acute care hospital discharges in the United States, restraints were used in 0.7% of overall hospitalizations and 7.4% of patients with a diagnosis of encephalitis. In an adjusted model in the sample as a whole, Black individuals had a greater likelihood of restraint than White individuals (OR 1.3, 95% CI 1.2–1.4), and men had a greater likelihood of restraint than women (OR 1.4, 95% CI 1.4–1.5) (Luccarelli et al. 2023). The same sample included 991,605 patients noted to have dementia with behavioral disturbances, with physical restraints being used in 6.5%. Individuals who were restrained, as compared to unrestrained, were more likely to be Black (15.2% vs. 11.8%, *P*<0.01), males (59.0% vs. 45.8%, *P*<0.01), and younger in age (mean age ± standard error: 78.7 ± 0.25 vs. 79.9 ± 0.34, *P*<0.01) (Singh et al. 2023).

Factors other than race, ethnicity, gender, or age can also introduce bias into decisions related to restraint. For example, a retrospective cohort study of general medical patients in Canada (Reppas-Rindlisbacher et al. 2022) observed 2.6-fold the risk of physical restraint use among patients who did not prefer English as their dominant language compared with patients who did prefer English (27.9% vs. 11.7%, adjusted RR 2.61, 95% CI 1.40–4.85).

### Grading of the Overall Supporting Body of Research Evidence for Use of Restraints

In the absence of a detailed systematic review on the topic of restraint use in a patient with delirium, no grading of the body of research evidence is possible.

### *Statement 6 – Person-Centered Treatment Planning*

APA recommends **(1C)** that patients with delirium have a documented, comprehensive, and person-centered treatment plan.

Support for this statement comes from the literature on delirium management and risk factors, which underscores the complexity of delirium and the importance of accounting for individual variability in symptoms, illness severity, and contributors when selecting appropriate treatments.

A detailed systematic review to support this statement is outside the scope of this guideline; however, a less comprehensive search of the literature did not find evidence on the specific benefits of treatment planning in patients with delirium. Nevertheless, best practices in clinical care and available information on the risks and management of delirium demonstrate the need for a comprehensive, personalized approach to treatment planning.

Delirium has multiple etiologies, heterogenous phenotypes, and according to a recent systematic literature review, 33 predisposing and 112 precipitating risk factors (Ormseth et al. 2023); because of this, management can be challenging and needs to be individualized (Devlin et al. 2018; Mart et al. 2021;

Ormseth et al. 2023). Multi-component non-pharmacologic treatments are the primary management tool for treating delirium (Mart et al. 2021; Oh and Park 2019) and evidence for those approaches is described in Appendix C, Statement 7.

Person-centered treatment planning can include consideration of how family and caregivers can be incorporated into care, as appropriate (Kukreja et al. 2015). A systematic review and meta-analysis of family and caregiver interventions for delirium found family-caregiver involvement in delirium management is associated with reduced length of hospital stay (10 days intervention vs. 14 days control, *P*=0.005) and reduced levels of family anxiety (McKenzie and Joy 2020). Although more research is needed to better understand the effects of including informal carers in delirium treatments, for some patients with delirium, family and caregivers could be valuable in providing patients support, functional assistance, and reassurance (McKenzie and Joy 2020; Pandhal and Van Der Wardt 2022).

### Grading of the Overall Supporting Body of Research Evidence for Person-Centered Treatment Planning

In the absence of a detailed systematic review on the topic of person-centered treatment planning for patients with delirium, no grading of the body of research evidence is possible.

## Non-Pharmacological Interventions

### *Statement 7 – Multi-Component Non-Pharmacological Interventions*

APA recommends **(1B)** that patients with delirium or who are at risk for delirium receive multi-component non-pharmacological interventions to manage and prevent delirium.

In general, non-pharmacological interventions have been shown to prevent delirium in at-risk populations but have not shown a consistent effect in reducing duration or severity of delirium once it is present. Importantly, however, these studies of non-pharmacological interventions have key limitations and should be interpreted cautiously. For example, studies have extensive differences in the extent to which components are delivered and how they are operationalized in various hospital settings. Studies differ in the specific combination of interventions used in each trial, and interventions are also combined differently in the study arms. In some instances, overlaps between intervention and treatment as usual groups are not well-defined, whereas in in other instances, the same intervention has been implemented in different ways. These features of the study designs make it difficult to know the extent to which an intervention was actually provided. In addition, most of the interventions would be impossible to deliver in a blinded fashion, and few studies included procedures to ensure fidelity and completion of interventions, further complicating a robust analysis of the data. Other interventions, such as family involvement, may take place regardless of study participation. Finally, several elements of care may be unrecognized and could have an effect but have not been studied, observed, or controlled for (e.g., having a private vs. a shared room).

### Non-Pharmacological Interventions for the Prevention of Delirium

A systematic review conducted by the Pacific Northwest EPC assessed outcomes from multi-component and single-component non-pharmacological interventions among clinical trials designed to prevent delirium. For both multi-component and single-component interventions, treatment groups had a significantly lower incidence of delirium than control groups. However, results were not significant for

subgroups of general inpatient, home care/long-term care, or ICU populations. A Cochrane review of multi-component interventions for the prevention of delirium similarly found a lower incidence of delirium with treatment versus control (Burton et al. 2021). Analyses of studies of ABCDEF bundle interventions found significant improvements in delirium symptoms compared with control patients, but this was highly dependent on the extent to which the patients completed every element of the bundle (Balas et al. 2022; Barnes-Daly et al. 2017; Pun et al. 2019; Sosnowski et al. 2023). Hospital Elder Life Program (HELP) interventions similarly demonstrated a reduction in delirium incidence with treatment (Chen et al. 2017; Hshieh et al. 2018; Inouye et al. 2000; Y.Y. Wang et al. 2020). Subgroup analyses looking for effects of multi-component interventions by their specific interventions were generally not significant.

### Multi-Component Interventions

The EPC systematic review identified 23 RCTs that are described in 26 publications (Abbasinia et al. 2021; Avendano-Cespedes et al. 2016; Boockvar et al. 2020; Boustani et al. 2012; Caplan et al. 2006; Chen et al. 2011, 2017; Dong et al. 2020; Guo et al. 2016; Hamzehpour et al. 2018; Hempenius et al. 2013, 2016; Hosie et al. 2020; Khan et al. 2013; Moon and Lee 2015; Lapane et al. 2011; Lundström et al. 2005, 2007; Rice et al. 2017; Rood et al. 2021; Siddiqi et al. 2016; Stenvall et al. 2012; Verloo et al. 2015; Y.Y. Wang et al. 2020; Watne et al. 2014; Young et al. 2020) and that compared a multi-component non-pharmacological intervention with usual care for the prevention of delirium. Sample sizes varied widely but were predominantly less than 200 subjects. Four trials were conducted in the United States, eight in Europe, three in China, two in Taiwan and Australia each, and one each in Iran and South Korea. Six trials were conducted post-operatively, with types of surgeries including cardiac, abdominal, orthopedic, oncologic, and other procedures. Other trials included seven conducted in general inpatient settings, three in ICUs, four in nursing home or home care settings, and one in a palliative care setting. A majority of the trials had a moderate risk of bias.

Evidence also included outcomes from a Cochrane review of multi-component non-pharmacological interventions (Burton et al. 2021). Additionally, studies on ABCDEF care bundles and from HELPs were also considered (Balas et al. 2022; Barnes-Daly et al. 2017; Chen et al. 2017; Hshieh et al. 2018; Inouye et al. 2000; Pun et al. 2019; Sosnowski et al. 2023; Y.Y. Wang et al. 2020), although they did not meet inclusion criteria for the formal systematic review.

#### *Overview of study characteristics*

Interventions were a mix of behavioral and other types of interventions, with a mean of six interventions (range 2 to 11; see Table C-1). Behavioral intervention studies included: sensory interventions (9 trials), orientation interventions (10 trials), cognitively stimulating activities (8 trials), and increasing self-/independent care (3 trials). Other types of interventions included: early mobilization (15 trials), early removal of urinary catheter (7 trials), avoidance of restraints (3 trials all of which also removed urinary catheters early), avoidance or reduction of certain medications (10 trials), sleep aids or promotion of good quality sleep (10 trials), scheduled liquid intake to avoid dehydration (13 trials), nutritional assistance or scheduled oral food intake (13 trials, 11 of which also scheduled liquid intake), and monitoring for infection (7 trials), need for transfusion (1 trials), need for oxygen (4 trials), need for pain medications (7 trials). In the majority of trials (11 trials), interventions were delivered by nursing staff

and, in other studies, multidisciplinary teams, research staff, or geriatric specialists were used. Only three trials involved family members in delivering the interventions. All control interventions were usual care of the hospital or facility where the trial was conducted and may have involved portions of the multi-component interventions but were not utilized as consistently as in the intervention groups.

761 Table C-1. Components in multi-component intervention trials for the prevention of delirium

| Author Year Trial Name | Setting Country | RF | Family[a] | Sensory[b] | Orient[c] | Early mobile | ↓Restraints[d] | Planned intake[e] | ↓Rxs[f] | Cognitive activities | ↑Self-care[g] | Sleep[h] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Abbasinia et al. 2021 | ICU Iran | | | X | X | X | | X | X | | | X |
| Avendano-Cespedes et al. 2016 | Inpatient Spain | X | X | X | | X | X | X | X | | | |
| Boockvar et al. 2020 HELP-LTC | Nursing home U.S. | X | | | X | X | | X | | X | | |
| Boustani et al. 2012, Khan et al. 2013 e-CHAMPS trial | Inpatient U.S. | | | | | | X | | X | | | |
| Caplan et al. 2006 The REACH-OUT trial | Inpatient Australia | X | | | | | | | | | | |
| Chen et al. 2011 mHELP | Inpatient Taiwan | | | | X | X | | X | | X | | |
| Chen et al. 2017 mHELP | Postop Taiwan | | | | X | X | | X | | | | |
| Dong et al. 2020 mHELP | Inpatient China | X | | X | | X | | X | X | X | | X |
| Guo et al. 2016 | Postop China | | | X | X | | X | | | X | | |
| Hamzehpour et al. 2018 | ICU Iran | X | | | | X | | X | | | | X |
| Hempenius et al. 2013, 2016 LIFE trial | Postop The Netherlands | X | | X | X | X | | | X | | | X |

| Author Year Trial Name | Setting Country | RF | Family[a] | Sensory[b] | Orient[c] | Early mobile | ↓Restraints[d] | Planned intake[e] | ↓Rxs[f] | Cognitive activities | ↑Self-care[g] | Sleep[h] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Hosie et al. 2020 PRESERVE Pilot Study | Palliative Australia | X | X | X | X | X | | X | | | | X |
| Moon and Lee 2015 | ICU S. Korea | X | | X | X | X | X | X | X | | | X |
| Lapane et al. 2011 GRAM software | Nursing home U.S. | X | | | | | | | X | | | |
| Lundström et al. 2005 | Inpatient Sweden | X | | | | | | | | | X | |
| Lundström et al. 2007, Stenvall et al. 2012 | Postop Sweden | X | | | | X | X | X | | | X | X |
| Rice et al. 2017 mHELP | ICU U.S. | X | | | | | | X | X | X | | X |
| Rood et al. 2021 | ICU The Netherlands | | | X | X | X | | | | X | | X |
| Siddiqi et al. 2016 Stop Delirium! | Nursing home U.K. | X | | X | | X | | X | | | | X |
| Verloo et al. 2015 | Home care Switzerland | X | | X | X | X | | X | X | X | X | X |
| Y.Y. Wang et al. 2020 t-HELP | Postop China | X | X | | X | X | X | X | X | X | | X |
| Watne et al. 2014 Oslo Orthogeriatric Trial | Postop Norway | X | | | | X | | X | X | | | |
| Young et al. 2020 | Inpatient U.K. | | | X | X | X | | X | | X | | |

[a] Family was involved in the delivery of the intervention.

[b] Such as glasses, hearing aids, good lighting, noise avoidance

[c] Such as date, time, location, reason for being there

[d] Either physical restraints or catheter

[e] Daily scheduled oral or IV administration of fluids (liquids) and/or nutritional assistance

[f] Decreased use or avoidance of use of psychotropic medications, opioids, anticholinergics, sedatives, and other drugs that may increase risk of delirium or sedation

[g] Increase patient's independent care for self, preferably to baseline

[h] Sleep aids such as ear plugs and/or eye masks, and decreased noise and light at night

*Abbreviations.* e-CHAMPS=enhanced Care for Hospitalized older Adults with Memory Problems; GRAM=Geriatric Risk Assessment MedGuide; HELP=Hospital Elder Life Program; HELP-LTC=Hospital Elder Life Program-Long Term Care; ICU=intensive care unit; LIFE=Liaison Intervention in Frail Elderly; mHELP=modified Hospital Elder Life Program; REACH-OUT=Rehabilitation Of Elderly And Care At Home Or Usual Treatment; RF=risk factor analysis; t-HELP=tailored Hospital Elder Life Program.

*Source*. Abbasinia et al. 2021; Avendano-Cespedes et al. 2016; Boockvar et al. 2020; Boustani et al. 2012; Caplan et al. 2006; Chen et al. 2011, 2017; Dong et al. 2020; Guo et al. 2016; Hamzehpour et al. 2018; Hempenius et al. 2013, 2016; Hosie et al. 2020; Khan et al. 2013; Moon and Lee 2015; Lapane et al. 2011; Lundström et al. 2005, 2007; Rice et al. 2017; Rood et al. 2021; Siddiqi et al. 2016; Stenvall et al. 2012; Verloo et al. 2015; Y.Y. Wang et al. 2020; Watne et al. 2014; Young et al. 2020.

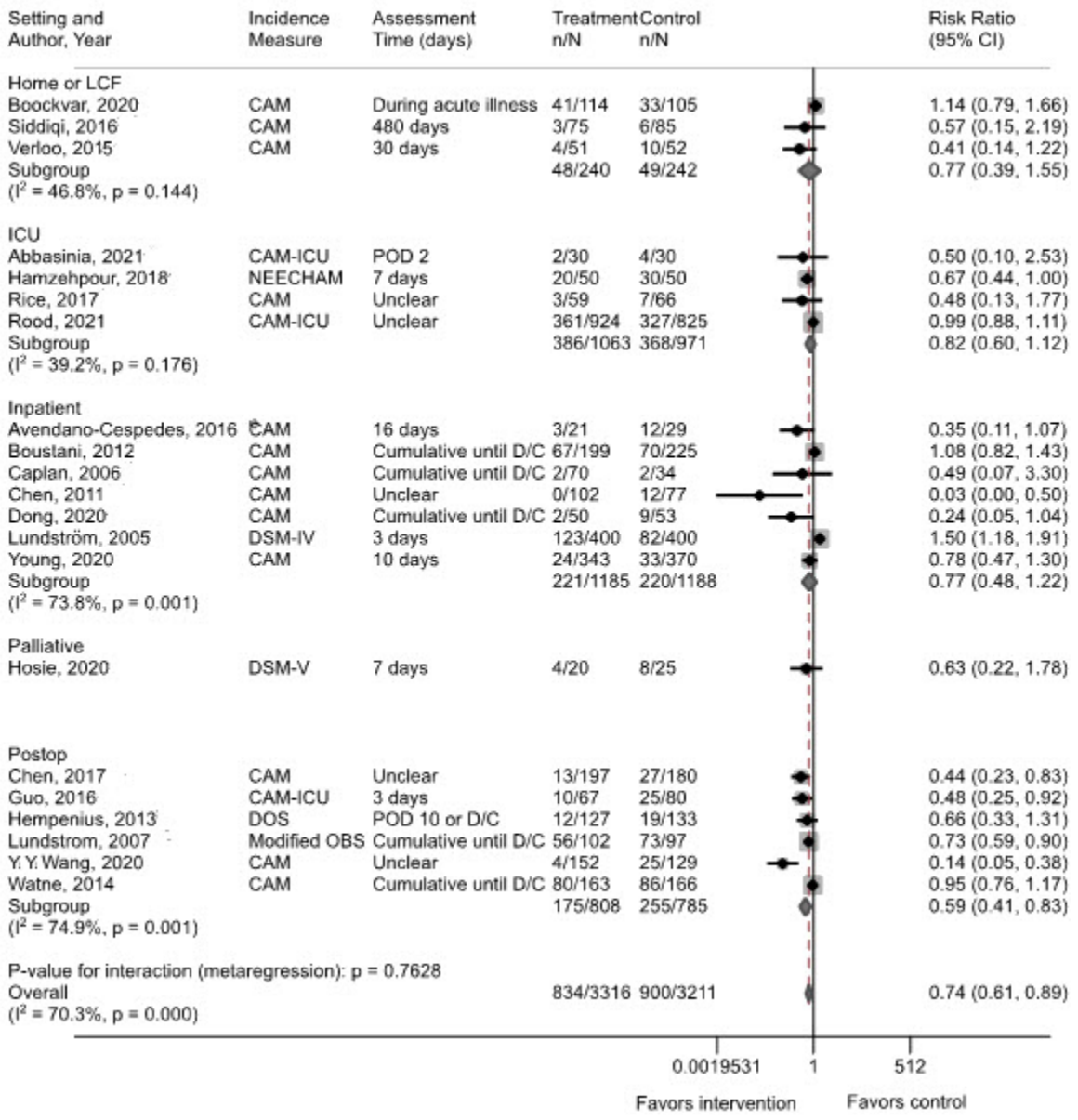
The weighted mean age of patients across these prevention trials was 77 years old, with 23 studies having a mean age 65 or older. Most patients were female (mean 56%; range 27% to 76%). Only six U.S. or U.K. based trials reported race: three of these studies had a majority of White participants, two included a population that was 59.5% White and 47% Black, and one trial included population that was 35.2% Black, 33.3% White, 29.7% Hispanic, and 1.8% Other. Six trials reported that participants had dementia at baseline (range from 4.5% to 52.5%). All trials that reported baseline functional status described patients as being within normal levels of functioning as measured by the Charlson Comorbidity Index, the Glasgow Coma Scale, the Acute Physiology and Chronic Health Evaluation (APACHE II), the Functional Independence Measure, or another function scale. In addition to the DSM-IV and DSM-5 criteria, four different measures were used to diagnosis delirium in the trials: three versions of the CAM (CAM, CAM-ICU, and Confusion Assessment Method-Nursing Homes [NH-CAM]), a modified Organic Brain Syndrome scale, Delirium Observational Scale, and Neelon-Champagne Confusion scale (NEECHAM). Although the goal of these studies was prevention of delirium, only three trials specifically excluded individuals with delirium at baseline, eight trials did not report on the presence of delirium at baseline, and six trials reported the presence of delirium at baseline in 1% to 30% of participants.

*Effect of multi-component interventions on delirium incidence*

Regarding delirium outcomes, 23 trials (described in 24 publications) reported incidence of delirium (Abbasinia et al. 2021; Avendano-Cespedes et al. 2016; Boockvar et al. 2020; Boustani et al. 2012; Caplan et al. 2006; Chen et al. 2011, 2017; Dong et al. 2020; Guo et al. 2016; Hamzehpour et al. 2018; Hempenius et al. 2013, 2016; Hosie et al. 2020; Khan et al. 2013; Lundström et al. 2005, 2007; Rice et al. 2017; Rood et al. 2021; Siddiqi et al. 2016; Stenvall et al. 2012; Verloo et al. 2015; Y.Y. Wang et al. 2020; Watne et al. 2014; Young et al. 2020), which was measured at discharge from hospital in five trials, at a specific follow-up time in five (3–480 days, 4 trials ≤30 days), during the acute illness in one, and with unclear timing in one. At baseline, two trials enrolled some patients with delirium (29.5% [Watne et al. 2014] and 26.3% [Lundström et al. 2007]) and did not exclude these individuals when reporting delirium prevalence at endpoint.

In a pooled analysis of 21 trials, the intervention groups had a significantly lower incidence of delirium compared with usual care (N=6,527; 25.1% vs. 28.0%, RR 0.74, 95% CI 0.61–0.89, $I^2$=70.3%) (see Figure C-1). Although subgroup analyses all favored the interventions and subgroup analyses of patients in post-operative settings favored the intervention group (8 trials, N=1,685; RR 0.66, 95% CI 0.47–0.92, $I^2$=70%), analyses stratified by setting for the general inpatient population (7 trials, N=2,373; RR 0.77, 95% CI 0.48–1.22, $I^2$=74%), home care or long-term care patients (3 trials, N=482; RR 0.77, 95% CI 0.39–1.55, $I^2$=47%), or patients in the ICU (4 trials, N=2,034; 36.3% vs. 37.9%, RR 0.82, 95% CI 0.60–1.12, $I^2$=39.2) did not show a statistically significant difference between intervention and control groups. Overall, the findings did not indicate a strong potential for publication bias.

Figure C-1. Delirium incidence with multi-component interventions versus usual care stratified by population or setting.




*Abbreviations*. CAM=Confusion Assessment Method; CAM-ICU=Confusion Assessment Method for the Intensive Care Unit; CI=confidence interval; D/C=discharge; DOS=Delirium Observation Screening; DSM-IV=Diagnostic Statistical Manual, 4th Edition; ICU=intensive care unit; LCF=long-term care facility; NEECHAM=Neelon-Champagne confusion scale; OBS=Organic Brain Syndrome Scale; POD=post-operative day; postop=post-operative.
*Source*. Abbasinia et al. 2021; Avendano-Cespedes et al. 2016; Boockvar et al. 2020; Boustani et al. 2012; Caplan et al. 2006; Chen et al. 2011, 2017; Dong et al. 2020; Guo et al. 2016; Hamzehpour et al. 2018; Hempenius et al. 2013; Lundström et al. 2005, 2007; Rice et al. 2017; Rood et al. 2021; Siddiqi et al. 2016; Verloo et al. 2015; Y.Y. Wang et al. 2020; Watne et al. 2014; Young et al. 2020.

One trial additionally reported that the point-prevalence of delirium at discharge was 15% in the tailored, family-involved HELP intervention group compared with 26% in the usual care group (*P*=0.01) (Watne et al. 2014). Two other trials examined a geriatric specialist ward intervention that involved individualized care with re-organization tasks and increasing self-care tasks (Lundström et al. 2005, 2007). In these trials, none of the patients with dementia (N=18 and 63) had delirium on day 7 or at discharge, whereas usual care groups included four of 18 and 15 of 63 patients with delirium, respectively (Lundström et al. 2005, 2007).

In addition to the Pacific Northwest EPC systematic review, a Cochrane review (Burton et al. 2021) demonstrated generally the same outcomes as described in this section. In the Cochrane review, the authors found moderate-certainty evidence regarding the benefit of multi-component non-pharmacological interventions for the prevention of delirium in hospitalized, non-ICU adults (14 studies; N=3,693). Specifically, interventions were estimated to reduce delirium incidence by 43% compared to usual care (10.5% incidence with treatment vs. 18.4% in the control group, RR 0.57, 95% CI 0.46–0.71, $I^2$=39%).

*Effect of multi-component interventions on delirium severity*

Nine trials reported the severity of delirium in those who developed it (Abbasinia et al. 2021; Avendano-Cespedes et al. 2016; Boockvar et al. 2020; Dong et al. 2020; Hamzehpour et al. 2018; Hempenius et al. 2013; Hosie et al. 2020; Watne et al. 2014; Young et al. 2020), with four trials reporting delirium severity at a specific time point (7–30 days), three trials the median value of delirium severity until discharge, and one trial reporting the highest severity of delirium during the acute illness. Three trials used the Delirium Rating Scale-Revised-98 (DRS-R-98) to measure delirium severity, three used the CAM-Severity scale (CAM-S), two used the Memorial Delirium Assessment Scale (MDAS), and one trial used the NEECHAM. In a pooled analysis there was no difference in severity of delirium between the intervention and usual care groups (8 trials, N=1,362; SMD 0.43, 95% CI -0.49–1.36, $I^2$=93%). However, when stratified by setting, the interaction term was significant (*P*=0.029). One trial conducted in nursing homes examined individuals who were suspected of having an onset of an acute illness or change in condition within the prior 24 to 48 hours and found no significant differences in delirium severity between the control group and those receiving an adapted version of HELP in Long-Term Care (HELP-LTC) on the CAM-S (Boockvar et al. 2020). In contrast, one of the trials conducted in non-surgical hospital settings reported that significantly more patients in the usual care group had severe delirium, reflected by a score of 18 or higher on the MDAS, as compared with a group that received tailored, family-involved HELP (9.6% vs. 1.5%, *P*=0.008 [Y.Y. Wang et al. 2020]). Another trial (N=60) also reported a lower severity of delirium in those receiving the HELP intervention compared with usual care, but the difference did not reach statistical significance and study ratings used the Richmond Agitation and Sedation Scale (RASS), which has problematic measurement properties and does not specifically assess delirium (Abbasinia et al. 2021). In a group of patients treated with the Roy adaptation model, which addresses physiological and behavioral effects of delirium, an ICU study found a significantly lower severity of delirium on the NEECHAM scale compared with patients who received usual care (mean 23.27 vs. 19, MD -0.59, 95% CI -1.17 to -0.01 [Hamzehpour et al. 2018]).

In the Cochrane review, evidence was very uncertain as to the effect on delirium severity (N=147; SMD -0.49, 95% CI -1.13–0.14, $I^2$=64% [Burton et al. 2021]).

*Effect of multi-component interventions on delirium duration*

Six trials (in 7 publications) reported the duration of delirium in those who developed it (Avendano-Cespedes et al. 2016; Guo et al. 2016; Lundström et al. 2007; Rood et al. 2021; Stenvall et al. 2012; Watne et al. 2014; Young et al. 2020). In a pooled analysis, the interventions resulted in a significantly shorter duration of delirium compared with usual care (6 trials, N=1,483; MD –0.70, 95% CI -1.53–0.13, $I^2$=87.1%). An additional trial that reported on individuals with co-occurring dementia also found a shorter duration of delirium in the intervention group as compared to usual care (Lundström et al. 2007).

In the Cochrane review, there was low-certainty evidence that multi-component non-pharmacological interventions resulted in a small reduction (i.e., approximately 1 day) in the duration of a delirium episode (N=351; MD -0.93, 95% CI -2.01–0.14 days, $I^2$=65% [Burton et al. 2021]).

*Effect of multi-component interventions on ICU and hospital length of stay*

Four trials reported the length of stay in the ICU (Abbasinia et al. 2021; Chen et al. 2017; Moon and Lee 2015; Rood et al. 2021). In a pooled analysis, the length of ICU stay was not significantly different between groups (4 trials, N=2,309; MD -0.18, 95% CI -0.61–0.24, $I^2$=16.3%); however, one of the studies reported higher rates of ICU re-admission during the same hospitalization in the usual care group compared with the intervention group (16% vs. 5%, *P*=0.05 [Moon and Lee 2015]).

Nine trials (in 11 publications [Boustani et al. 2012; Caplan et al. 2006; Chen et al. 2011; Dong et al. 2020; Khan et al. 2013; Lundström et al. 2005, 2007; Stenvall et al. 2012; Y.Y. Wang et al. 2020; Watne et al. 2014; Young et al. 2020]) reported data on the length of hospital stay. In a pooled analysis, length of hospital stay was significantly shorter in the intervention groups compared with usual care, with a small statistically significant difference (11 trials, N=4,489; MD -1.88 days, 95% CI -3.88–0.12, $I^2$=95%). Results were statistically significant for trials in general inpatients (6 trials, N=1,923; MD -2.88 days, 95% CI -5.37 to -0.39, $I^2$=92.8%), but was not significant for the trials conducted in post-operative patients (4 trials, N=817; MD -1.39 days, 95% CI -5.89–3.11, $I^2$=97.2%).

In the Cochrane review, low-certainty evidence also suggested a small reduction in hospital length of stay compared to usual care (N=3,351; MD -1.30 days, 95% CI -2.56 to -0.04 days, $I^2$=91% [Burton et al. 2021]).

*Effect of multi-component interventions on mortality and adverse events*

Twelve trials (in 15 publications) reported mortality (Boustani et al. 2012; Caplan et al. 2006; Hempenius et al. 2013, 2016; Khan et al. 2013; Moon and Lee 2015; Lundström et al. 2007; Rood et al. 2021; Siddiqi et al. 2016; Stenvall et al. 2012; Verloo et al. 2015; Y.Y. Wang et al. 2020; Watne et al. 2014; Young et al. 2020). In terms of deaths from any cause, a pooled analysis of 11 trials did not find a significant difference between groups (N=4,439; 27.0% vs. 26.5%, RR 1.00, 95% CI 0.85–1.18, $I^2$=34.0%). An additional trial was not able to be incorporated into the pooled analysis but reported no deaths in either group (Y.Y. Wang et al. 2020). One trial conducted in a long-term nursing home facility that also

provided short-term post-operative rehabilitation reported the hazard ratio (HR) for mortality separately for home residents (long-term care) and new admits (short-term care). For interventions compared with usual care the HR for mortality of in-home residents was 0.89 (95% CI 0.73–1.08) and for new admits was 0.88 (95% CI 0.66–1.16 [Lapane et al. 2011]).

Eight trials reported adverse events (Boustani et al. 2012; Hempenius et al. 2013; Hosie et al. 2020; Lapane et al. 2011; Lundström et al. 2007; Rood et al. 2021; Y.Y. Wang et al. 2020; Watne et al. 2014), with six reporting no differences between groups in complications (Boustani et al. 2012; Hempenius et al. 2013), hospitalizations due to adverse events (Lapane et al. 2011), and total number of adverse events (Hosie et al. 2020; Rood et al., 2021; Y.Y. Wang et al. 2020). In contrast, two trials reported significant differences between the intervention and usual care groups in specific adverse events. In a study of early mobilization, scheduled liquid intake to avoid dehydration, scheduled nutritional assistance, avoidance and/or reduction of certain medications, and oxygen monitoring to prevent hypoxia, urinary tract infections (UTI) occurred less frequently in the intervention group (16% vs. 25%, *P*=0.05), whereas falls occurred slightly more frequently in the intervention group (9% vs. 7%, *P*=0.05) (Watne et al. 2014). Another study reported significantly lower frequencies of decubitus ulcers (8.8% vs. 22.1%, *P*=0.010), UTIs (31.4% vs. 51.0%, *P*=0.005), sleeping problems (27.5% vs. 45.4%, *P*=0.009), and falls (11.8% vs. 26.8%, *P*=0.006) in the intervention group receiving care in a specialized geriatric ward that included early mobilization compared with the usual care group (Lundström et al. 2007). An additional study that was not included in the systematic review also found more adverse events with early mobilization in the ICU setting (Patel et al. 2023).

In the Cochrane review, the authors found little or no effect of interventions on inpatient mortality (10 studies, N=2,640) compared to usual care (5.2% in the intervention group vs. 4.5% in the control group, RR 1.17, 95% CI 0.79–1.74, $I^2$=15%) (Burton et al. 2021).

*Effect of multi-component interventions on other outcomes*

Six trials (N=1,259) reported on admission or readmission to the hospital (Boockvar et al. 2020; Boustani et al. 2012; Caplan et al. 2006; Hempenius et al. 2016; Rood et al. 2021; Siddiqi et al. 2016). Three trials reported no differences between the intervention and usual care groups in readmission rates within 30 days (18.6% vs. 16.4%, *P*=0.53 [Boustani et al. 2012]) or 90 days (23% vs. 18%, OR 1.32, 95% CI 0.69–2.53 [Hempenius et al. 2016]) of discharge or within 28 days from the end of rehabilitation (21% vs. 24%, *P*-value not reported [Caplan et al. 2006]). Another trial reported similar readmission rates (11% vs. 10%, *P*=0.69) between the intervention and control groups but did not specify the duration of follow-up observations (Rood et al. 2021). Two trials conducted in nursing home residents reported no differences in the time to hospital admission between the intervention and usual care groups (STOP Delirium intervention: HR 0.72, 95% CI 0.38–1.36 [Siddiqi et al. 2016] and HELP-LTC intervention: 14% vs. 17%, *P*=0.52 [Boockvar et al. 2020]). In the Cochrane review, multi-component non-pharmacological interventions were associated with little to no difference in new admissions to long-term care at the time of hospital discharge (N=536; RR 0.77, 95% CI 0.55–1.07 [Burton et al. 2021]).

Three trials found no significant difference between groups in quality of life or functional measures. One found no differences between groups in quality of life as measured by the Short Form survey 36 Item

(SF-36) Physical Functioning or Mental Health subscales (OR 1.02, 95% CI 0.56–1.86 and OR 0.80, 95% CI 0.50–1.40) or the SF-36 General Health scale (OR 0.84, 95% CI 0.50–1.40) (Hempenius et al. 2013). Another found no differences between groups on the EuroQol-5 Dimension (mean 0.42, standard deviation [SD] 0.39 with the intervention vs. mean 0.38, SD 0.42 in the control group [Siddiqi et al. 2016]). One trial reported that there was not a significant difference between the intervention and usual care groups in risk for decline in daily function (OR 1.19, 95% CI 0.70–2.02), increased need for care assistance (OR 0.93, 95% CI 0.52–1.65), or return to independent pre-operative living situation (OR 2.02, 95% CI 0.84–4.87) (Hempenius et al. 2013, 2016).

Three trials measured depressive symptoms using the Geriatric Depression Scale, with conflicting findings. In a study conducted in China, the scale was rescaled so that higher scores reflect fewer depressive symptoms (Chen et al. 2011). This study found that the control group's score worsened significantly more than the intervention group's score (mean change -4.4 vs. -0.3, $P<0.001$ [Chen et al. 2011]). The other trials, conducted in the United Kingdom and Australia, reported that the difference between groups was not significant at 1 month (mean 8.84 vs. 8.17, $P=0.63$ [Caplan et al. 2006] and mean 4.7 vs. 4.2, *P*-value not reported [Young et al. 2020]) or 6 months (mean 7.80 vs. 7.14, $P=0.62$ [Caplan et al. 2006]). The trial conducted in the United Kingdom also reported no differences in anxiety as measured by the clinical anxiety scale at 1 month (mean 16.8 vs. 16.9 [Young et al. 2020]).

Five trials (N=888) reported on cognitive decline in patients after receiving the intervention (Chen et al. 2011; Dong et al. 2020; Hempenius et al. 2016; Verloo et al. 2015; Y.Y. Wang et al. 2020). Four trials reported significantly more decline in the usual care group than the intervention group when measured with the Mini-Mental State Evaluation (MMSE; mean at follow-up 23.81 vs. 25.06, $P=0.15$ [Verloo et al. 2015] and mean change from baseline -1.4 vs. -0.4, $P=0.05$ [Chen et al. 2011]) or the Short Portable Mental Status Questionnaire (7.0% vs. 0.8%, $P=0.009$ [Y.Y. Wang et al. 2020]) and 4% vs. 24.5%, $P=0.012$ [Dong et al. 2020]), whereas the other trial reported no differences between groups (14.1% vs. 23.1%, OR 1.83, 95% CI 0.74–4.56 [Hempenius et al. 2016]).

Several trials reported on the use of or avoidance of other specific interventions. Although findings were not statistically significant, one trial reported less use of restraint in the intervention group compared with usual care (9% vs. 17%), and another trial reported more orders to discontinue the use of restraints in the intervention groups compared with usual care (5% vs. 0%) (Boustani et al. 2012). One trial reported similar re-intubation rates (7% vs. 7%, $P=0.99$) between the intervention and control groups (Rood et al. 2021) as well as similar rates of physical restraint use (37% vs. 40%, $P=0.43$). Five trials reported on the use of other medications but in heterogeneous ways. Only one study reported statistically significant findings: 15% vs. 42% received sedatives ($P=0.008$) and 31% vs. 62% received opioids ($P=0.004$) in the intervention and control groups, respectively (Lundström et al. 2007). Two others found a reduced use of other medications in the intervention group as compared to usual care but the decrease was not statistically significant; the mean number of medications prescribed per participant during study was 8.7 vs. 9.1 in one trial (Siddiqi et al. 2016) with 33% vs. 48% of patients receiving "neuroleptics" in the other trial (Avendano-Cespedes et al. 2016). Additionally, one study reported more orders to discontinue use of anticholinergics in the intervention group (49% vs. 31%

[Boustani et al. 2012]). Finally, one study reported that the use of benzodiazepines was similar in the intervention group compared with usual care (43% vs. 41% [Avendano-Cespedes et al. 2016]).

### *Effects of the ABCDEF Bundle*

The ABCDEF bundle represents an evidence-based method of coordinated, holistic, multidisciplinary care designed to optimize patient outcomes in delirium (Marra et al. 2017; Mart et al. 2019). The bundle interventions are largely non-pharmacologic in nature but do include some overlap with principles of good pharmacology practice (e.g., avoiding benzodiazepines, deprescribing whenever possible). Studies of ABCDEF bundles did not meet criteria for inclusion in the systematic review but nonetheless offer important information about the effectiveness of non-pharmacological approaches to managing delirium. The specific elements of the ABCDEF bundle are described in Table 6, under Statement 7, Implementation.

In the largest ABCDEF study to date, with over 15,000 participants from 68 academic, community, and Veterans Administration ICUs in 29 states and Puerto Rico, Pun and colleagues (2019) found widespread symptom improvement with patients who completed every element of the bundle. Notably, patients with complete bundle performance had a higher likelihood of ICU discharge (adjusted HR 1.7, CI 1.05–1.30), higher likelihood of hospital discharge (adjusted HR 1.19, CI 1.01–1.40), lower risk of death at any time (adjusted HR 0.32, CI 0.17–0.62), and lower risks of next-day mechanical ventilation use (adjusted OR 0.28, 95% CI 0.22–0.36), coma (adjusted OR 0.35, 95% CI 0.22–0.56), delirium (adjusted OR 0.60, CI 0.49–0.72), and need for physical restraints (adjusted OR 0.37, CI 0.30–0.46). A dose-response relationship was observed with tight confidence intervals, suggesting that outcomes were better if more elements of the bundle were completed.

A prospective quality improvement study among 7 California hospitals (Barnes-Daly et al. 2017) also found a dose-response relationship between complete or partial ABCDEF bundle adherence and increased odds of hospital survival (OR 1.07, 95% CI 1.04–1.11 and OR 1.15, 95% CI, 1.09–1.2, respectively). Complete and partial bundle adherence were also associated with more days alive and free of delirium and coma (incident rate ratio 1.02, 95% CI 1.01–1.04 and incident rate ratio 1.15, 95% CI, 1.09–1.22, respectively).

### *Effects of the Hospital Elder Life Program*

HELP is an evidence-based model of preventing delirium and functional decline that targets hospitalized older adults (see Table 6, Statement 7, Implementation) (Hshieh et al. 2018). As with ABCDEF bundle studies, HELP studies include important and useful information about the effectiveness of non-pharmacological interventions for delirium but did not meet inclusion criteria for the formal systematic review. A meta-analysis of 14 studies found HELP effectively reduced delirium incidence and rate of falls, with a trend toward reducing length of stay and preventing institutionalization (Hshieh et al. 2018). Overall, in comparative studies of HELP, there were significant reductions in delirium incidence (14 studies: OR 0.47, 95% CI 0.37–0.59), and the rate of falls decreased by 42% among intervention patients (3 studies: OR 0.58, 95% CI 0.35–0.95) (Hshieh et al. 2018).

### Grading of the Overall Supporting Body of Research Evidence for Multi-component Interventions in Prevention of Delirium

- Magnitude of effect: Low. The magnitude of the effect of multi-component interventions is small in reducing the incidence and the duration of delirium. There was little or no effect on the severity of delirium or mortality associated with delirium.

- Risk of bias: Moderate. Although three studies had a high risk of bias, the remaining studies had a moderate risk of bias. Key factors that contributed bias were unclear procedures for random assignment and concealment as well as inadequate masking of patients and care providers. Some studies also did not provide information on how missing data was accounted for in their statistical analysis.

- Applicability: The findings of these studies are applicable to older patients, those in critical care and medical inpatient settings as well as post-operative patients (specifically following orthopedic or cardiac procedures). Applicability to younger individuals and those in other clinical settings is likely to be reduced. Demographic information on study participants was often not reported and non-white individuals were often under-represented when demographic information was available.

- Directness: Direct. Outcomes were directly related to delirium or its associated adverse effects, including mortality.

- Consistency: Varies with outcome. For delirium incidence and duration and for mortality associated with delirium, study findings were consistent whereas, for other outcomes, findings were inconsistent.

- Precision: Varies with outcome. For delirium incidence and severity, the findings were precise whereas for other outcomes, findings were imprecise.

- Dose-response relationship: Present. For multi-component interventions, there was evidence that greater adherence to specific interventions and adherence with a greater number of interventions was associated with improved outcomes in studies of the ABCDEF bundle.

- Confounding factors (including likely direction of effect): The data may be confounded by variations in delirium assessment due to rater training. Individuals with hypoactive delirium may have been less likely to be identified than those with hyperactive delirium. However, the direction of effect from these potential confounding factors is not clear.

- Publication bias: Not identified. There was no evidence of publication bias for studies related to the incidence of delirium. For other outcomes, there was insufficient information to make a determination.

- Overall strength of research evidence: Low to Moderate. The strength of research evidence for multi-component interventions is moderate for incidence and severity of delirium and low for duration of delirium. For other outcomes, there was insufficient information to make a determination.

### Single-Component Interventions

Because multi-component non-pharmacologic interventions are comprised of multiple independent interventions, the Pacific Northwest EPC systematic review considered the effectiveness outcomes from single-component studies as well as assessing effects of each component within the multi-component trials.

#### *Overview of study characteristics*

Thirty-six trials (Alvarez et al. 2017; Arttawejkul et al. 2020; Browning et al. 2020; Brummel et al. 2014; Chevillon et al. 2015; Dai et al. 2021; Eghbali-Babadi et al. 2017; Fahimi et al. 2020; Fazlollah et al. 2021; Giraud et al. 2016; Humeidan et al. 2021; Jeffs et al. 2013; Johnson et al. 2018; Karadas and Ozdemir 2016; Khan et al. 2020; Leong et al. 2021; Martinez et al. 2012; Martinez-Velilla et al. 2019; Mitchell et al. 2017; Morris et al. 2016; Munro et al. 2017; Nydahl et al. 2020, 2022; O'Gara et al. 2020; Obanor et al. 2021; Ono et al. 2011; Potharajaroen et al. 2018; Rosa et al. 2019; Schweickert et al. 2009; Shirvani et al. 2020; Simons et al. 2016; Taguchi et al. 2007; Van Rompaey et al. 2012; Vlisides et al. 2019; Xue et al. 2020; K.S. Zhang et al. 2021) compared a single behavioral intervention with usual care for the prevention of delirium. Sample sizes ranged from 6 to 1,685 (total N=6,811). Thirteen trials were conducted in the United States; four in Iran; two each in Australia, Chile, China, Germany, Japan, and Thailand; and one each in Belgium, Brazil, The Netherlands, Singapore, Spain, Turkey, and the United Kingdom. In terms of risk of bias, only one trial had a low risk of bias, whereas 26 trials had a moderate risk of bias and nine trials had a high risk of bias.

The single behavioral interventions assessed were family member interventions (increased visitations, 5 trials [Eghbali-Babadi et al. 2017; Martinez et al. 2012; Mitchell et al. 2017; Munro et al. 2017; Rosa et al. 2019]), exercise interventions (range of motion/mobilization, twice daily exercise program, 8 trials [Jeffs et al. 2013; Karadas and Ozdemir 2016; Martinez-Velilla et al. 2019; Morris et al. 2016; Nydahl et al. 2020, 2022; Schweickert et al. 2009; Shirvani et al. 2020]), bright light therapy (5 trials [Ono et al. 2011; Potharajaroen et al. 2018; Simons et al. 2016; Taguchi et al. 2007; K.S. Zhang et al. 2021]), listening to music (3 trials [Browning et al. 2020; Johnson et al. 2018; Khan et al. 2020]), massage (1 trial [Fazlollah et al. 2021]), occupational therapy (OT; 1 trial [Alvarez et al. 2017]), sleeping with earplugs (2 trials [Arttawejkul et al. 2020; Van Rompaey et al. 2012]), use of earplugs plus an eye mask (2 trials [Leong et al. 2021; Obanor et al. 2021]), use of mirrors for orientation (1 trial [Giraud et al. 2016]), individualized pre-operative educational (3 trials [Chevillon et al. 2015; Fahimi et al. 2020; Xue et al. 2020]), cognitive exercises or tests (4 trials [Dai et al. 2021; Humeidan et al. 2021; O'Gara et al. 2020; Vlisides et al. 2019]), early and intensive occupational therapy (1 trial [Alvarez et al. 2017]), and cognitive therapy plus physical therapy (PT; 1 trial [Brummel et al. 2014]). The control group was usual care in all trials.

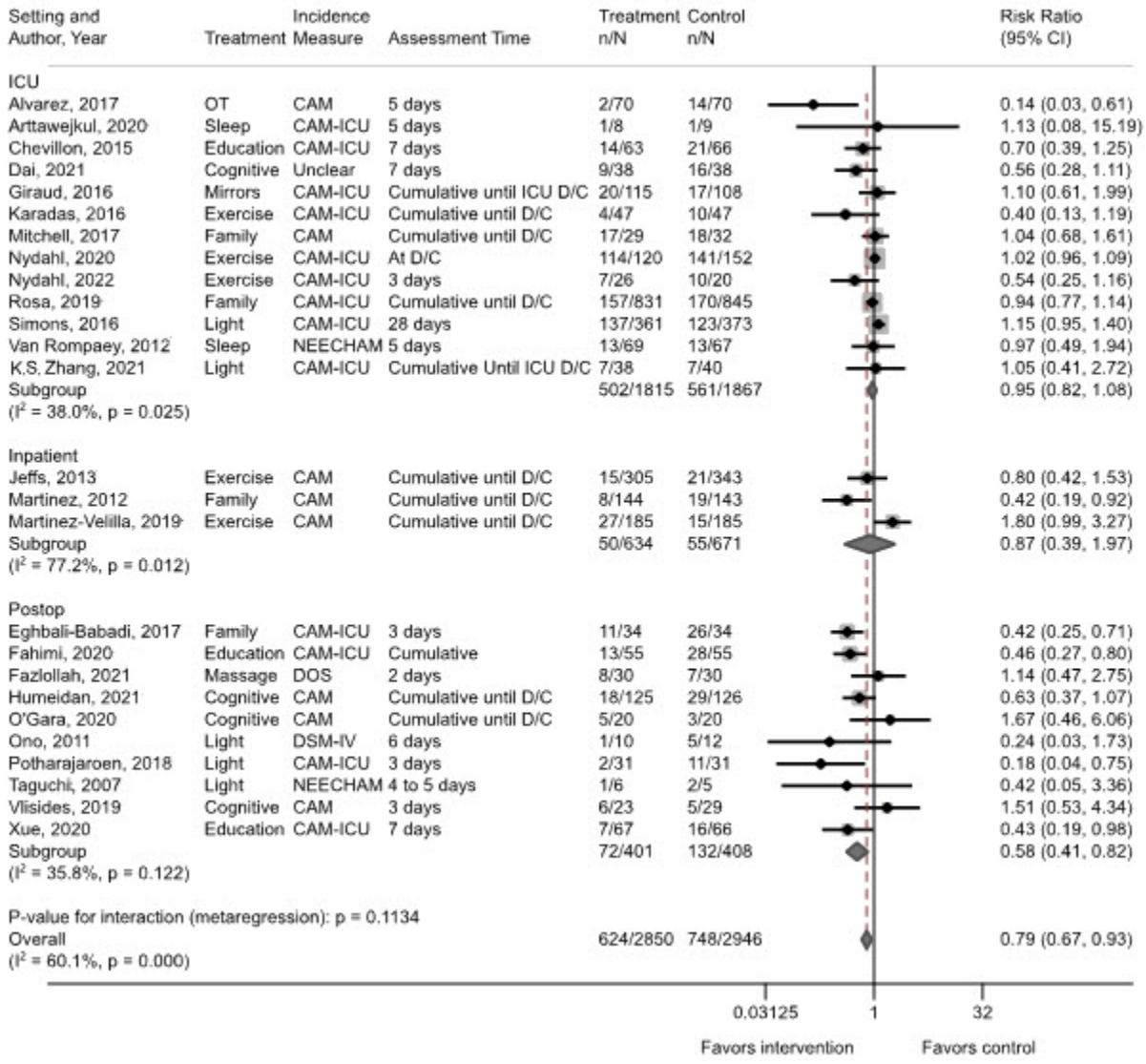
Most of the studies included individuals of all adult ages, but nine studies limited the sample to older adults. In the 28 trials that reported the mean age of the sample, 12 had a mean age 65 or older. There was a predominance of men in eight trials, a predominance of women in six trials, and between 40% and 60% women in the remaining 22 trials. Of trials that reported race/ethnicity, five included mostly White participants (range 67% to 85%), two trials reported that about half the participants were Black (range 56% and 59%), and two trials reported a predominance of Asian patients (range 84% to 100%). The remaining 27 trials did not provide information on race or ethnicity. Seven trials excluded patients with

dementia, two trials reported that 1% and 6% of patients had dementia at baseline, and the remaining 27 trials did not report on dementia status. Eighteen trials reported patients' baseline functioning as measured by the APACHE II, Charlson Comorbidity Index, Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), or the Barthel Index, whereas the other 18 trials did not report information on functioning status. Three different measures of delirium were used to diagnose delirium in the trials—two versions of the CAM (CAM and CAM-ICU), DSM-IV criteria, the NEECHAM, and the confusion scale of the NEECHAM. For most studies, the goal was prevention of delirium and fourteen trials excluded patients with delirium at baseline. However, two trials reported that 13% to 14% of patients had delirium at the onset of the study and 20 trials did not report information on whether delirium was present.

### *Effect of single-component interventions on delirium incidence*

Twenty-eight trials reported the incidence of delirium (Alvarez et al. 2017; Arttawejkul et al. 2020; Chevillon et al. 2015; Dai et al. 2021; Eghbali-Babadi et al. 2017; Fahimi et al. 2020; Fazlollah et al. 2021; Giraud et al. 2016; Humeidan et al. 2021; Jeffs et al. 2013; Johnson et al. 2018; Karadas and Ozdemir 2016; Martinez et al. 2012; Martinez-Velilla et al. 2019; Mitchell et al. 2017; Nydahl et al. 2020, 2022; Obanor et al. 2021; O'Gara et al. 2020; Ono et al. 2011; Potharajaroen et al. 2018; Rosa et al. 2019; Simons et al. 2016; Taguchi et al. 2007; Van Rompaey et al. 2012; Vlisides et al. 2019; Xue et al. 2020; K.S. Zhang et al. 2021). More than half of the trials measured the incidence of delirium cross-sectionally at a specific time after the intervention was started (3–28 days), whereas the rest measured the cumulative incidence of delirium until discharge from the hospital. One trial reported risk incidence ratios and reported a much lower risk in the intervention group compared with usual care (0.15 vs. 6.66 [Alvarez et al. 2017]). A pooled analysis of single-component interventions showed a significantly lower incidence of delirium than usual care (26 trials, N=5,796; 21.9% vs. 25.4%, RR 0.79, 95% CI 0.67–0.93, $I^2$=60.1%). A subgroup analysis showed single-component interventions were associated with a significant reduction of delirium incidence in post-operative patients (10 trials, N=809; RR 0.58, 95% CI 0.41–0.82, $I^2$=35.8%) and with education (3 trials, N=372; RR 0.53, 95% CI 0.37–0.76, $I^2$=0%) and OT (1 trial, N=140; RR 0.14, 95% CI 0.03–0.61) as compared to usual care. However, other subgroup analyses showed no significant differences either by setting (*P*=0.11 for interaction; Figure C-2) or by intervention (*P*=0.48 for interaction; Figure C-3). Analysis for potential publication bias suggested a strong possibility of unpublished small studies.

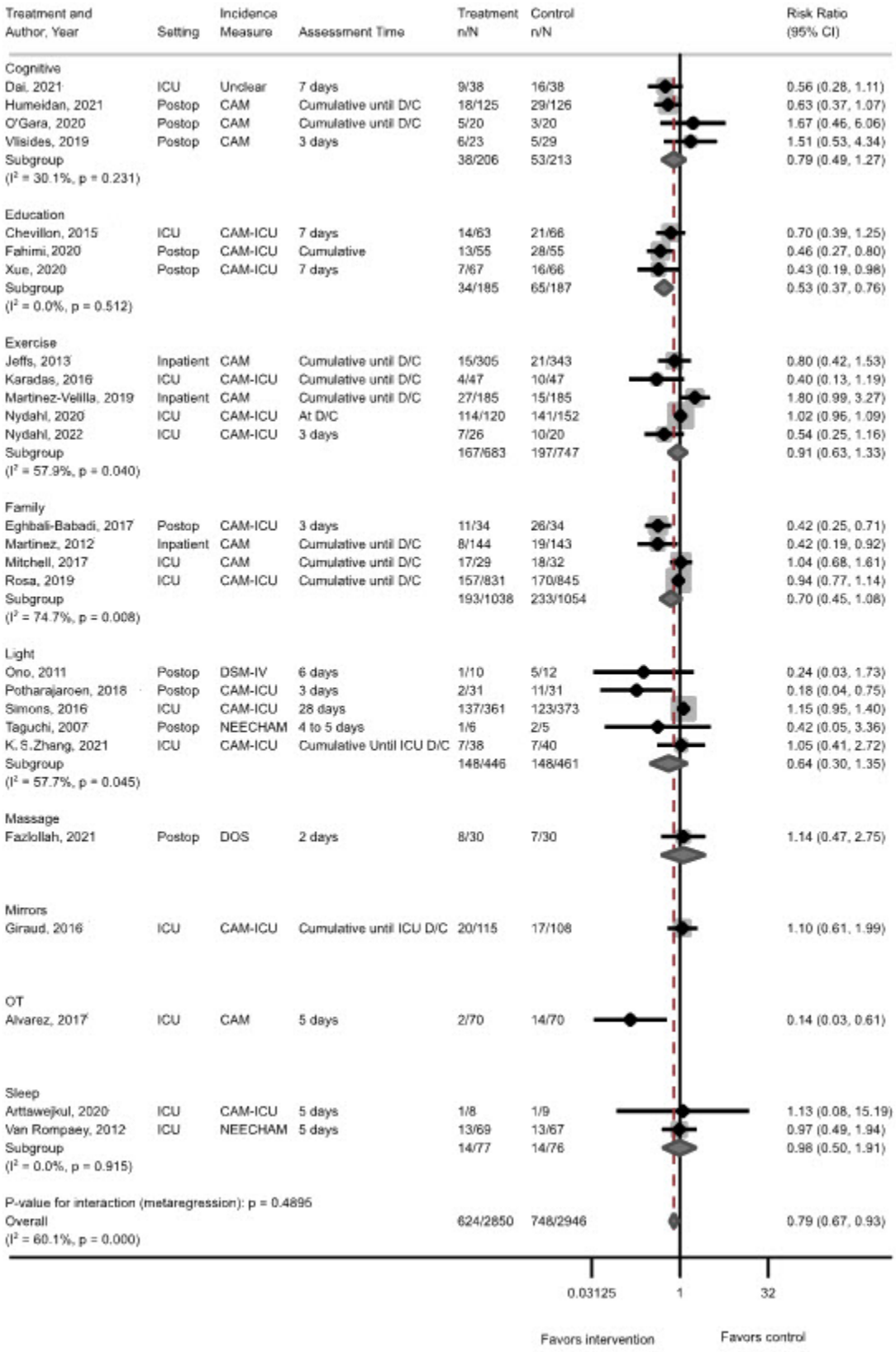
Figure C-2. Delirium incidence with single-component interventions versus usual care stratified by population or setting.




*Abbreviations*. CAM=Confusion Assessment Method; CAM-ICU=Confusion Assessment Method for the Intensive Care Unit; CI=confidence interval; D/C=discharge; DOS=Delirium Observation Screening; DSM-IV=*Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition; ICU=intensive care unit; NEECHAM=Neelon-Champagne confusion scale; OT=occupational therapy; postop=post-operative.

*Source*. Alvarez et al. 2017; Arttawejkul et al. 2020; Chevillon et al. 2015; Dai et al. 2021; Eghbali-Babadi et al. 2017; Fahimi et al. 2020; Fazlollah et al. 2021; Giraud et al. 2016; Humeidan et al. 2021; Jeffs et al. 2013; Karadas and Ozdemir 2016; Martinez et al. 2012; Martinez-Velilla et al. 2019; Mitchell et al. 2017; Nydahl et al. 2020, 2022; O'Gara et al. 2020; Ono et al. 2011; Potharajaroen et al. 2018; Rosa et al. 2019; Simons et al. 2016; Taguchi et al. 2007; Van Rompaey et al. 2012; Vlisides et al. 2019; Xue et al. 2020; K.S. Zhang et al. 2021.

Figure C-3. Delirium incidence with single-component interventions stratified by intervention.



*Abbreviations*. CAM=Confusion Assessment Method; CAM-ICU=Confusion Assessment Method for the Intensive Care Unit; CI=confidence interval; D/C=discharge; DOS=Delirium Observation Screening; DSM-IV=*Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition; ICU=intensive care unit; NEECHAM=Neelon-Champagne confusion scale; OT=occupational therapy; postop=post-operative.
*Source*. Alvarez et al. 2017; Arttawejkul et al. 2020; Chevillon et al. 2015; Dai et al. 2021; Eghbali-Babadi et al. 2017; Fahimi et al. 2020; Fazlollah et al. 2021; Giraud et al. 2016; Humeidan et al. 2021; Jeffs et al. 2013; Karadas and Ozdemir 2016; Martinez et al. 2012; Martinez-Velilla et al. 2019; Mitchell et al. 2017; Nydahl et al. 2020, 2022; O'Gara et al. 2020; Ono et al. 2011; Potharajaroen et al. 2018; Rosa et al. 2019; Simons et al. 2016; Taguchi et al. 2007; Van Rompaey et al. 2012; Vlisides et al. 2019; Xue et al. 2020; K.S. Zhang et al. 2021.

### *Effect of single-component interventions on delirium severity*

Five trials reported the severity of delirium in those who developed it (N=81 [Alvarez et al. 2017; Jeffs et al. 2013; Khan et al. 2020; Taguchi et al. 2007; Van Rompaey et al. 2012]). Interventions in the trials were varied (i.e., OT, exercise, music, light therapy, ear plugs), and some trials had only one event per group; thus, study findings could not be pooled for meta-analysis. One small trial (N=15) used the NEECHAM Confusion Scale to measure the severity of delirium and reported significantly lower delirium severity in the group that received light therapy compared with usual care, although only three patients developed delirium (Taguchi et al. 2007). Another trial also used the NEECHAM Confusion Scale and found lower delirium severity in the group that was given earplugs to sleep as compared to controls (Van Rompaey et al. 2012). The remaining three trials used either the CAM, CAM-ICU, or the DRS to measure the severity of delirium and found no significant differences between the control group and either intensive OT (Alvarez et al. 2017), exercise (Jeffs et al. 2013), or music listening (Khan et al. 2020). One trial of early mobilization reported significant decreases in mild and moderate to severe delirium from post-operative day 1 to post-operative day 2 in the intervention group compared with usual care (87% to 11% vs. 98% to 87% [Shirvani et al. 2020]).

### *Effect of single-component interventions on delirium duration*

Fourteen trials reported the duration of delirium in those that developed it (N=3,183 [Alvarez et al. 2017; Chevillon et al. 2015; Giraud et al. 2016; Humeidan et al. 2021; Jeffs et al. 2013; Karadas and Ozdemir 2016; Martinez et al. 2012; Mitchell et al. 2017; Morris et al. 2016; Munro et al. 2017; Nydahl et al. 2022; Schweickert et al. 2009; Simons et al. 2016; K.S. Zhang et al. 2021]). In a pooled analysis of the nine trials that were able to be combined, the difference between groups was small and not significant (9 trials, N=487; MD -0.18 days, 95% CI -0.62–0.26, $I^2$=8.0% [Chevillon et al. 2015; Giraud et al. 2016; Humeidan et al. 2021; Jeffs et al. 2013; Karadas and Ozdemir 2016; Martinez et al. 2012; Nydahl et al. 2022; Simons et al. 2016; K.S. Zhang et al. 2021]). There were no differences when analyses were stratified by setting or intervention.

A number of trials reported results in a way that could not be combined with the other studies in a meta-analysis. Two trials reported that the intervention group had significantly fewer days in the ICU with delirium compared with usual care (median 2 days vs. 4 days, *P*=0.03 [Schweickert et al. 2009]) and fewer days overall in the hospital with delirium (median 2 days vs. 4 days, *P*=0.02 [Schweickert et al. 2009]; mean 0.3 days vs. 0.9 days, *P*=0.04 [Munro et al. 2017]). A third trial reported no differences between days in the ICU with delirium (median 0 day vs. 0 day [Morris et al. 2016]). Another trial reported similar median days with delirium (1 day vs. 1 day) but did not report a variance measure

(Mitchell et al. 2017). One trial also reported significantly larger proportions of time with delirium for the usual care group compared with the intervention group in the ICU (57% vs. 33%, *P*=0.02) or during hospitalization (41% vs. 28%, *P*=0.01 [Schweickert et al. 2009]). In terms of the number of hospital days that were free of delirium, three trials reported similar numbers between the intervention and usual care groups (a median of 2 days vs. 2 days with 7 days of observation [Khan et al. 2020], a median of 26 days vs. 27 days with 28 days of observation [Simons et al. 2016], and a median of 27 days vs. 28 days with observation to the time of discharge [Brummel et al. 2014]).

*Effect of single-component interventions on ICU and hospital length of stay*

Seventeen trials reported the length of stay in the ICU (Alvarez et al. 2017; Arttawejkul et al. 2020; Brummel et al. 2014; Chevillon et al. 2015; Giraud et al. 2016; Karadas and Ozdemir 2016; Mitchell et al. 2017; Morris et al. 2016; Munro et al. 2017; Obanor et al. 2021; O'Gara et al. 2020; Ono et al. 2011; Rosa et al. 2019; Schweickert et al. 2009; Shirvani et al. 2020; Simons et al. 2016; Vlisides et al. 2019; Xue et al. 2020; K.S. Zhang et al. 2021). Four trials were conducted in post-operative patients (3 after cardiac surgery and 1 after thoracotomy), whereas the other trials had a mix of general inpatients and surgical patients. In the trials that could be pooled, the intervention group had a shorter length of stay that was small in magnitude but statistically significant (14 trials, N=3,766; MD -0.09 days, 95% CI -0.32–0.15, $I^2$=59.6%). The findings did not differ when analyses were separated by setting or intervention.

Eighteen trials reported the length of stay in the hospital (Alvarez et al. 2017; Arttawejkul et al. 2020; Brummel et al. 2014; Chevillon et al. 2015; Humeidan et al. 2021; Jeffs et al. 2013; Martinez-Velilla et al. 2019; Martinez et al. 2012; Mitchell et al. 2017; Morris et al. 2016; O'Gara et al. 2020; Ono et al. 2011; Schweickert et al. 2009; Shirvani et al. 2020; Simons et al. 2016; Vlisides et al. 2019; Xue et al. 2020; K.S. Zhang et al. 2021). In the trials that could be pooled, the difference was not significant (13 trials, N=2,799; MD 0.15 days, 95% CI -0.05–0.34, $I^2$=0%). One trial did not report variance data and could not be included in the meta-analysis (Martinez-Velilla et al. 2019).

*Effect of single-component interventions on mortality and adverse events*

Several trials excluded patients who died during their hospital stay or during the study from their analyses. However, 12 trials (N=3,839) did report mortality (Alvarez et al. 2017; Brummel et al. 2014; Dai et al. 2021; Khan et al. 2020; Martinez-Velilla et al. 2019; Nydahl et al. 2020, 2022; Rosa et al. 2019; Schweickert et al. 2009; Simons et al. 2016; Xue et al. 2020; K.S. Zhang et al. 2021). In a pooled analysis of 12 trials, there were no significant differences in rates of mortality between intervention and control groups overall (N=3,730; 13% vs. 12.5%, RR 1.03, 95% CI 0.87–1.21, $I^2$=0%) or when the analysis was separated by setting or intervention.

Seven trials reported no adverse events or described any adverse events as unrelated to the intervention (Alvarez et al. 2017; Jeffs et al. 2013; Khan et al. 2020; Potharajaroen et al. 2018; Simons et al. 2016; Taguchi et al. 2007; K.S. Zhang et al. 2021). Similar proportions of falls were noted between groups in a study of family member education versus usual care (0% vs. 3% [Martinez et al. 2012]) and exercise sessions versus usual care (3% vs. 0% [Martinez-Velilla et al. 2019]). One trial of flexible family visitation reported no differences in ICU-acquired pneumonia, infection, UTI, and bloodstream infection (Rosa et al. 2019). Two other trials reported no differences in total complications with pre-operative

individualized education in cardiac surgery patients (Xue et al. 2020) or in total number of adverse events with standardized rehabilitation therapy in acute respiratory failure patients (Morris et al. 2016). However, one of these trials reported that a patient experienced an episode of asymptomatic bradycardia lasting less than 1 minute, which the authors noted might be related to the progressive resistance exercise intervention (Morris et al. 2016). Another trial reported that 16.6% of the early mobilization group experienced an "unwanted safety event" (Nydahl et al. 2022). The remaining trials did not report adverse events.

*Effect of single-component interventions on other outcomes*

Other outcomes were reported inconsistently across studies. One trial that assessed readmission rates found no significant differences between exercise sessions and usual care groups at 3 months (HR 2.4, 95% CI 1.7– 3.2 vs. 2.5, 95% CI 1.8–3.3, *P*=0.82 [Martinez-Velilla et al. 2019]). However, in comparison with usual care, the same trial reported that the exercise group showed significantly greater improvements in depression measured by the Geriatric Depression Scale (MD -2.0, 95% CI -2.5 to -1.6) and quality of life measured by the EuroQol-5 Dimension (MD 13.2, 95% CI 8.2–18.2 [Martinez-Velilla et al. 2019]). One trial (N=129) of individualized pre-operative education compared with usual care reported no differences in trait or state anxiety on the Impact of Events Scale but did not report the data (Chevillon et al. 2015). One trial reported more patients in an OT group compared with usual care were functioning at a normal level at discharge based on the Functional Independence Measure (81.5% vs. 47.7% [Alvarez et al. 2017]). Two trials of exercise compared with usual care found no differences between groups in the proportion who were able to return to their previous residence (75% vs. 79% [Jeffs et al. 2013], 92% vs. 91% [Martinez-Velilla et al. 2019]).

One trial of pre-operative cognitive training reported more post-operative cognitive decline in the intervention group compared with usual care (37% vs. 53%), although this difference was not statistically significant (O'Gara et al. 2020). Another trial reported statistically significantly higher MMSE scores at 1 week in a group receiving cognitive training compared with usual care (mean 25.94 vs. 21.94, *P*<0.001 [Dai et al. 2021]). An additional trial of cognitive training plus PT compared with usual care reported similar MMSE scores, in the no cognitive impairment range, at discharge from the ICU between groups (median 28.0 vs. 25, *P*=0.09 [Brummel et al. 2014]). With an exercise intervention, one trial reported significantly greater increases in MMSE scores from baseline to discharge for the intervention group compared with usual care (MD 1.8, 95% CI 1.3–2.3 [Martinez-Velilla et al. 2019]), but patients had a mean score of 22 on the MMSE at baseline, consistent with mild dementia.

Two trials reported significantly better sleep in the intervention groups compared with usual care (mean Richards-Campbell Sleep Questionnaire score [0 to 100, 100=better sleep] of 59.1 vs. 35.3, *P*=0.0003 for eye mask and ear plugs [Obanor et al. 2021] and mean Pittsburgh Sleep Quality Index score at 1 week of 6.89 vs. 9.54, *P*<0.001 for cognitive testing [Dai et al. 2021]), whereas one trial reported no difference between groups (had good quality of sleep on post-operative day 2: 70% vs. 83.3%, *P*=0.24 [Fazlollah et al. 2021]).

Several trials reported on the effects of interventions on use of antipsychotic, benzodiazepine, opioid, or other sedating medications. One trial of light therapy as compared to usual care reported a comparable

use of haloperidol in each group (35% vs. 31%, *P*=0.35), with a similar cumulative dose (median 11 mg, interquartile range [IQR] 4–22 mg vs. median 14 mg, IQR 5–28 mg, *P*=0.42 [Simons et al. 2016]); another reported no significant difference between groups in the number of days using sedatives (mean 3.9 days, SD 1.0 vs. mean 4.1 days, SD 1.3, *P*=0.57 [Ono et al. 2011]). A third trial of light therapy reported no difference in the administration of additional medications (i.e., fentanyl, dexmedetomidine, quetiapine, midazolam, and haloperidol) as compared to usual care (K.S. Zhang et al. 2021). Finally, a trial of cognitive training plus PT compared to usual care reported no differences in rates of benzodiazepine (49% vs. 55%, *P*=0.46), propofol (98% vs. 59%, *P*=0.47), dexmedetomidine (37% vs. 14%, *P*=0.83), and opioid (98% vs. 95%, *P*=0.95) usage (Brummel et al. 2014).

### *Effectiveness of single-component interventions based on multi-component trial data and network meta-analysis*

To identify individual components that may be responsible for, or at least contribute meaningfully to, the overall results of multi-component interventions, the Pacific Northwest EPC conducted subgroup analyses based on whether each study included an individual component. For example, they analyzed studies based on whether the study did or did not include a mobilization component. They compared the findings for each subgroup to determine whether differences were statistically significantly different. Table C-2 shows the results of these analyses. When trials were compared based on the individual components they included, no individual components affected the results to a statistically significant degree. In addition, analysis of the overall findings did not indicate a strong potential for publication bias.

Table C-2. Pooled analyses of individual components in multi-component trials to prevent delirium

| Component | RR in studies including (95% CI) | RR in studies without (95% CI) | P-value* |
|---|---|---|---|
| Sensory | 0.796 (0.599 to 1.057) | 0.674 (0.512 to 0.886) | P=0.637 |
| Orientation | 0.467 (0.284 to 0.768) | 0.870 (0.696 to 1.086) | P=0.076 |
| Mobilization | 0.686 (0.557 to 0.846) | 0.917 (0.590 to 1.425) | P=0.229 |
| Restraint avoidance | 0.637 (0.306 to 1.326) | 0.738 (0.597 to 0.911) | P=0.878 |
| Medication reduction | 0.572 (0.384 to 0.850) | 0.798 (0.630 to 1.011) | P=0.226 |
| Catheter removal | 0.556 (0.344 to 0.899) | 0.808 (0.655 to 0.995) | P=0.291 |
| Sleep aids | 0.619 (0.465 to 0.822) | 0.828 (0.621 to 1.104) | P=0.131 |
| Cognitive stimulation | 0.560 (0.369 to 0.849) | 0.798 (0.627 to 1.017) | P=0.400 |
| Liquid intake | 0.674 (0.529 to 0.858) | 0.831 (0.611 to 1.128) | P=0.239 |

| Component | RR in studies including (95% CI) | RR in studies without (95% CI) | P-value* |
|---|---|---|---|
| Nutrition | 0.633 (0.485 to 0.825) | 0.909 (0.697 to 1.185) | P=0.225 |

*For interaction
*Abbreviations.* CI=confidence interval; RR=risk ratio.

Burton and colleagues (2021) conducted an exploratory component network meta-analysis to assess the comparative effectiveness of individual components of the multi-component interventions. A decreased risk of incident delirium was associated with re-orientation (including use of familiar objects), cognitive stimulation, and sleep hygiene. Additionally, attention to nutrition and hydration, oxygenation, medication review, assessment of mood, and bowel and bladder care likely had an association with lower incident delirium, but this could not be determined definitively because estimates included the possibility of no benefit or harm. Finally, reducing sensory deprivation, identification of infection, mobilization, and pain control were associated with potential increases in delirium incidence, but the evidence was highly uncertain.

### Grading of the Overall Supporting Body of Research Evidence for Use of Single-Component Non-Pharmacological Interventions in Prevention of Delirium

- Magnitude of effect: Minimal. The magnitude of the effect of single interventions is minimal in most patient subgroups in reducing the incidence, severity, or duration of delirium or in terms of mortality associated with delirium. Statistically significant differences were noted with single-component interventions in post-operative patients, but interventions were varied. Education and OT were associated with statistically significant reductions in delirium incidence, but studies were small. Reductions in ICU length of stay were statistically significant but very small in magnitude for single-component interventions taken together; there is unlikely to be clinical significance of this decrease.

- Risk of bias: Moderate to High. Of the single-component studies, nine had a high risk of bias and 26 had a moderate risk of bias with only one study that had a low risk of bias. The factors that most often contributed to a higher risk of bias included lack of blinding or lack of information about blinding or allocation concealment, particularly in patients and clinicians.

- Applicability: The findings of these studies are applicable to older patients, those in critical care settings, and post-operative patients. Applicability to younger individuals and those in other clinical settings is likely to be reduced. Demographic information on study participants was often not reported and non-White individuals were often under-represented when demographic information was available.

- Directness: Direct. Outcomes were directly related to delirium or its associated adverse effects, including mortality.

- Consistency: Consistent. Study findings were consistent for delirium incidence, duration, and severity, and for mortality associated with delirium.

- Precision: Varies with outcome. For delirium incidence and duration, the findings were precise whereas for other outcomes, findings were imprecise.
- Dose-response relationship: No available information.
- Confounding factors (including likely direction of effect): The data may be confounded by variations in delirium assessment due to rater training. Individuals with hypoactive delirium may have been less likely to be identified than those with hyperactive delirium. However, the direction of effect from these potential confounding factors is not clear.
- Publication bias: Identified. There was possible evidence of publication bias for studies related to the incidence of delirium, with small studies likely to have gone unpublished.
- Overall strength of research evidence: Low to Moderate. The strength of research evidence for single interventions is moderate for the duration of delirium and low for the incidence and severity of delirium as well as for mortality associated with delirium. For other outcomes, there was insufficient information to make a determination.

### Non-Pharmacological Interventions for the Treatment of Delirium

A systematic review conducted by the Pacific Northwest EPC assessed outcomes from multi-component and single-component non-pharmacological interventions among clinical trials designed to treat delirium. For multi-component interventions, there were no group differences in delirium improvement, although one trial of general inpatients demonstrated an effect that favored the intervention group (Pitkälä et al. 2006). For single-component interventions, there was a non-significant group difference in the resolution of delirium.

### Multi-Component Interventions

The systematic review assessed evidence from eight clinical trials (Cole et al. 1994, 2002; Khalifezadeh et al. 2011; Kolanowski et al. 2011, 2016; Marcantonio et al. 2001, 2010; Pitkälä et al. 2006, 2008) comparing a multi-component intervention with usual care to treat delirium.

#### *Overview of study characteristics*

The interventions were a mix of behavioral and care-related interventions (Table C-3). Behavioral interventions included sensory interventions, orientation interventions, cognitively stimulating activities, increasing self/independent-care activities, or emotional support. Care-related interventions included early mobilization, early removal of urinary catheter, avoidance of restraints, avoidance or reduction of certain medications, use of sleep aids or promotion of good quality sleep, scheduled liquid intake to avoid dehydration, nutritional assistance or scheduled oral food intake, and monitoring for infections, blood transfusion necessity, or pain. Several trials involved family members in the intervention. Most of the interventions would be considered good practice or even standard of care (e.g., early removal of catheter); they are not usually considered controversial or harmful. All control interventions were usual care and may have contained portions of the multi-component interventions, but they were not actively monitored for adherence or treatment fidelity.

1342 Table C-3. Individual components in multi-component intervention trials to treat delirium

| Author Year | Setting/ Population Country | RF | Family[a] | Sensory[b] | Orientation[c] | Early mobilize | Decreased restraints[d] | Planned intake[e] | Decreased medications[f] | Cognitive activities | Increased self-care[g] | Sleep[h] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cole et al. 1994 | Inpatient Canada | X | X | X | X | X | X | | | | X | |
| Cole et al. 2002 | Inpatient Canada | X | X | X | X | X | X | | | | X | |
| Khalifezadeh et al. 2011 | Postop, neurosurgery Iran | | X | | X | | | | | | | |
| Kolanowski et al. 2011 | Rehab U.S. | | | | | | | | | X | | |
| Kolanowski et al. 2016 | Rehab U.S. | | | | | | | | | X | | |
| Marcantonio et al. 2001 | Nursing home U.S. | X | | X | X | X | | X | X | | | |
| Marcantonio et al. 2010 | Nursing home U.S. | X | X | X | X | X | X | X | X | | X | X |
| Pitkälä et al. 2006 | Inpatient Finland | X | | | X | X | | X | X | | | |

1343 [a] Family was involved in the delivery of the intervention.
1344 [b] Such as glasses, hearing aids, good lighting, and noise avoidance
1345 [c] Such as date, time, location, and reason for being there
1346 [d] Either physical restraints or catheter
1347 [e] Daily scheduled oral or intravenous administration of fluids (liquids) and/or nutritional assistance
1348 [f] Decreased use or avoidance of use of opioids, anticholinergics, sedatives, and other psychoactive drugs that may increase risk of delirium or sedation

[g] Increase patient's independent care for self, preferably to baseline

[h] Sleep aids, such as ear plugs and/or eye masks, and decreased noise and light at night

*Abbreviations*. RF=risk factor analysis.

*Source.* Cole et al. 1994, 2002; Khalifezadeh et al. 2011; Kolanowski et al. 2011, 2016; Marcantonio et al. 2001, 2010; Pitkälä et al. 2006.

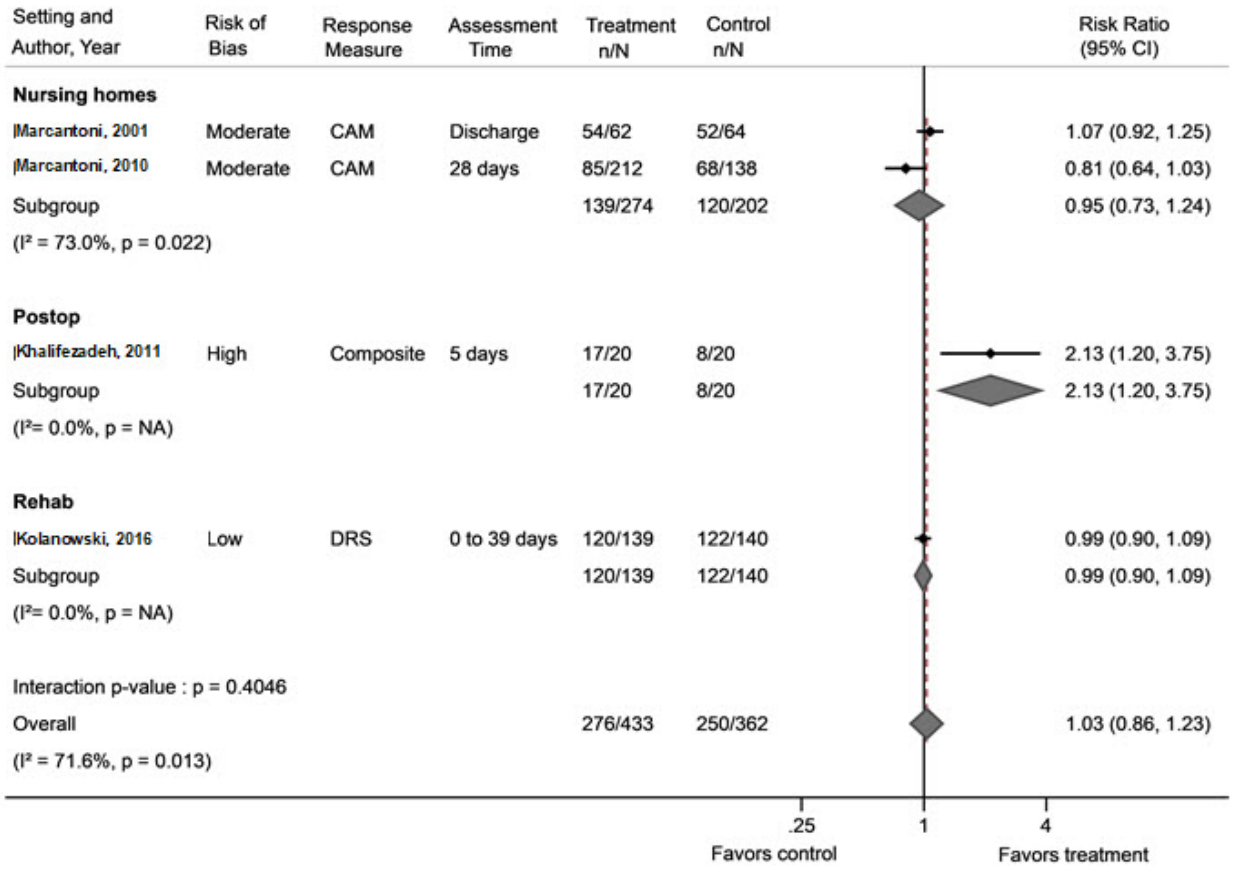
Trials were generally small in size (N<200) and were mostly conducted in the United States (4 trials) and Canada (2 trials) with one trial conducted in Iran and another trial in Finland. Risk of bias was low in two trials, moderate in five trials, and high in one trial. The weighted mean age was 84 years across those trials that reported age, and samples were predominantly female (mean 65%, range 54% to 74%). Participants were mostly White, in the 4 trials that reported information on race/ethnicity. Study settings included post-operative neurosurgery, general inpatient, nursing homes, and rehabilitation centers. Co-occurring dementia was excluded in one study, present in all participants in two studies, and present in a portion of the sample in the other studies. In all trials, participants' baseline functional status was within normal ranges based on the Charlson Comorbidity Index, the Clinical Dementia Rating Scale, the Crichton Geriatric Behavioral Scale, or the RASS. All patients were diagnosed with delirium with a validated assessment scale (i.e., the CAM, DRS, MDAS, and a composite scale).

*Effect of multi-component interventions on delirium severity*

The systematic review identified five individual clinical trials that reported on the response of delirium to multi-component non-pharmacological interventions (Khalifezadeh et al. 2011; Kolanowski et al. 2016; Marcantonio et al. 2001, 2010; Pitkälä et al. 2006). A pooled analysis of the four trials that could be combined found no significant differences between groups (N=795; RR 1.03, 95% CI 0.86–1.23, $I^2$=72%) (Khalifezadeh et al. 2011; Kolanowski et al. 2016; Marcantonio et al. 2001, 2010) (see Figure C-4). A trial of general inpatients (N=174) found significantly greater sustained improvement of 4 points or more on the MDAS at day 8 in the intervention group compared with usual care (47% vs. 21%, *P*=0.002 [Pitkälä et al. 2006]).

Two trials (N=16 and 283) from the systematic review that were conducted in dementia patients in rehabilitation centers found a non-significantly lower severity of delirium in the intervention group compared with usual care as measured by the DRS (Kolanowski et al. 2011, 2016). A trial (N=126) conducted in nursing homes, which included rehabilitation patients as well as long-term care residents, found more patients in the usual care group had severe delirium compared with the intervention group (RR 0.40, 95% CI 0.18–0.89), although baseline severity was not reported (Marcantonio et al. 2001).

Figure C-4. Delirium response with multi-component interventions versus usual care.




*Abbreviations*. CAM=Confusion Assessment Method; CI=confidence interval; DRS=Delirium Rating Scale; NA=not applicable; postop=post-operative; Rehab=rehabilitation.
*Source*. Khalifezadeh et al. 2011; Kolanowski et al. 2016; Marcantonio et al. 2001, 2010.

### *Effect of multi-component interventions on delirium duration*

The systematic review identified four trials that reported on outcomes related to the duration of delirium (Cole et al. 2002; Kolanowski et al. 2011, 2016; Marcantonio et al. 2001). One trial in rehabilitation center patients with dementia reported a large but non-significant difference in the mean number of days with delirium (3.27 vs. 7, *P*=0.11 [Kolanowski et al. 2011]). Another trial, among patients with hip fracture, also did not find a significant difference in mean hospital days of delirium per episode (2.9 vs. 3.1, *P*=0.72 [Marcantonio et al. 2001]). Kolanowski and colleagues (2016) found a non-significant difference in the time to resolution of delirium symptoms (6.88 days vs. 7.39 days, *P*=0.79) and in the proportion of delirium-free days (64.8% vs. 68.7%, *P*=0.37) in patients with dementia. Finally, a trial of older inpatients reported that the time to improvement in the Delirium Index score was not significantly different between groups (HR 1.09, 95% CI 0.74–1.60 [Cole et al. 2002]). There was also no difference in delirium improvement when the analysis was restricted to patients without dementia (HR 1.54, 95% CI 0.80–2.97 [Cole et al. 2002]).

*Effect of multi-component interventions on length of stay*

Among four trials (N=810) that reported the length of hospital stay (Cole et al. 2002; Kolanowski et al. 2016; Marcantonio et al. 2001; Pitkälä et al. 2006), three trials showed a similar length of stay between intervention and usual care groups (Cole et al. 2002; Marcantonio et al. 2001; Pitkälä et al. 2006). In contrast, a single trial of patients with dementia in a rehabilitation center found significantly longer stay in the usual care group compared with the intervention group (mean 53.13 days vs. 36.09 days, *P*=0.01 [Kolanowski et al. 2016]).

*Effect of multi-component interventions on mortality*

In a pooled analysis of six trials (N=1,245; Cole et al. 1994, 2002; Kolanowski et al. 2011, 2016; Marcantonio et al. 2010; Pitkälä et al. 2006), there were no differences between groups in rates of mortality (RR 1.07, 95% CI 0.85–1.36). None of the trials reported adverse events, and one trial excluded individuals who died during the study.

*Effect of multi-component interventions on other outcomes*

One trial (N=174), conducted in general hospitalized patients, reported higher health-related quality of life in the intervention group compared with usual care, as measured by the generic 15-dimensional questionnaire (*P*=0.020 [Pitkälä et al. 2008]). In the same trial, more patients in the intervention group reported feeling "healthy" or "quite healthy" at discharge (71% vs. 49%, *P*=0.050). In three trials (N=417), the MMSE was used to assess cognitive decline in patients with delirium. One found no differences in intervention and control groups at 3-month follow-up (mean 18.6 vs. 18.3) but did find a benefit of the multi-component intervention at 6-month follow-up (mean 18.4 vs. 15.8, *P*=0.047 [Pitkälä et al. 2006]). The other two studies found no group differences (improvement at 36 days: HR 1.10, 95% CI 0.74–1.63 [Cole et al. 2002] and mean at discharge: 16.84 vs. 16.25, *P*=0.5233 [Kolanowski et al. 2011]). Lastly, two trials (N=227 and 174) failed to find any differences in mean scores on the Barthel Index, a disability assessment, between intervention groups at discharge (47.74 vs. 43.41, *P*=0.965 [Kolanowski et al. 2011]) or at 6-month follow-up (70.2 vs. 63.8, *P*=0.144 [Pitkälä et al. 2006]) as compared to usual care.

### Grading of the Overall Supporting Body of Research Evidence for Use of Multi-Component Non-Pharmacological Interventions in the Treatment of Delirium

- Magnitude of effect: Minimal. No significant differences were noted in the magnitude of effects on outcomes including delirium remission, severity, or duration with multi-component interventions.

- Risk of bias: Moderate. The majority of trials on multi-component interventions for the treatment of delirium had a moderate risk of bias with a high risk of bias in two of eight studies. Factors that most commonly affected the risk of bias were a lack of specification of the methods for random allocation and concealment as well as a lack of patient and clinician masking.

- Applicability: The majority of studies on use of multi-component interventions to treat delirium were done in the United States or Canada, primarily in nursing homes or rehabilitation facilities with some studies in acute care settings. Older individuals predominated in the majority of the studies and, in most studies, co-occurring dementia was present in some or all of the participants. Most of the

studies included a greater proportion of women than men. Little information was available on the race and ethnicity of participants for many of the studies and when this information was specified, the sample was predominantly White.

- Directness: Direct. Outcomes were directly related to delirium or its associated adverse effects, including mortality.
- Consistency: Variable. Studies on delirium remission and mortality showed consistent findings whereas for other outcomes, only one study was available, and the consistency of findings was unknown.
- Precision: Imprecise. Findings were imprecise for all outcomes.
- Dose-response relationship: No available information.
- Confounding factors (including likely direction of effect): The data may be confounded by variations in delirium assessment due to rater training. Many of the studies included individuals with concomitant dementia, which may have delayed resolution of delirium in those subjects.
- Publication bias: Unclear. Although publication bias was not reported, there was an insufficient number of trials to make an assessment.
- Overall strength of research evidence: Low. The strength of research evidence was low for response of delirium to multi-component interventions and rates of mortality within the studies of delirium treatment using multi-component interventions.

### Single-Component Interventions

Because multi-component non-pharmacologic interventions are comprised of multiple independent interventions, the Pacific Northwest EPC systematic review considered the effectiveness outcomes from single-component studies as well as assessing effects of each component within the multi-component trials.

#### *Overview of study characteristics*

Six trials (Campbell et al. 2019; Khan et al. 2019; Levy et al. 2022; Mailhot et al. 2017; Makinian et al. 2015; Yang et al. 2012) compared a single behavioral intervention with usual care for the treatment of delirium. The single behavioral interventions assessed were computerized decision-support interventions to interrupt orders for strong anticholinergics (Campbell et al. 2019; Khan et al. 2019), a family member-delivered delirium management intervention (Mailhot et al. 2017), bright light therapy (Yang et al. 2012), massage (Makinian et al. 2015), and acupuncture (Levy et al. 2022). The control group was usual care in all trials. Two trials also provided adjunct antipsychotics to both groups—risperidone (starting at 0.5 mg/day and increased to a mean of 2.0 mg/day) with light therapy (Yang et al. 2012) or haloperidol (given as a single dose to both groups) with massage (Makinian et al. 2015).

Trials were generally small in size, with the number of subjects ranging from 30 to 351. Two trials were conducted in the United States and 1 each in Canada, South Korea, Israel, and Iran. Trial settings

included post-operative cardiac surgery, ICU, general inpatient, and hospital psychiatry. All the trials were rated as having a moderate risk of bias. The weighted mean age was 63 years, with four trials having a mean age 70 or older. Several trials were predominantly female, although the range of female participants was 36% to 62%. In the two U.S. trials, Black participants comprised 42% and 52% of the study population; no other trials reported race/ethnicity. All trial participants were within normal levels of functioning at the start of the study, as measured by the APACHE II, Charlson Comorbidity Index, or the Clinical Global Impressions-Severity. In both ICU trials, nearly three-quarters of participants were on mechanical ventilation. All patients were diagnosed with delirium as per a validated assessment tool (i.e., the CAM, CAM-ICU, DRS, or the NEECHAM Confusion Scale).

*Effect of single-component interventions on delirium response*

A pooled analysis of three trials found no differences in the response of patients with delirium to a single-component intervention (3 trials, N=191; 32.3% vs. 17.4%, RR 1.92, 95% CI 1.13–3.25, $I^2$=0%) (Levy et al. 2022; Mailhot et al. 2017; Makinian et al. 2015). A trial of ICU patients reported more delirium-/coma-free days in the intervention group compared with usual care by day 8 (median 4 vs. 5, *P*=0.36) or day 30 (median 25 vs. 26.5, *P*=0.10), but the differences were not significant (Campbell et al. 2019). The trial of acupuncture reported that the intervention group had more patients without delirium compared with the usual care (24% vs. 11%, *P*=0.002) as well as a significantly shorter time to first remission of delirium for (HR 0.267, 95% CI 0.098– 0.010) and more delirium-free days (median of 5.5 vs. 0, *P*<0.001).

*Effect of single-component interventions on delirium severity*

Five trials reported delirium severity was lower in the intervention group, but results were significant in only two of the trials. One trial reported significantly lower mean scores on day 5 for the intervention group compared with usual care (12 vs. 18, *P*<0.05 [Yang et al. 2012]), and the other reported a significantly larger decrease in mean scores at discharge in the intervention group compared with usual care (-3.2 vs. -2.5, *P*=0.046 [Khan et al. 2019]). The other three trials did not report significant differences (Campbell et al. 2019; Mailhot et al. 2017; Makinian et al. 2015), although all reported lower scores or larger decreases in the intervention group. Studies used different scales, and the interventions were heterogeneous; thus, they were not combined in the meta-analysis. Updated analyses indicated similar results as the previous meta-analysis, with no differences between groups.

*Effect of single-component interventions on length of stay*

Regarding length of stay, one trial (N=200) reported significantly longer ICU stay in the intervention group (computer decision support) compared with usual care (median 10 days vs. 8 days, *P*=0.019 [Campbell et al. 2019]), whereas four trials (N=399) found no group differences in hospital length of stay (Campbell et al. 2019; Levy et al. 2022; Mailhot et al. 2017; Makinian et al. 2015). Of those four trials, two found shorter hospital stays in the intervention groups (mean 6.3 vs. 12.1 and 4.11 vs. 4.6 days [Mailhot et al. 2017; Makinian et al. 2015]) and two found longer hospital stays for the intervention group (median days: 12 vs. 11 and 13 vs. 12 days [Campbell et al. 2019; Levy et al. 2022]).

*Effect of single-component interventions on mortality*

In two ICU trials (N=551), there were no group differences on rates of mortality at discharge (11% vs. 8% [Campbell et al. 2019] and OR 0.61, 95% CI, 0.32–1.16 [Khan et al. 2019]) or at 30 days post-discharge

(15% vs. 10% [Campbell et al. 2019] and OR 0.62, 95% CI 0.35–1.12 [Khan et al. 2019]). One trial (N=81) found no group differences in in-hospital mortality (16% vs. 23%, P=0.574 [Levy et al. 2022]). In three trials, there were also no group differences in number of serious adverse events (N=581) (27% vs. 22% [Campbell et al. 2019] and 26% vs. 32% [Khan et al. 2019]) or in caregiver anxiety at day 4 (mean HADS score: 36.67 vs. 43.86 [Mailhot et al. 2017]). The remaining three trials did not report adverse events.

### *Effect of single-component interventions on other outcomes*

Regarding health/functional status and medication use outcomes, Sickness Impact Profile scores were significantly lower (i.e., better) in the intervention group compared with usual care in a family intervention in post-cardiac surgery patients (N=30; mean 4.80 vs. 9.50, *P*=0.01 [Mailhot et al. 2017]). In a trial of ICU patients (N=200), an intervention aimed at reducing medications with increased potential for causing delirium (e.g., strong anticholinergics and benzodiazepines) was not successful, as greater proportions of intervention patients were prescribed benzodiazepines (60.6% vs. 56.0%, *P*=0.50), haloperidol (29.3% vs. 20.0%, *P*=0.14), and anticholinergic drugs (34.3% vs. 26.0%, *P*=0.22 [Campbell et al. 2019]). Finally, the trial of acupuncture reported the same number of psychotropic drug-free days in each group (median 7 days each group, *P*=0.253) and equivalent scores on the Katz Index of Independence in Activities of Daily Living at discharge (median 2 in each group, *P*=0.945) (Levy et al. 2022).

### *Effectiveness of single-component interventions based on multi-component trial data and network meta-analysis*

To identify individual components that may be responsible for, or at least contribute meaningfully to, the overall results of multi-component interventions, the Pacific Northwest EPC conducted subgroup analyses based on whether each study included an individual component. The findings for each subgroup were compared to determine whether they were statistically significantly different (Table C-4). When trials were compared based on the individual components they included, none of the individual components had significantly lower risk of delirium compared with the trials not including these interventions.

Table C-4. Pooled analyses of individual components in multi-component trials to treat delirium

| Component | RR in studies including (95% CI) | RR in studies without (95% CI) | P-value* |
|---|---|---|---|
| Sensory | 0.948 (0.725 to 1.241) | 1.375 (0.656 to 2.884) | 0.472 |
| Orientation | 1.115 (0.783 to 1.588) | 0.991 (0.904 to 1.086) | 0.786 |
| Mobilization | 0.948 (0.725 to 1.241) | 1.375 (0.656 to 2.884) | 0.472 |
| Restraint avoidance | 0.814 (0.643 to 1.030) | 1.107 (0.904 to 1.355) | 0.446 |
| Medication reduction | 0.948 (0.725 to 1.241) | 1.375 (0.656 to 2.884) | 0.472 |

| Component | RR in studies including (95% CI) | RR in studies without (95% CI) | P-value* |
|---|---|---|---|
| Catheter removal | 0.814 (0.643 to 1.030) | 1.107 (0.904 to 1.355) | 0.446 |
| Sleep aids | 0.814 (0.643 to 1.030) | 1.107 (0.904 to 1.355) | 0.446 |
| Cognitive stimulation | 0.991 (0.904 to 1.086) | 1.115 (0.783 to 1.588) | 0.786 |

*For interaction
*Abbreviations.* CI=confidence interval; RR=risk ratio.

### Grading of the Overall Supporting Body of Research Evidence for Use of Single-Component Non-Pharmacological Interventions in the Treatment of Delirium

- Magnitude of effect: Minimal to low. On pooled analyses, there was no significant effect of single-component interventions; however, in some individual studies with outcomes that were not amenable to meta-analysis, there was a small benefit of the intervention.

- Risk of bias: Moderate to high. Two-thirds of trials on single-component interventions for the treatment of delirium had a moderate risk of bias whereas the other trials had a high risk of bias. Factors that most commonly affected the risk of bias were a lack of specification of the methods for random allocation and concealment as well as a lack of patient and clinician masking. Several trials also had intervention and control groups with dissimilar characteristics at baseline.

- Applicability: Most individuals in the trials of single-component interventions were older, but other demographic information was often not reported, and the samples may not be representative of usual clinical populations. Half of the trials were conducted in the United States or Canada. The single-component interventions that were studied are not typically used in clinical settings in patients with delirium; however, the analysis of individual components of multi-component interventions includes common non-pharmacological approaches.

- Directness: Direct. Outcomes were directly related to delirium or its associated adverse effects, including mortality.

- Consistency: Varies with outcome. Findings on delirium remission and severity were consistent whereas findings on delirium duration and mortality were inconsistent. For other outcomes, findings were only available from one study.

- Precision: Varies with outcome. For delirium severity, the findings were precise whereas for other outcomes, findings were imprecise.

- Dose-response relationship: No available information.

- Confounding factors (including likely direction of effect): The data may be confounded by variations in delirium assessment due to rater training. Several of the trials had significant differences in

the characteristics of intervention and control groups at baseline, which may also have confounded results.

- Publication bias: Unclear. Although publication bias was not reported, there was an insufficient number of trials to make an assessment.

- Overall strength of research evidence: Low to moderate. The strength of research evidence was moderate for delirium severity and low for delirium response and serious adverse events.

## Pharmacological Interventions

### *Statement 8 – Principles of Medication Use*

APA recommends **(1C)** that antipsychotic agents and other medications to address neuropsychiatric disturbances of delirium be used only when all the following criteria are met:

- verbal and non-verbal de-escalation strategies have been ineffective;
- contributing factors have been assessed and, insofar as possible, addressed; and
- the disturbances cause the patient significant distress and/or present a risk of physical harm to the patient or others.

Evidence in support of this statement is primarily indirect and comes from a small number of studies on the pharmacological treatment of delirium.

The systematic literature review of pharmacological treatments for delirium that was conducted by the Pacific Northwest EPC included antipsychotics, sedatives, sleep-related medications, cholinesterase inhibitors, and miscellaneous medication (i.e., the benzodiazepine antagonist flumazenil). Findings are consistent with those from a systematic review from the AHRQ, which showed no effect of antipsychotics in the treatment of delirium in hospitalized adults (Nikooie et al. 2019) and generally indicated no significant effect of pharmacological treatments in improving delirium response, delirium severity, adverse events, or mortality. Studies of antipsychotic medications are described in this statement whereas studies of dexmedetomidine, benzodiazepines, melatonin, ramelteon, and other sleep-related medications are described in Statements 10, 11, 12, and 13.

### Use of Antipsychotic Medications for the Treatment of Delirium

#### Overview of study characteristics

There were 29 studies on treatment of delirium with antipsychotic medications that were identified in the systematic review (Agar et al. 2017; Atalan et al. 2013; Bakri et al. 2015; Boettger et al. 2011, 2015; Boncyk et al. 2021; Breitbart et al. 1996; Devlin et al. 2010; Fox et al. 2020; Fukata et al. 2017; Girard et al. 2018; Grover et al. 2016; Han and Kim 2004; Hatta et al. 2014a; Jain et al. 2017; Kim et al. 2010; Lee et al. 2005; Lin et al. 2008; Liu et al. 2004, 2021; Maneeton et al. 2013; Skrobik et al. 2004; Smit et al. 2021; Tagarakis et al. 2012; Tahir et al. 2010; Thom et al. 2018; van der Vorst et al. 2020; Weaver et al. 2017; Yoon et al. 2013). Studies were conducted in a wide range of countries with eleven in the United States, four in South Korea, three in India, two in Japan, and one each in Australia, Canada, China, Greece, Netherlands, Northern Taiwan, Saudi Arabia, Taiwan, Thailand, The Netherlands, Turkey, and the United Kingdom. Fifteen of the studies had a mean or median age 65 or greater, 16 had a mean or

median age less than 65, and one trial did not report this information. Fourteen studies enrolled a predominance of men, four studies enrolled a predominance of women, 12 enrolled comparable proportions of men and women, and two did not report this information. Twenty-five studies did not report information on race or ethnicity and one study enrolled only Asian participants. In the other studies, White participants represented 13% to 83% of the sample, and Black participants represented 9% to 57% of participants. Individuals with dementia were excluded from 12 of the trials and constituted 10% to 25% of the sample in three trials. In the remaining seventeen trials, no information on the presence of dementia was reported.

Studies on the treatment of delirium included a mix of RCTs and prospective and retrospective cohort studies. Among the RCTs (N=2,111, range 28 to 566), the risk of bias was low in two studies, moderate in nine studies, and high in seven studies. Among the cohort studies (N=12,682 range 40 to 7,879), the risk of bias was moderate in six studies and high in five studies.

Studies on antipsychotic medications included post-operative patients (Atalan et al. 2013; Bakri et al. 2015; Fukata et al. 2017; Tagarakis et al. 2012) as well as patients in ICUs (Andersen-Ranberg et al. 2022; Devlin et al. 2010; Girard et al. 2018; Skrobik et al. 2004; Thom et al. 2018; Weaver et al. 2017), general inpatient (Breitbart et al. 1996; Grover et al. 2016; Han and Kim 2004; Jain et al. 2017; Kim et al. 2010; Lee et al. 2005; Maneeton et al. 2013; Tahir et al. 2010; van der Vorst et al. 2020), and palliative care (Agar et al. 2017; Lin et al. 2008; Boettger et al. 2015) settings.

In terms of specific treatments, four trials compared haloperidol with other drugs or no treatment among post-operative patients (Atalan et al. 2013; Bakri et al. 2015; Fukata et al. 2017; Tagarakis et al. 2012). Regarding ICU populations, the largest of the antipsychotic trials (N=1000) compared haloperidol to placebo (Andersen-Ranberg et al. 2022). Another large trial (N=566; Girard et al. 2018) included both ziprasidone and haloperidol arms but reported only comparisons of each drug with placebo. The other placebo-controlled trial, assessing quetiapine, was small (N=36; Devlin et al. 2010) and the 1 comparative effectiveness trial had high risk of bias (Skrobik et al. 2004). Two observational studies assessed ICU patients with delirium treated with any antipsychotic. One compared early treatment (within 48 hours of diagnosis) with late treatment and no treatment (Thom et al. 2018), the other treatment with no treatment (Weaver et al. 2017). Five trials in general inpatient populations compared treatment response with second-generation antipsychotics to that with haloperidol , using various delirium measures and thresholds (Grover et al. 2016; Han and Kim 2004; Jain et al. 2017; Maneeton et al. 2013; van der Vorst et al. 2020). Concerning palliative care patients, a study from Australia with moderate risk of bias assessed 247 patients treated with risperidone, haloperidol, or placebo; all patients also received non-drug treatment and treatment for potential causes of delirium (Agar et al. 2017). The study with a high risk of bias compared olanzapine with haloperidol and analyzed 12 of 30 patients randomized (Lin et al. 2008). The study by Boettger and colleagues (2015) was an observational study of four antipsychotics in a cancer treatment hospital.

### Effect of antipsychotic medications on delirium response

In four trials of antipsychotic medication among post-surgical patients, one trial that compared haloperidol to no treatment found a greater rate of response to delirium in the haloperidol group (Table

C-5 [Fukata et al. 2017]). The other trials—two of which assessed 3 to 5 days of haloperidol versus morphine (Atalan et al. 2013) or ondansetron (Bakri et al. 2015) and one that assessed a single dose of haloperidol or ondansetron (Tagarakis et al. 2012)—did not find significant differences between treatments.

An observational study of the timing of antipsychotic administration in ICU patients did not show statistically significant differences in the resolution of delirium or coma with either early (adjusted HR 1.24, 95% CI 0.77–1.99) or late treatment (adjusted HR 1.91, 95% CI 0.98–3.73) compared with no treatment (Thom et al. 2018).

Table C-5. Haloperidol versus other treatments for post-operative delirium

| **Study<br>Risk of Bias<br>N analyzed** | **Drug and dose** | **Comparison treatment** | **Duration (follow-up)** | **Surgery type<br>Diagnostic tool<br>Age/mean age** | **Delirium outcomes** |
|---|---|---|---|---|---|
| Study: Fukata et al. 2017<br>RoB: Moderate<br>N: 201 | Haloperidol 5 mg IV once daily | No treatment | 5 days (day 10) | Surgery type: Abdominal/orthopedic<br>Diagnostic Tool: NEECHAM 20–24<br>Age: >75 years | Response: 82% vs. 68%, RR 1.21, 95% CI 1.03–1.42<br>Duration: 2 days vs. 2 days |
| Study: Atalan et al. 2013<br>RoB: High<br>N: 53 | Haloperidol 5 mg IM hourly (max 20 mg/day) | Morphine 5 mg IM hourly (max 20 mg/day) | 5 days (day 10) | Surgery type: Cardiac<br>Hyperactive delirium<br>Diagnostic Tool: RASS >2 (0–4)<br>Age: 66 years | Severity RASS: 0 vs. 0.39, *P*=0.33<br>Duration: 1.5 days vs. 1.5 days |
| Study: Bakri et al. 2015<br>RoB: Moderate<br>N: 96 | Haloperidol 5 mg IV twice daily | Ondansetron 4 mg IV twice daily | 3 days (day 3) | Surgery type: Trauma<br>Diagnostic Tool: ICDSC (0–8)<br>Age: Mean 31 years | Response: 81% vs. 94%, RR 1.14, 95% CI 0.95–1.38<br>Severity ICDSC: 1.2 vs. 4.9, *P*=0.7 |
| Study: Tagarakis et al. 2012<br>RoB: High<br>N: 80 | Haloperidol 5 mg IV x 1 preop | Ondansetron 8 mg IV x 1 preop | One dose (NR) | Surgery type: Cardiac<br>Diagnostic Tool: 4-point scale<br>Age: Mean 71 years | Response: 85% vs. 83%, RR 1.03, 95% CI 0.84–1.25<br>Severity: 1.2 vs. 1.3, *P*=NR ("not significant") |

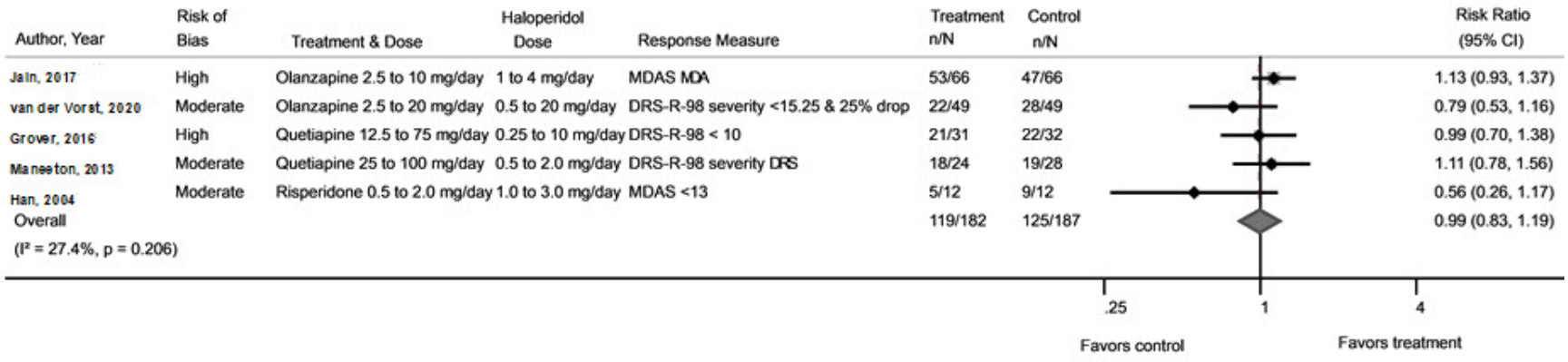
*Abbreviations*. CI=confidence interval; ICDSC=Intensive Care Delirium Screening Checklist; IM=intramuscular; IV=intravenous; N=number; NEECHAM=Neelon and Champagne Confusion Scale; NR=not reported; preop=pre-operative; RASS=Richmond Agitation and Sedation Scale; RoB=risk of bias; RR=risk ratio.
*Source*. Atalan et al. 2013; Bakri et al. 2015; Fukata et al. 2017; Tagarakis et al. 2012.

A pooled analysis of five trials in general inpatient populations (see Figure C-5) showed no difference in treatment response between haloperidol and second-generation antipsychotic agents (65% vs. 67%, RR 0.99, 95% CI 0.83–1.19, $I^2$=27%) (Grover et al. 2016; Han and Kim 2004; Jain et al. 2017; Maneeton et al. 2013; van der Vorst et al. 2020). Two small trials, each enrolling about 30 patients, compared second-generation antipsychotics with each other, and neither found statistically significant differences.

Response was not different between olanzapine and risperidone (73% vs. 65%, *P*=0.71 [Kim et al. 2010]) or between amisulpride and quetiapine (81% vs. 80%, *P*=0.93 [Lee et al. 2005]).

An observational study of 84 patients with delirium in a cancer treatment hospital compared haloperidol with three second-generation antipsychotics (Boettger et al. 2015). It did not find a statistically significant difference between the four drugs in rates of delirium response after 4 to 7 days (*P*=0.42), with rates ranging from 62% for olanzapine to 86% for risperidone.

Figure C-5. Delirium response with second-generation antipsychotics versus haloperidol in inpatients.




*Abbreviations*. CI=confidence interval; DRS=Delirium Rating Scale; DRS-R-98=Delirium Rating Scale-Revised-98; MDAS=Memorial Delirium Assessment Scale.
*Source*. Grover et al. 2016; Han and Kim 2004; Jain et al. 2017; Maneeton et al. 2013; van der Vorst et al. 2020.

### Effect of antipsychotic medications on delirium duration

Among post-surgical patients, two trials assessed whether haloperidol affected the duration of delirium and found no difference, either in comparison to no treatment (Fukata et al. 2017) or treatment with morphine (Atalan et al. 2013) (see Table C-5).

Two RCTs of antipsychotic medication in ICU populations reported measures of delirium duration; the smaller trial found a shorter duration with quetiapine treatment (Devlin et al. 2010), but the larger one showed no difference between either ziprasidone or haloperidol and placebo in the duration of delirium (Girard et al. 2018) (see Table C-6). An observational study in ICU patients found that delirium lasted longer with antipsychotic treatment (36 hours vs. 14 hours, *P*<0.001 [Weaver et al. 2017]).

Table C-6. Delirium outcomes of antipsychotics versus other interventions to treat delirium in the ICU

| **Study**<br>**Risk of Bias**<br>**N analyzed** | **Comparison** | **Delirium outcomes** | **Length of stay** |
|---|---|---|---|
| Study: Andersen-Ranberg et al. 2022<br>RoB: NR<br>N: 1000 | Haloperidol vs. placebo | NR | Hospital: 28.8 days vs. 26.4 days |
| Study: Devlin et al. 2010<br>RoB: Low<br>N: 36 | Quetiapine vs. placebo | Hours in delirium: median 36 vs. 120, *P*=0.006 | ICU: Median 16 days vs. 16 days, *P*=0.28<br>Hospital: Median 24 days vs. 26 days, *P*=0.32 |
| Study: Girard et al. 2018<br>RoB: Low<br>N: 566 | Ziprasidone vs. placebo; haloperidol vs. placebo | Days with delirium: adjusted OR 1.02 (95% CI 0.69–1.51); 1.12 (95% CI 0.86–1.46) | ICU: HR 1.02 (95% CI 0.88–1.17); HR 0.95 (95% CI 0.81–1.12)<br>Hospital: HR 1.05 (95% CI 0.88–1.25); HR 1.03 (95% CI 0.85–1.23) |
| Study: Skrobik et al. 2004<br>RoB: High<br>N: 73 | Olanzapine vs. haloperidol | Delirium severity: no difference between groups, *P*=0.64 | NR |

*Abbreviations*. CI=confidence interval; HR=hazard ratio; ICU=intensive care unit; NR=not reported; OR=odds ratio; RoB=risk of bias; RR=relative risk.
*Source.* Andersen-Ranberg et al. 2022; Devlin et al. 2010; Girard et al. 2018; Skrobik et al. 2004.

In a general inpatient population, two trials of second-generation antipsychotics compared with haloperidol found different results for duration of delirium, suggesting longer duration associated with olanzapine compared with haloperidol (MD 1.70 days, 95% CI 0.08–3.32 [van der Vorst et al. 2020]) but not with quetiapine compared with haloperidol (MD -0.20 days, 95% CI -0.79–0.39 [Maneeton et al. 2013]). These were both small trials.

### Effect of antipsychotic medications on delirium severity

Among post-surgical patients, three trials assessed whether haloperidol affected the severity of delirium and found no difference, either in comparison to treatment with morphine (Atalan et al. 2013) or ondansetron (Bakri et al. 2015; Tagarakis et al. 2012) (see Table C-5).

A trial with a high risk of bias comparing olanzapine and haloperidol reported delirium severity in ICU patients, measured by the Delirium Index (Skrobik et al. 2004). Their analysis of variance analysis found no effect of treatment choice on severity in the 73 patients studied (group-time interaction, *P*=0.64; Skrobik et al. 2004).

In general inpatients, trials did not find significant differences between groups in the effects of treatment on delirium severity. All trials showed severity scores that were similar between treatment groups at baseline. Change from baseline in delirium severity did not differ significantly between groups in pooled analysis of three trials of second-generation antipsychotics and haloperidol using the DRS-R-98 (total or severity score; MD -0.11, 95% CI, -0.42–0.21, $I^2$=0% [Grover et al. 2011, 2016; Maneeton et al. 2013]). Effect of treatment on severity was similar between second-generation antipsychotics and haloperidol in two other trials that could not be pooled (Han and Kim 2004; Jain et al. 2017), between olanzapine and risperidone in two trials (MD 0.30, 95% CI -0.15–0.76, $I^2$=0% [Grover et al. 2011; Kim et al. 2010]), and between amisulpride and quetiapine in a single small trial with high risk of bias (Lee et al. 2005). Compared with placebo, DRS-R-98 scores improved more quickly with quetiapine, but final scores did not differ in one study (Tahir et al. 2010). In a trial comparing 2 first-generation antipsychotics, haloperidol and chlorpromazine, severity (DRS scores) declined with treatment in both groups, but the difference between groups was not significant (endpoint score 11.64 vs. 11.85, *P*=0.94 [Breitbart et al. 1996]).

In a pooled analysis of studies of palliative care patients, delirium severity (using MDAS) in palliative care patients was not significantly different between second-generation antipsychotics and haloperidol (N=259; MD 0.03, 95% CI -0.31–0.38, $I^2$=0%). The trial of risperidone, haloperidol, and placebo used three items from the Nursing Delirium Screening Scale (NuDESC) as the primary outcome, with severity scores ranging from 0 to 6 (lower better [Agar et al. 2017]). At the end of the trial, delirium symptoms were higher with either antipsychotic than with placebo (risperidone MD 0.48, 95% CI 0.09–0.86 and haloperidol 0.24, 95% CI 0.06–0.42). While significant, the differences are small. In an observational palliative care study that compared haloperidol with three second-generation antipsychotics, delirium severity after treatment ranged from 6.8 points on the MDAS for haloperidol to 11.7 for olanzapine, but the difference was not statistically significant across the four drugs (*P*=0.25; Boettger et al. 2015).

### Effect of antipsychotic medications on length of stay

Table C-6 also shows ICU and hospital length of stay for the two trials that reported it (Devlin et al. 2010; Girard et al. 2018). Treatment with any antipsychotic compared with placebo had no effect on length of stay in either trial. A retrospective cohort study of 510 patients suggested longer ICU stay with antipsychotic treatment compared with no treatment (5.7 days vs. 3.8 days, *P*=0.005 [Weaver et al. 2017]). In terms of ICU readmission, no statistically significant difference was observed with either ziprasidone (HR 0.73, 95% CI 0.49–1.10) or haloperidol (HR 1.13, 95% CI 0.62–2.09) treatment as compared to placebo (N=566; Girard et al. 2018).

### Effect of antipsychotic medications on mortality and adverse events

In four trials of haloperidol among post-surgical patients, adverse events were not reported or reported as none (Atalan et al. 2013; Bakri et al. 2015; Fukata et al. 2017; Tagarakis et al. 2012).

Two RCTs in ICU populations did not show a statistically significant difference for in-hospital or 30-day mortality with antipsychotic treatment compared with placebo. One trial (N=566) found that neither 30-day nor 90-day mortality were different between ziprasidone (up to 40 mg daily) or haloperidol (up to 20 mg daily) and placebo (Table C-7; Girard et al. 2018); however, 89% of the sample had hypoactive delirium and results may not be applicable to patients with hyperactive delirium. An additional trial (N=1,000), in which 54% of the sample had hypoactive delirium, found no difference in 90-day mortality or in days alive and out of the hospital at 90 days (Andersen-Ranberg et al. 2022). Adverse events did not differ between patients receiving antipsychotics and placebo in the same studies, though few events were reported. The study of olanzapine and haloperidol reported only extrapyramidal symptoms; these occurred with haloperidol and not with olanzapine, although the difference was not statistically significant (Skrobik et al. 2004). One observational study in ICU patients found that late treatment (>48 hours) with any antipsychotic was associated with a decrease in 10-day mortality (adjusted HR 0.30, 95% CI 0.10–0.88), although a post hoc subgroup analysis excluding comatose patients found no difference in mortality (Thom et al. 2018). Another observational study showed no effect of antipsychotic treatment on mortality as compared to placebo (17.4% vs. 18.3%, *P*=0.87 [Weaver et al. 2017]).

Table C-7. Mortality and adverse events of antipsychotics versus other interventions to treat delirium in the ICU

| **Study<br>Risk of Bias<br>N analyzed** | **Comparison** | **Mortality** | **Adverse events** |
|---|---|---|---|
| Study: Andersen-Ranberg et al. 2022<br>RoB: NR<br>N: 1,000 | Haloperidol vs. placebo | 90-day: 36.3% vs. 43.3%; adjusted RR 0.84 (0.72–0.98) | Serious adverse reaction in ICU: 2.2% vs. 1.9 %; adjusted RR 1.20 (0.33–5.45) |
| Study: Devlin et al. 2010<br>RoB: Low<br>N: 36 | Quetiapine vs. placebo | In hospital: 11% vs. 17%, *P*=1.0 | Any drug-related AE: 28% vs. 11%, *P*=0.4<br>EPS, SAEs, and WAEs: 0 vs. 0 events |
| Study: Girard et al. 2018<br>RoB: Low<br>N: 566 | Ziprasidone vs. placebo; haloperidol vs. placebo | 30-day: HR 1.07 (95% CI 0.77–1.47); HR 1.03 (95% CI 0.73–1.46)<br>90-day: HR 1.02 (95% CI 0.79–1.30); HR 1.17 (95% CI 0.99–1.40) | EPS: 1 vs. 1; 1 vs. 1 event<br>Dystonia: 0 vs. 0; 1 vs. 0 events |
| Study: Skrobik et al. 2004<br>RoB: High<br>N: 73 | Olanzapine vs. haloperidol | NR | EPS: 0% vs. 13%, *P*=0.15 |

*Abbreviations*. AE=adverse event; CI=confidence interval; EPS=extrapyramidal symptoms; HR=hazard ratio; ICU=intensive care unit; N=number; NR=not reported; RoB=risk of bias; RR=relative risk; SAE=serious adverse event; WAE=withdrawal due to adverse event.

*Source.* Andersen-Ranberg et al. 2022; Devlin et al. 2010; Girard et al. 2018; Skrobik et al. 2004.

Three trials in general hospital inpatients (N=282) did not show a statistically significant difference in mortality between patients treated with second-generation antipsychotics and those given haloperidol (RR 1.08, 95% CI 0.55–2.09, $I^2$=0% [Jain et al. 2017; Maneeton et al. 2013; van der Vorst et al. 2020]). In a placebo-controlled trial of 42 patients, four died in the quetiapine group and three in the placebo group (Tahir et al. 2010). A pooled analysis of three trials of second-generation antipsychotics compared with haloperidol did not find a significant difference in incidence of any adverse effect (N=293; 12% vs. 17%, RR 0.74, 95% CI 0.43–1.29, $I^2$=0% [Grover et al. 2011; Jain et al. 2017; van der Vorst et al. 2020]). Sedation and extrapyramidal symptoms were the most common side effects reported. Study withdrawal due to adverse events also did not differ significantly in a pooled analysis of three trials (N=254; 8.0% vs. 13%, RR 0.60, 95% CI 0.25–1.45, $I^2$=0% [Han and Kim 2004; Maneeton et al. 2013; van der Vorst et al. 2020]). Comparisons of second-generation antipsychotics with each other, first-generation antipsychotics with each other, and quetiapine with placebo also did not find significant difference in adverse events (Breitbart et al. 1996; Kim et al. 2010; Lee et al. 2005; Tahir et al. 2010). These were very small trials, with inadequate statistical power to assess differences.

In a large palliative care study (N=247; Agar et al. 2017) mortality for patients receiving antipsychotics was reported to be greater than for those receiving placebo, with the difference significant for haloperidol. Median survival for patients receiving placebo was 26 days, compared with 16 days for haloperidol (HR 1.73, 95% CI 1.20–2.50) and 17 days for risperidone (HR 1.29, 95% CI 0.91–1.84). Both antipsychotic groups had worse symptoms on the Extrapyramidal Symptom Rating Scale compared with placebo (risperidone MD 0.73, 95% CI 0.09–1.37, *P*=0.03 and haloperidol MD 0.79; 95% CI 0.17–1.41, *P*=0.01). An observational study of four antipsychotics in a cancer treatment hospital found a statistically significant difference in rates of any adverse event between drugs (*P*=0.009), with the lowest rate for risperidone (4.8%) and highest for olanzapine (43%) (Boettger et al. 2015). Extrapyramidal symptoms were highest with haloperidol (19% for parkinsonism, *P*=0.012 compared with second-generation antipsychotics). Among olanzapine patients, 29% experienced an increase in sedation, which was not seen with other antipsychotics (*P*=0.001 across drugs).

### Effect of antipsychotic medications on other outcomes

Patients in the ICU given quetiapine spent less time agitated than those given placebo in one small trial (6 hours vs. 36 hours with Sedation Agitation Score [SAS] ≥5, *P*=0.02 [Devlin et al. 2010]). The same trial suggested less use of rescue haloperidol and sedatives by various measures in patients given scheduled quetiapine, but differences were not statistically significant in this trial of 36 patients. Rates of rescue haloperidol use appeared lower in patients given olanzapine than those given scheduled haloperidol in the other small ICU trial, but again, differences were not statistically significant (39% vs. 53%, *P*=0.26 [Skrobik et al. 2004]). In the large placebo-controlled trial of haloperidol (Andersen-Ranberg et al. 2022) no differences were noted in the use of restraint or in receipt of rescue medications, including propofol, α-2-agonist, benzodiazepine, or open-label antipsychotic medication.

In a trial of risperidone, haloperidol, and placebo in palliative care patients, fewer individuals needed rescue midazolam in the placebo group than in the combined risperidone and haloperidol groups, with differences statistically significant on each study day (Agar et al. 2017).

### Grading of the Overall Supporting Body of Research Evidence for Use of Antipsychotic Agents to Address Neuropsychiatric Disturbances of Delirium

- Magnitude of effect: Minimal to none. Studies using antipsychotic medications, including haloperidol and second-generation antipsychotic medications, were quite consistent in showing minimal to no effects of antipsychotic medication in terms of delirium response or reducing the severity, duration, or associated length of hospital or ICU stay. In a single large study in palliative care patients, use of an antipsychotic medication was associated with more adverse effects and a greater severity of delirium.

- Risk of bias: Moderate to high. Approximately half of studies had a moderate risk of bias with almost all of the remaining studies having a high risk of bias. There were also a number of observational studies that were likely to have biases due to a lack of random assignment. Among the RCTs, factors contributing to risk of bias included inadequate or unclear random assignment or allocation concealment, inadequate masking, and in some studies, problems with attrition or statistical analysis.

- Applicability: The largest number of studies was conducted in the United States, with other studies conducted in a wide range of countries. A broad range of ages were included in the trials but about half of the studies excluded individuals less than age 65. Men and women were represented in the trials also the proportions of men and women in each study varied and there was more often a predominance of men than women. Most studies did not include information on race or ethnicity, limiting the ability to draw conclusions about demographic applicability. Only three trials included individuals with co-occurring dementia; the other trials did not report this information or excluded patients with dementia. Most studies were done in acute care populations, including post-operative, general medical and ICU patients with no studies in longer-term care facilities.

- Directness: Direct. The vast majority of studies provided direct information on delirium related outcomes including response, severity, and duration.

- Consistency: Consistent. When information was available from more than one study for a given intervention-control comparison and outcome measure, the findings were consistent. Many of the comparisons and outcomes only had information available from one study, however.

- Precision: Imprecise. Confidence intervals were wide and sample sizes were small for virtually all of the comparisons, yielding significant imprecision in terms of optimal information sizes.

- Dose-response relationship: No available information.

- Confounding factors (including likely direction of effect): The data may be confounded by variations in delirium assessment due to rater training. Individuals with hypoactive delirium may have been less likely to be identified than those with hyperactive delirium and the response to antipsychotic medications or other treatments may differ. However, the direction of effect from these potential confounding factors is not clear.

- Publication bias: Not identified. There was insufficient information to make a determination due to the small number of trials in each treatment setting.

- Overall strength of research evidence: Low. For many of the outcomes, there was insufficient evidence to identify any effect related to antipsychotic medication treatment of delirium. Where evidence was sufficient, it had a low strength of evidence. These outcomes included response or duration of delirium to haloperidol post-operatively as compared to no treatment, response or severity of delirium to second-generation antipsychotics as compared to first-generation antipsychotics or another second-generation antipsychotic in general inpatient settings, severity of delirium as compared to placebo in palliative care settings, and adverse events either compared to placebo or second-generation antipsychotics.

### *Statement 9 – Antipsychotic Agents*

APA recommends **(1C)** that antipsychotic agents not be used to prevent delirium or hasten its resolution.

This statement is supported by direct evidence from trials of antipsychotic medications in preventing or treating delirium. Studies of treatment are discussed in more detail in Appendix C, Statement 8, and generally show minimal or no effects of medication, including findings of well-designed, large-scale, multicenter trials like the Agents Intervening against Delirium in Intensive Care Unit (AID-ICU) trial (Andersen-Ranberg et al. 2022) and the Modifying the Impact of ICU-Associated Neurological Dysfunction–USA (MIND-USA) trial (Girard et al. 2018). Although haloperidol has been most often assessed, second-generation antipsychotics including risperidone, olanzapine, and quetiapine have also failed to show consistent treatment benefits for patients with delirium.

#### Use of Antipsychotic Medications for the Prevention of Delirium

The Pacific Northwest EPC reviewed the literature for studies that assessed the use of antipsychotics in preventing delirium, mostly in post-operative and ICU settings and commonly with haloperidol. Overall, the evidence was not sufficiently consistent and compelling that antipsychotics effectively prevent incident delirium or reduce delirium duration, hospital/ICU length of stay, or mortality and other adverse events.

#### Overview of study characteristics

Fourteen studies (N=4,449 subjects, range 37 to 1,796) compared an antipsychotic medication to placebo or no treatment (Abdelgalel 2016; Abraham et al. 2021; Al-Qadheeb et al. 2016; Fukata et al. 2014; Hollinger et al. 2021; Kalisvaart et al. 2005; Khan et al. 2018; Y. Kim et al. 2019; Larsen et al. 2010; Mokhtari et al. 2020; Prakanrattana and Prapaitrakool 2007; Schrijver et al. 2018; Thanapluetiwong et al. 2021; van den Boogaard et al. 2018; Wang et al. 2012). The risk of bias was low in six trials, moderate in eight trials, and high in one trial. Studies were conducted in various countries with four in the United States, three in The Netherlands, two in Thailand, and one each in China, Egypt, Iran, Japan, South Korea, and Switzerland. In seven of the studies, participants were limited to older adults, and the mean age was ≥65 years in nine of the trials. Six trials had a predominance of men, and two trials had a predominance of women; in the remaining seven trials the proportion of men and women was similar.

Only two trials reported the race or ethnicity of participants and, in both, almost all participants were White. In ten of the trials, the presence of delirium excluded a subject from participation, but five trials did not report whether participants had delirium at baseline. One trial included patients with co-occurring dementia whereas nine trials specifically excluded individuals with dementia or severe dementia.

Eight trials (N=1,979) assessed antipsychotics compared with placebo or no treatment to prevent delirium among post-operative patients (Fukata et al. 2014; Hollinger et al. 2021; Kalisvaart et al. 2005; Khan et al. 2018; Larsen et al. 2010; Mokhtari et al. 2020; Prakanrattana and Prapaitrakool 2007; Wang et al. 2012). Three trials enrolled adults undergoing cardiac, thoracic, or neurological surgeries (1 trial of each) with expected ICU stays (Khan et al. 2018; Mokhtari et al. 2020; Prakanrattana and Prapaitrakool 2007); one enrolled older adults undergoing noncardiac surgeries who were admitted to an ICU (Wang et al. 2012); three enrolled older adults undergoing elective orthopedic or abdominal surgeries (Fukata et al. 2014; Kalisvaart et al. 2005; Larsen et al. 2010); and one enrolled older adults undergoing a variety of elective and emergency surgeries (Hollinger et al. 2021). Haloperidol dosing and route of administration varied widely among the studies. It was given intravenously in three trials (a bolus of 0.5 mg, followed by intravenous (IV) infusion of 0.1 mg/hour for up to 7 days [Wang et al. 2012]; 2.5 mg once daily for 3 days [Fukata et al. 2014], and 5 mcg/kg pre-operatively [Hollinger et al. 2021]) and orally (0.5 mg 3 times a day) in two studies (Kalisvaart et al. 2005; Khan et al. 2018). The study of a single pre-operative dose of haloperidol also had a ketamine arm and a combination (haloperidol/ketamine) arm (Hollinger et al. 2021). Aripiprazole was given as 15 mg orally daily for 7 days in a single study (Mokhtari et al. 2020). Two studies evaluated single doses of second-generation antipsychotics (olanzapine 5 mg pre-operatively and risperidone 1 mg oral disintegrating tablets upon regaining consciousness [Larsen et al. 2010; Prakanrattana and Prapaitrakool 2007]).

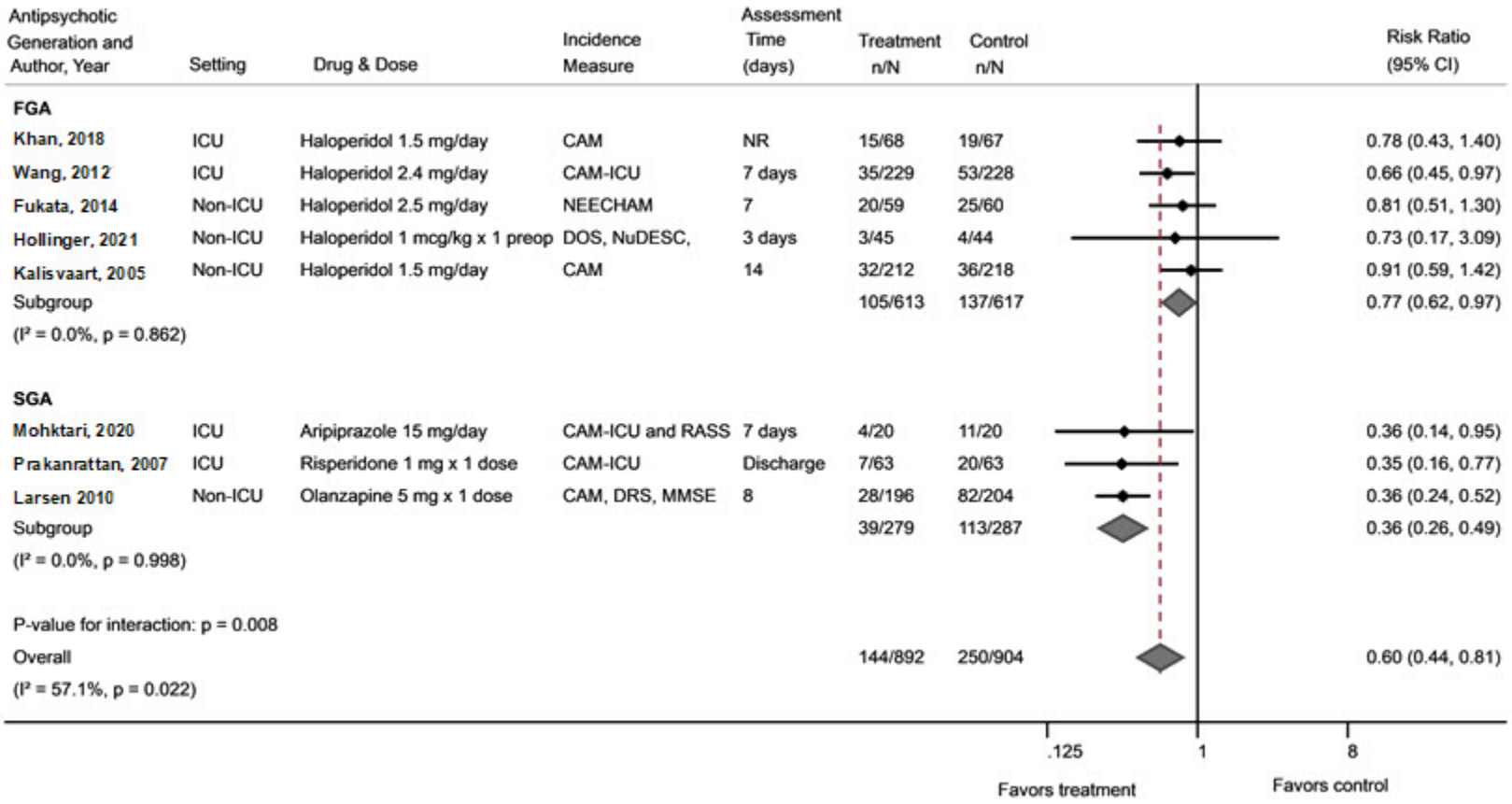
Concerning patients in the ICU, five trials (N=1,673) assessed antipsychotics to prevent delirium (Abdelgalel 2016; Abraham et al. 2021; Al-Qadheeb et al. 2016; Y. Kim et al. 2019; van den Boogaard et al. 2018). One large trial (N=1,439) accounted for 86% of these patients, a study from the Netherlands with low risk of bias that compared 6 mg/day of IV haloperidol with placebo (van den Boogaard et al. 2018). There were two other placebo-controlled trials of IV haloperidol, with disparate doses (2.5 mg bolus if needed, then 12 mg/day to 48 mg/day [Abdelgalel 2016] or 4 mg/day [Al-Qadheeb et al. 2016]). Two small trials (N=106) administered 12.5 mg/day to 25 mg/day of oral quetiapine (Abraham et al. 2021; Y. Kim et al. 2019); one had high risk of bias (N=71 [Abraham et al. 2021]).

Two additional studies examined patients in a general inpatient unit (Schrijver et al. 2018; Thanapluetiwong et al. 2021). One trial with a low risk of bias, conducted in the Netherlands, assessed patients (N=245) ages 70 and older who were at risk for delirium and randomly assigned to haloperidol or placebo 1 mg orally twice daily for a maximum of 14 doses (Schrijver et al. 2018). In the other trial, conducted in Thailand, patients (N=122) ages 65 and older were randomly assigned to quetiapine 12.5 mg or placebo once daily at bedtime for a maximum 7-day duration (Thanapluetiwong et al. 2021).

### Effect of antipsychotic medications on delirium incidence

In a pooled analysis of all eight trials, antipsychotics reduced the incidence of post-operative delirium significantly (N=1,796; 16% vs. 28%, RR 0.60, 95% CI 0.44–0.81, $I^2$=57%), but there was significant heterogeneity in the findings and study designs (see Figure C-6) (Fukata et al. 2014; Hollinger et al. 2021; Khan et al. 2018; Kalisvaart et al. 2005; Larsen et al. 2010; Mohktari et al. 2020; Prakanrattana and Prapaitrakool 2007; Wang et al. 2012). A subgroup analysis by first- versus second-generation drugs was significant (*P*=0.008 for interaction), with the studies of haloperidol showing a smaller, but still significant, reduction in risk (17% vs. 22%, RR 0.77, 95% CI 0.62–0.97, $I^2$=0%) compared with the studies of second-generation drugs (14% vs. 39%, RR 0.36, 95% CI 0.26–0.4, $I^2$=0%). A subgroup analysis of the post-operative setting (ICU vs. non-ICU) was not significant. Delirium-free days were reported in two studies of patients admitted to the ICU post-operatively—one of aripiprazole and one of haloperidol, both given for seven days (Mokhtari et al. 2020; Wang et al. 2012). Neither study reported a difference between antipsychotic and placebo groups on this measure.

Figure C-6. Delirium incidence with antipsychotics in surgical patients post-operatively.




*Abbreviations*. CAM=Confusion Assessment Method; CAM-ICU=Confusion Assessment Method for the Intensive Care Unit; CI=confidence interval; DOS=Delirium Observation Screening; DRS=Delirium Rating Scale; FGA=first-generation antipsychotic; ICU=intensive care unit; MMSE=Mini-Mental State Evaluation; NEECHAM=Neelon-Champagne Confusion Scale; NR=not reported; NuDESC=Nursing Delirium Screening Scale; RASS=Richmond Agitation and Sedation Scale; SGA=second-generation antipsychotic.

*Source*. Fukata et al. 2014; Hollinger et al. 2021; Khan et al. 2018; Kalisvaart et al. 2005; Larsen et al. 2010; Mohktari et al. 2020; Prakanrattan and Prapaitrakool 2007; Wang et al. 2012.

In ICU patients, the five placebo-controlled trials did not show a statistically significant effect of antipsychotic treatment on delirium incidence (34% vs. 36%, RR 0.90, 95% CI 0.69–1.17, $I^2$=38%). Almost all the evidence was about haloperidol (N=1,567). The two small trials of quetiapine (N=106) suggested a decrease in delirium incidence with quetiapine compared with placebo. However, statistical significance was borderline (46% vs. 71%, RR 0.66, 95% CI 0.45–0.98, $I^2$=0%), and incidence in the control groups differed between trials (78% in a study with high risk of bias [Abraham et al. 2021] vs. 55% in a smaller trial with low risk of bias [Y. Kim et al. 2019]).

Among general inpatient populations, no significant difference in the incidence of delirium was noted either with haloperidol (OR 1.43, 95% CI 0.72–2.78 [Schrijver et al. 2018]) or with quetiapine (8.8% vs. 14% at day 7, *P*=0.381 [Thanapluetiwong et al. 2021]) as compared to placebo.

### Effect of antipsychotic medications on delirium duration

Four trials (N=1,085) reported on duration of delirium in post-operative patients who developed it (Fukata et al. 2014; Kalisvaart et al. 2005; Khan et al. 2018; Larsen et al. 2010). Overall, the antipsychotics did not reduce the duration compared with controls (MD 0.35, 95% CI 1.49–0.78, $I^2$=85%), although there is a high degree of heterogeneity in the analysis. One trial reported a large significant benefit with haloperidol (-6.4 days, 95% CI -9.5 to -3.3 days) when measured at 14 days after surgery, whereas the other three measured at 4, 7, and 8 days after surgery and found no effect (Kalisvaart et al. 2005).

Two small trials in ICU patients reported delirium duration and did show a difference with treatment. Delirium episodes for patients given haloperidol (Al-Qadheeb et al. 2016) or quetiapine (Y. Kim et al. 2019) were a day and a half shorter than for those given placebo (MD -1.51 days, 95% CI -2.09 to -0.93, $I^2$=0%).

Among general inpatients, neither haloperidol (median 4 days vs. 3 days, *P*=0.37 [Schrijver et al. 2018]) nor quetiapine (N=13; median 3 days vs. 4 days, *P*=0.557 [Thanapluetiwong et al. 2021]) was associated with a change in the duration of delirium relative to placebo a trial did not find a significant effect of haloperidol on duration.

### Effect of antipsychotic medications on delirium severity

Two trials (N=925) reported on the severity of delirium in post-operative patients, but data were not combinable (Kalisvaart et al. 2005; Larsen et al. 2010). Olanzapine, given as a single pre-operative dose, resulted in a greater total severity score on the DRS-R-98 scale on the first day it was diagnosed (16.4 vs. 14.5, *P*=0.02 [Larsen et al. 2010]). Haloperidol, given orally for up to 6 days post-operatively, resulted in a significantly lower maximum score on the same scale compared with placebo (14.4 vs. 18.4, *P*=0.001 [Kalisvaart et al. 2005]). Although these differences were statistically significant, the absolute differences are small on a 0 to 45 scale.

Among general inpatients, one trial did not find a significant effect of haloperidol on severity of delirium as measured by the DRS-R-98 and Delirium Observation Screening Scale (DOSS) (Schrijver et al. 2018).

### Effect of antipsychotic medications on length of stay

In post-operative patients, the length of stay in the ICU was not different between antipsychotic and placebo groups in four studies (MD -0.07 days, 95% CI -0.17–0.02, $I^2$=0% [Khan et al. 2018; Mokhtari et al. 2020; Prakanrattana and Prapaitrakool 2007; Wang et al. 2012]). A subgroup analysis by antipsychotic generation (2 trials of haloperidol, 1 each of aripiprazole and risperidone) did not show a significant effect. The overall length of hospital stay was also not different between treatment and control groups in four studies, one of risperidone and three of haloperidol (MD -0.61 days, 95% CI -1.77–0.55, $I^2$=50% [Kalisvaart et al. 2005; Khan et al. 2018; Prakanrattana and Prapaitrakool 2007; Wang et al. 2012]). A subgroup analysis by whether the patients were in the ICU or not was not significant.

For non-surgical patients in an ICU setting, three placebo-controlled trials (Abdelgalel 2016; Al-Qadheeb et al. 2016; van den Boogaard et al. 2018) did not show a difference in length of ICU stay with haloperidol (MD -0.08, 95% CI -0.66–0.50, $I^2$=46.5%). Two trials of quetiapine (1 with high risk of bias) were associated with a statistically significant decrease in the length of ICU stay with treatment, and the magnitude of the difference was large (RR -4.2 days, 95% CI -8.3–0.14, $I^2$=19% [Abraham et al. 2021; Y. Kim et al. 2019]). Antipsychotic treatment did not have a statistically significant effect on hospital stay in the four trials reporting it (MD -1.6 days, 95% CI -4.0–0.92, $I^2$=75% [Abdelgalel 2016; Abraham et al. 2021; Y. Kim et al. 2019; van den Boogaard et al. 2018]). The pooled treatment effect showed substantial heterogeneity, which did not improve for haloperidol when it was analyzed separately from quetiapine ($I^2$=88% for the 2 haloperidol trials pooled). However, the two quetiapine trials together showed a large and statistically significant decrease in hospital length of stay with treatment, without statistical heterogeneity (MD -5.6 days, 95% CI -10.63 to -0.59, $I^2$=0%).

Among general inpatients, the overall length of hospital stay did not differ between treatment and placebo groups for either haloperidol (Schrijver et al. 2018) or quetiapine (Thanapluetiwong et al. 2021).

### Effect of antipsychotic medications on mortality and adverse events

Mortality was not reported in six of the seven post-operative trials. A moderate risk of bias study of haloperidol in older patients who had undergone noncardiac surgeries, but were admitted to an ICU, reported that 28-day mortality was slightly greater in the placebo group but not statistically significant (0.9% vs. 2.6%, RR 0.33, 95% CI 0.07–1.6 [Wang et al. 2012]). Although heterogeneously reported, no study found differences between groups on adverse events reported.

Mortality was not affected by antipsychotic treatment in the five ICU trials; 17% of treated patients and 17% of untreated patients died (RR 0.97, 95% CI 0.78–1.20, $I^2$=0%). The largest study reported mortality at 28 days (van den Boogaard et al. 2018), whereas the shorter trials assessed earlier time points (Abraham et al. 2021; Al-Qadheeb et al. 2016; Y. Kim et al. 2019) or did not report assessment time (Abdelgalel 2016). A subgroup analysis based on specific antipsychotic (haloperidol or quetiapine) did not show a significant effect (*P*=0.403 for interaction). The large Dutch trial (N=1,439; van den Boogaard et al. 2018) reported no significant differences between haloperidol and placebo in episodes of QTc prolongation or in six specific extrapyramidal symptoms, although they did not compare an overall measure of adverse events across groups. They reported that only three of their 1,439 patients had a serious adverse event. A smaller placebo-controlled trial of haloperidol found no significant differences

in serious adverse events or withdrawals due to adverse events (Al-Qadheeb et al. 2016), and one of quetiapine (Y. Kim et al. 2019) observed no adverse events in either group.

Among general inpatient populations, no differences in mortality were noted between treatment and placebo groups for either haloperidol (Schrijver et al. 2018) or quetiapine (Thanapluetiwong et al. 2021). In terms of adverse events, rates were comparable for haloperidol and placebo (14% vs. 16%, *P*=0.57 [Schrijver et al. 2018]). In the trial of quetiapine as compared to placebo, no adverse events were reported (Thanapluetiwong et al. 2021).

### Effect of antipsychotic medications on other outcomes

A study of haloperidol in thoracic surgery patients measured cognitive changes using the Repeatable Battery for the Assessment of Neuropsychological Status (Khan et al. 2018). At the first clinic follow-up, only 18 patients of 135 randomized completed the assessment. Patients in the placebo group improved, whereas those in the haloperidol group did not (percentile change scores haloperidol: median 13, IQR 0–24; placebo: median -2, IQR -18–0; *P*=0.05).

Among ICU patients, a study with 68 participants found that haloperidol reduced the percent of hours spent agitated (0% vs. 2%, *P*=0.008), as measured by a SAS of 5 or more (where a SAS score of 1 indicates coma) (Al-Qadheeb et al. 2016). This study also used sedative treatment for all patients, with titration to a SAS score of 3. Another trial (N=35) found no effect of quetiapine on hours spent agitated (6% vs. 5%, *P*=0.54) using a RASS score greater than +2 (where -5 is unarousable [Y. Kim et al. 2019]).

Four of the trials in ICU patients reported rescue medication use, but only one suggested an effect of antipsychotic treatment on its use. The largest study found no difference in number of days and dose of additional open-label haloperidol between patients treated with 6 mg/day scheduled haloperidol and those given placebo (van den Boogaard et al. 2018). Two other trials did not show differences in the use of dexmedetomidine, other sedatives, or non-study antipsychotics between treatment groups (Al-Qadheeb et al. 2016; Y. Kim et al. 2019). The final trial showed lower doses of midazolam and propofol in patients treated with haloperidol than in those given placebo (*P*<0.05) but no statistically significant differences between treatment arms in the number of patients given these drugs (Abdelgalel 2016).

In a general inpatient population, there was no effect of haloperidol as compared to placebo on hospital readmission within 6 months (Schrijver et al. 2018). Furthermore, the large haloperidol trial from the Netherlands (Rood et al. 2019; van den Boogaard et al. 2018) did not show statistically significant differences in ICU readmission.

Quality of life was only assessed in one study and did not show statistically significant differences between patients treated with haloperidol and those given placebo as measured by the SF-36 at 6 months (Rood et al. 2019; van den Boogaard et al. 2018).

### Use of Antipsychotic Medications as a Risk Factor for Delirium

Although delirium risk factors were not part of the scope for the systematic review for this guideline, a targeted search of the recent literature found some studies that assessed pharmacological risk factors for delirium, including prior or in-hospital treatment with antipsychotics. A systematic review and meta-

analysis that included post-surgical, mixed medical/surgical, and ICU populations found haloperidol did not significantly increase the risk of delirium (OR 0.96, 95% CI 0.72–1.28 [Reisinger et al. 2023]). Conversely, several other observational studies of first- and second-generation antipsychotic medications noted an association between use of an antipsychotic and delirium risk in post-surgical (Kang et al. 2019), emergency (Kennedy et al. 2022), and medical/surgical patients (Aloisi et al. 2019) as well as patients with and without dementia (Aloisi et al. 2019). Thus, it is not clear whether antipsychotic medications may contribute to delirium or whether individuals who receive an antipsychotic medication for behavioral issues have previously unrecognized delirium.

### Grading of the Overall Supporting Body of Research Evidence for Use of Antipsychotic Agents in the Prevention or Treatment of Delirium

- Magnitude of effect: Minimal to Low. The magnitude of effect differed with the setting and the outcome. In post-operative patients, there was a benefit of antipsychotic medication in reducing the incidence of delirium but little or no effect on the duration or severity of delirium. In contrast, in ICU patients, there was a small effect on the duration of delirium but no difference in delirium incidence. In general inpatients, there was no effect of antipsychotic on delirium incidence, duration, or severity.

- Risk of bias: Moderate. For individual studies, one had a high risk of bias, eight had a moderate risk of bias and six had a low risk of bias. For studies with a moderate or high risk of bias, they sometimes used an analytic method other than an intent-to-treat analysis or comparable approach. In addition, some studies did not report on the baseline characteristics of the treatment groups or assess for their comparability.

- Applicability: Only five studies were conducted in the United States or Canada with the remaining studies conducted in a wide range of countries. The trials included a mix of ages and included men as well as women; however, most studies did not include information on race or ethnicity. Individuals with dementia were excluded in about half of studies, but the presence of dementia was not reported in many studies. Most studies were done in acute care populations, including post-operative, general medical, and ICU patients with no studies in longer-term care facilities.

- Directness: Direct. The vast majority of studies provided direct information on delirium related outcomes including incidence, severity, and duration.

- Consistency: Inconsistent. A number of the comparisons and outcomes only had information available from one study. However, when information was available from more than one study for a given intervention-control comparison and outcome measure, the findings were inconsistent in different settings and, in some instances, inconsistent within a specific setting of care.

- Precision: Variable. For post-operative patients, delirium incidence, severity, and duration had precise measures; however, for all other settings and outcomes, the measures were imprecise.

- Dose-response relationship: No available information.

- Confounding factors (including likely direction of effect): There was significant variation in the protocols used in these studies, which likely contributed to the heterogeneity of results. The data may be confounded by variations in delirium assessment due to rater training. Individuals with hypoactive delirium may have been less likely to be identified than those with hyperactive delirium and the response to antipsychotic medications or other treatments may differ. However, the direction of effect from these potential confounding factors is not clear.

- Publication bias: Not identified. There was insufficient information to make a determination due to the small number of trials in each treatment setting.

- Overall strength of research evidence: Low to moderate. The strength of research evidence was moderate for the incidence of delirium in ICU settings and in post-operative patients; however, for other settings and outcomes, the strength of research evidence was low.

### *Statement 10 – Benzodiazepines*

APA recommends **(1C)** that benzodiazepines not be used in patients with delirium or who are at risk for delirium, including those with pre-existing cognitive impairment, unless there is a specific indication for their use.

This statement is supported by direct evidence from trials of benzodiazepines in preventing or treating delirium as well as indirect evidence that benzodiazepines may serve as a risk factor for the development of delirium. Benzodiazepines have also been used as a comparison condition in studies of other sedating medications, such as dexmedetomidine. These studies are described further in Appendix C, Statements 10 and 11.

#### Overview of study characteristics

In the studies that examined use of benzodiazepines to prevent delirium, eight RCTs (Aizawa et al. 2002; Hassan et al. 2021; He et al. 2018; Kurhekar et al. 2018; Silva-Jr et al. 2019; Spence et al. 2020; Sultan 2010; Yu et al. 2017) were included from a systematic review (Wang et al. 2023). Studies did not require a DSM or clinical diagnosis of delirium for inclusion, and sample sizes ranged from 40 to 800 participants. All but one of the studies included individuals over age 60, most of the studies involved non-cardiac surgery, and five compared use of a benzodiazepine to dexmedetomidine. There was a predominance of men in three trials and between 40% and 60% women in four trials. One trial did not report information on sex, and none of the trials reported information on race or ethnicity. Two trials excluded patients with delirium at baseline, and one trial excluded patients with dementia; the other trials did not report whether participants had delirium or dementia at baseline.

Three studies were identified that examined use of benzodiazepines to treat delirium (Breitbart et al. 1996; Hui et al. 2017; Yapici et al. 2011). In one study with a moderate risk of bias that was conducted in Turkey, participants had undergone elective coronary artery bypass graft surgery, valve replacement, or both and had failed at least one attempt at extubation (Yapici et al. 2011). Interventions included midazolam (n=34) and dexmedetomidine (n=38). The mean age of the sample was 60 years, and 63% were female. Information on race, ethnicity, or dementia was not reported. In a moderate risk of bias trial conducted in the United States (N=90; analyzed N=58), participants who experienced an episode of

agitation were given a single dose of lorazepam or placebo, in addition to ongoing treatment with haloperidol (Hui et al. 2017). The mean age of participants was 65 years, 47% were female, and 76% were White. In another small study (N=30) in the United States that was limited to inpatients with AIDS, the effects of lorazepam were compared to haloperidol and chlorpromazine (Breitbart et al. 1996). This study had a moderate risk of bias. The mean age of the participants was 39, 23% were female, 57% were Black, and participants with a diagnosis of dementia were excluded.

### Use of Benzodiazepines for the Prevention of Delirium

In its systematic literature review, the Pacific Northwest EPC identified a cluster crossover trial that examined the use of benzodiazepines as a pharmacological approach to the prevention of delirium (Spence et al. 2020). This large Canadian trial (N=800) compared restricted intra-operative benzodiazepine use with liberal intra-operative use in post-operative cardiac surgery patients. Midazolam was the most often administered benzodiazepine. Investigators found no difference in incident delirium (18% vs. 14%, RR 1.24, 95% CI 0.90–1.71), length of ICU stay (median 24 days vs. 24 days, *P*=0.148), hospital stay (median 7 days vs. 7 days, *P*=0.393), or in-hospital mortality (1.2% vs. 1%, *P*=0.801)**.**

A subsequent systematic review assessed effects of benzodiazepines on post-operative delirium and intra-operative awareness (Wang et al. 2023). For the RCTs taken together, there was no significant association of perioperative benzodiazepine use with post-operative delirium (N=1,352; RR 1.43, 95% CI 0.90–2.27, $I^2$=72%, *P*=0.13; very low quality of evidence). In subgroup analysis, the studies that compared benzodiazepines to dexmedetomidine showed worse outcomes with benzodiazepines (RR 1.83, 95% CI 1.24–2.72, $I^2$=13%, *P*=0.002), whereas the other studies showed possible benefits of benzodiazepines in reducing post-operative delirium (*P*=0.02). Among six observational studies that included sufficient data for meta-analysis, perioperative benzodiazepine use appeared to be associated with a greater likelihood of development of delirium (N=3,269; OR 2.93, 95% CI 1.96–4.36, $I^2$ =34%, *P*<0.00001; very low quality of evidence).

### Use of Benzodiazepines for the Treatment of Delirium

In post-operative patients who had undergone elective coronary artery bypass graft surgery, valve replacement or both, dexmedetomidine (0.3–0.7 µg/kg/hour IV) was compared to midazolam (0.05–0.2 mg/kg/hour IV) in effects on delirium and assistance with weaning from mechanical ventilation (Yapici et al. 2011). When assessed at 60 hours after surgery, patients who received dexmedetomidine had significantly lower rates of delirium than patients who received midazolam (2.7% vs. 21%, *P*<0.05).

The Pacific Northwest EPC identified one palliative care trial that treated patients for delirium using benzodiazepines (Hui et al. 2017). Delirium severity, measured by the change in MDAS score from baseline to 8 hours, in agitated patients did not show a statistically significant difference between patients given a single dose of lorazepam or placebo (MD 2.1, 95% CI -1.0–5.2). Mean duration of stay in the palliative care unit was 6 days in each group (*P*=0.35). Overall survival did not differ significantly between lorazepam and placebo (mean 68 hours vs. 73 hours, HR 1.2, 95% CI 0.7–2.2). Changes in specific extrapyramidal symptoms and most adverse events also showed no difference between lorazepam and placebo, although there was no aggregate measure of harms. Drowsiness was greater

with lorazepam. Agitation 8 hours after treatment, measured by a RASS score of 1 to 4, occurred in fewer patients treated with lorazepam than placebo (3.8% vs. 31%, *P*=0.001), and they required less rescue treatment with haloperidol (median 2.0 mg vs. 4.0 mg, *P*=0.009).

In another trial that assessed the effects of 6 days of antipsychotic medication or benzodiazepine in inpatients with AIDS, all six patients who received lorazepam showed no improvement (mean DRS score 18.33 [SD 2.58] at baseline to 17.33 [SD 4.18] on day 2; *P*<0.63) and experienced treatment limiting adverse effects (Breitbart et al. 1996). In contrast, treatment with antipsychotic medication reduced symptoms of delirium from baseline to day 2 (mean 20.45 [SD 3.45] at baseline to 12.45 [SD 5.87], *P*<0.001 for haloperidol; mean 20.62 [SD 3.88] at baseline to 12.08 [SD 6.5], *P*<0.001 for chlorpromazine).

### Use of Benzodiazepines as a Risk Factor for Delirium

Although delirium risk factors were not part of the scope for the systematic review for this guideline, a targeted search of the recent literature found multiple observational and database studies that assessed whether use of benzodiazepines is a risk factor for delirium. Interpretation of such studies is challenging because a benzodiazepine may be prescribed to a patient who is exhibiting behavioral changes due to unrecognized delirium. In addition, benzodiazepines, like alcohol, can have stimulant-like as well as sedative-like effects (Holdstock and de Wit 1998) making it important to consider dose-related and patient-specific variability in responses.

Findings on the effects of benzodiazepines on the incidence of delirium are mixed. A systematic review and meta-analysis of studies that assessed medication-related incident delirium among heterogenous populations (e.g., ICU, surgical, mixed populations) found the use of benzodiazepines had no effect on the development of delirium in four prospective cohort studies (N=1,345; adjusted OR 0.94, 95% CI 0.63–1.41 [Reisinger et al. 2023]). Two studies of surgical patients also showed no association with post-operative delirium. In one large study (N=1,266), midazolam given immediately before surgery did not increase risk of delirium post-operatively (OR 0.91, 95% CI 0.65–1.29, *P*=0.67 [Wang et al. 2021]). Another study of non-cardiac surgery patients in Thailand (N=249) found no association of pre-operative benzodiazepine use with post-operative delirium in a multivariate predictor model (adjusted RR 1.41, 95% CI 0.66–3.01, *P*=0.37 [Iamaroon et al. 2020]). Using data from the 2014 to 2017 National Hospital Ambulatory Medical Care Survey, there were no differences in the use of sedatives, which were primarily benzodiazepines, in patients with and without delirium who were ages 65 and older and visited the emergency department (Kennedy et al. 2022).

In contrast, many other studies do show an association between benzodiazepine use and delirium. For example, in a systematic review, one study of ICU patients (N=520) showed a significant association between benzodiazepines and incident delirium and a dose–response relationship with higher benzodiazepine doses associated with increased delirium risk in 4 studies (3 in ICU populations and 1 in surgical), leading the authors to conclude that benzodiazepines do present a strong risk of increased delirium in ICU settings (Reisinger et al. 2023). Furthermore, a predictive algorithm among ICU patients (H. Zhang et al. 2021) found use of benzodiazepines significantly and independently predicted development of delirium (N=304; OR 4.503, RR 5.503, *P*=0.013). Study authors also observed a

substantially higher rate of benzodiazepine use in patients who were assessed as having delirium versus those who did not (65.2% vs 23.7%) (H. Zhang et al. 2021). Similarly, perioperative use of benzodiazepines in 250 ICU patients more than doubled the risk of delirium (adjusted OR 2.26, *P*=0.029) and was significantly more prevalent in patients with delirium versus without (44.3% vs 19.1%, *P*<0.001 [Chaiwat et al. 2019]). ICU patients treated with midazolam specifically (N=9,348) also had more than double the odds of developing delirium (OR 2.54, 95% CI 2.31–2.79, *P*<0.001) compared with patients not treated with midazolam (Shi et al. 2022). Finally, a multicenter study of 69 ICUs (Pun et al. 2021) reported a 59% higher risk of delirium with benzodiazepine infusion in patients with COVID-19 (OR 1.59, 95% CI 1.33–1.91, *P*<0.0001). In surgical populations (N=32,734), a predictive model found that post-operative benzodiazepine use increased the risk of incident delirium more than threefold (OR 3.52, 95% CI 3.06–4.06, *P*<0.001 [Vacas et al. 2022]). Another study on adults ages 70 and older undergoing major elective surgery (N=560) also found post-operative use of benzodiazepines was associated with an increased risk of delirium (adjusted HR 3.23, 95% CI 2.10–4.99 [Duprey et al. 2022]). In emergency settings, one study found that older adults (75 years and older) who received benzodiazepines prior to being hospitalized (N=472) had a clinically but not statistically significant increase in the risk of incident delirium compared with patients who did not receive benzodiazepines (37.3% vs 6.5%, adjusted OR 3.85, 95% CI 0.77–15.19 [Silva et al. 2021]). In addition, another study of older adults (65 years and older) treated with benzodiazepines in the emergency department (N=7,927) found benzodiazepine use increased the odds of delirium by 1.37 (95% CI 1.13–1.65 [Lee et al. 2022]).

### Grading of the Overall Supporting Body of Research Evidence for Use of Benzodiazepines in the Prevention or Treatment of Delirium

- Magnitude of effect: Minimal to low. Although findings are mixed, most analyses suggest that benzodiazepines are associated either with no benefit or with slightly worse outcomes related to delirium.

- Risk of bias: Moderate to high. Factors that tended to contribute to the moderate to high risk of bias included inadequate or poorly described procedures for randomization and masking as well as potential for selective reporting.

- Applicability: Studies were predominantly conducted in older patients. Many studies did not include sufficient detail to determine whether the study demographic characteristics were representative of usual clinical populations. Most studies were done in acute care populations, particularly post-operative patients, which limits the generalizability of results.

- Directness: Direct. The studies provided direct information on delirium related outcomes including incidence and severity.

- Consistency: Inconsistent. A number of the comparisons and outcomes only had information available from one study. However, when information was available from more than one study, the findings were inconsistent.

- Precision: Imprecise. Confidence intervals were wide and sample sizes were small for virtually all of the comparisons, yielding significant imprecision in terms of optimal information sizes.

- Dose-response relationship: No available information.

- Confounding factors (including likely direction of effect): There was significant variation in the protocols used in these studies, which likely contributed to the heterogeneity of results. The data may be confounded by variations in delirium assessment due to rater training. Individuals with hypoactive delirium may have been less likely to be identified than those with hyperactive delirium and the response to benzodiazepines or other treatments may differ. However, the direction of effect from these potential confounding factors is not clear.

- Publication bias: Not identified. There was no evidence of publication bias in studies that examined the incidence of delirium. There was insufficient information to make a determination due to the small number of trials in each treatment setting for other outcome measures.

- Overall strength of research evidence: Low. The strength of research evidence was low due to the small number of studies, the lack of consistency in the findings, and the significant risk of bias in many of the studies.

### *Statement 11 – Dexmedetomidine to Prevent Delirium*

APA suggests **(2B)** that dexmedetomidine be used rather than other sedating agents to prevent delirium in patients who are undergoing major surgery or receiving mechanical ventilation in a critical care setting.

The Pacific Northwest EPC conducted a systematic literature review of pharmacological preventions for delirium that involved the use of dexmedetomidine. Evidence consistently pointed to a significant reduction in incident delirium with dexmedetomidine in both post-surgical and ICU populations.

#### Overview of study characteristics

In post-surgical patients, 42 trials (N=9,184) assessed dexmedetomidine to prevent delirium in the post-operative period (Chang et al. 2018; Chen et al. 2021; Djaiani et al. 2016; Hassan et al. 2021; He et al. 2018; Hu et al. 2020; Huyan et al. 2019; J.A. Kim et al. 2019; Lee et al. 2018, 2019; X. Li et al. 2017; Li et al. 2020; Likhvantsev et al. 2021; X. Liu et al. 2016; Y. Liu et al. 2016; Maldonado et al. 2009; Massoumi et al. 2019; Mei et al. 2018; B. Mei et al., 2020; Momeni et al. 2021; Park et al. 2014; Shehabi et al. 2009; Sheikh et al. 2018; Shi et al. 2019, 2020; Shokri and Ali 2020; Shu et al. 2017; Soh et al. 2020; Su et al. 2016; Sun et al. 2019; Susheela et al. 2017; Tang et al. 2018; C. Tang et al. 2020; Turan et al. 2020; van Norden et al. 2021; Wu et al. 2016; Xin et al. 2021; Xuan et al. 2018; Yang et al. 2015; Yu et al. 2017; Zhang et al. 2020; Zhao et al. 2020). In four trials, dexmedetomidine was given prior to surgery (He et al. 2018; Huyan et al. 2019; J.A. Kim et al. 2019; Shu et al. 2017) and was continued during surgery in three of those trials (Huyan et al. 2019; J.A. Kim et al. 2019; Shu et al. 2017). In two trials, dexmedetomidine was given prior to surgery and continued both during the surgery and after the surgery (Hassan et al. 2021; Zhao et al. 2020). In eight trials, dexmedetomidine was begun during surgery and continued during the post-operative period (Lee et al. 2019; X. Li et al. 2017; Likhvantsev et al. 2021; Soh et al. 2020; C. Tang et al. 2020; Turan et al. 2020; van Norden et al. 2021; Yang et al. 2015). In the remaining trials, dexmedetomidine was given either during surgery (Chen et al. 2021; Djaiani et al. 2016; Hu et al. 2020; Lee et al. 2018; Li et al. 2020; Y. Liu et al. 2016; Mei et al. 2018; B. Mei et al. 2020; Sheikh et al.

2018; Shi et al. 2019, 2020; Tang et al. 2018; Xin et al. 2021; Yu et al. 2017; Zhang et al. 2020) or was limited to the post-operative period (Chang et al. 2018; X. Liu et al. 2016; Maldonado et al. 2009; Massoumi et al. 2019; Momeni et al. 2021; Park et al. 2014; Shehabi et al. 2009; Shokri and Ali 2020; Su et al. 2016; Sun et al. 2019; Susheela et al. 2017; Wu et al. 2016; Xuan et al. 2018).

28 trials compared dexmedetomidine with normal saline or usual care (Chen et al. 2021; He et al. 2018; Hu et al. 2020; Huyan et al. 2019; J.A. Kim et al. 2019; Lee et al. 2018, 2019; X. Li et al. 2017; Li et al. 2020; Likhvantsev et al. 2021; Y. Liu et al. 2016; Massoumi et al. 2019; Momeni et al. 2021; Shi et al. 2019, 2020; Shu et al. 2017; Soh et al. 2020; Su et al. 2016; Sun et al. 2019; Tang et al. 2018; C. Tang et al. 2020; Turan et al. 2020; van Norden et al. 2021; Wu et al. 2016; Xin et al. 2021; Xuan et al. 2018; Yang et al. 2015; Zhang et al. 2020; Zhao et al. 2020), and 16 trials made head-to-head comparisons between dexmedetomidine and another medication such as propofol or midazolam (Chang et al. 2018; Djaiani et al. 2016; Hassan et al. 2021; He et al. 2018; Lee et al. 2018; X. Liu et al. 2016; Maldonado et al. 2009; Mei et al. 2018; B. Mei et al. 2020; Park et al. 2014; Shehabi et al. 2009; Sheikh et al. 2018; Shokri and Ali 2020; Susheela et al. 2017; C. Tang et al. 2020; Yu et al. 2017). Two trials included both a placebo and an active intervention arm that was compared with dexmedetomidine (He et al. 2018; Lee et al. 2018). Cardiac surgery was performed in 17 trials (Djaiani et al. 2016; Hassan et al. 2021; X. Li et al. 2017; Likhvantsev et al. 2021; X. Liu et al. 2016; Maldonado et al. 2009; Massoumi et al. 2019; Momeni et al. 2021; Park et al. 2014; Shehabi et al. 2009; Sheikh et al. 2018; Shi et al. 2019; Shokri and Ali 2020; Shu et al. 2017; Susheela et al. 2017; Turan et al. 2020; van Norden et al. 2021), orthopedic surgery in five trials (Y. Liu et al. 2016; Mei et al. 2018; B. Mei et al. 2020; Xuan et al. 2018; Zhang et al. 2020), and the remaining trials enrolled participants having noncardiac, nonorthopedic major surgery.

Of the 27 studies in post-surgical patients that compared dexmedetomidine to normal saline or usual care, sample sizes ranged from 60 to 798 with 6,642 participants overall. There was a low risk of bias in 13 studies and a moderate risk of bias in 14 studies. Most of these studies were conducted in China (16), with four in South Korea, two in the United States, and one each in Belgium, Germany, Iran, Russia, and Taiwan. In 16 of the studies, the sample was limited to older adults whereas in the other 11 studies the sample included adults of all ages. Mean age was reported in 25 studies and was 65 years or greater in 16 of the studies. There was a predominance of men in 10 trials, a predominance of women in three trials, and between 40% and 60% women in 13 trials. One trial did not report information on the sex of participants. In the single trial that reported race or ethnicity, 92% of participants were White. Five trials excluded patients with delirium at baseline, but the other 22 trials did not report whether participants had delirium at baseline. Thirteen trials excluded patients with dementia; the remaining 14 trials did not report on dementia status.

Of the 18 studies in post-surgical patients that compared dexmedetomidine to another active intervention, sample sizes ranged from 12 to 432 with 3,262 participants overall. There was a low risk of bias in three studies whereas 14 studies had a moderate risk of bias and one had a high risk of bias. Studies were conducted in various countries with six done in China, three in the United States, two in Egypt, two in South Korea, and one each in Australia, Canada, India, Pakistan, and Taiwan. In 11 of the studies, the sample was limited to older adults whereas in the other seven studies the sample included adults of all ages. Mean age was reported in 17 studies and was 65 years or greater in 10 of the studies.

There was a predominance of men in five trials and between 40% and 60% women in 11 trials. Two trials did not report information on the sex of participants. None of the trials reported information on race or ethnicity. Four trials excluded patients with delirium at baseline, but the other 14 trials did not report whether participants had delirium at baseline. Nine trials excluded patients with dementia; the remaining nine trials did not report on dementia status.

In ICU patients, the Pacific Northwest EPC identified nine trials (N=1,559) of dexmedetomidine to prevent delirium (Abdelgalel 2016; Jakob et al. 2012; Li et al. 2019; MacLaren et al. 2015; Ruokonen et al. 2009; Shu et al. 2019; Skrobik et al. 2018; Winings et al. 2021). One publication (Jakob et al. 2012) included two distinct trials—the PRODEX trial comparing dexmedetomidine with the anesthetic propofol, and MIDEX comparing it with midazolam, a benzodiazepine. PRODEX and MIDEX together accounted for most of the dexmedetomidine patients (N=998, 70%). One trial included both haloperidol as an active comparator and a third group given placebo (Abdelgalel 2016). Another compared treatment only with placebo (Skrobik et al. 2018), and the other three used midazolam or propofol as comparators (Li et al. 2019; MacLaren et al. 2015; Shu et al. 2019). A tenth study, with a high risk of bias, compared midazolam and propofol in 120 patients on mechanical ventilation (Chen 2020). In most studies, all patients were on mechanical ventilation, with two trials that included a mix of patients who were and were not mechanically ventilated (Li et al. 2019; Skrobik et al. 2018). Studies with placebo arms did allow use of nonstudy sedative medications.

Of the nine studies of dexmedetomidine in ICU patients, there was a low risk of bias in three studies and a moderate risk of bias in six. Studies were conducted in various countries with two done in China, two in the United States, two in Europe (one of which included Russia) and one each in Egypt, Canada, and Finland. In one of the studies, the sample was limited to older adults whereas in seven studies the sample included adults of all ages. Mean age was reported in seven studies and was 65 years or greater in three of the studies. There was a predominance of men in seven trials and between 40% and 60% women in two trials. None of the trials reported information on race or ethnicity. One trial excluded patients with delirium at baseline and three trials excluded patients with dementia; the other trials did not report whether participants had delirium or dementia at baseline.

### Effect of dexmedetomidine on delirium incidence

In post-surgical patients, there was a significant reduction in incident delirium with dexmedetomidine that was maintained even when looking only at noncardiac surgery populations and at dexmedetomidine administration either during or after surgery. Head-to-head comparisons with specific medications (e.g., haloperidol, propofol, midazolam, clonidine, opioids) generally also revealed a lower incidence with dexmedetomidine in post-surgical and ICU populations.

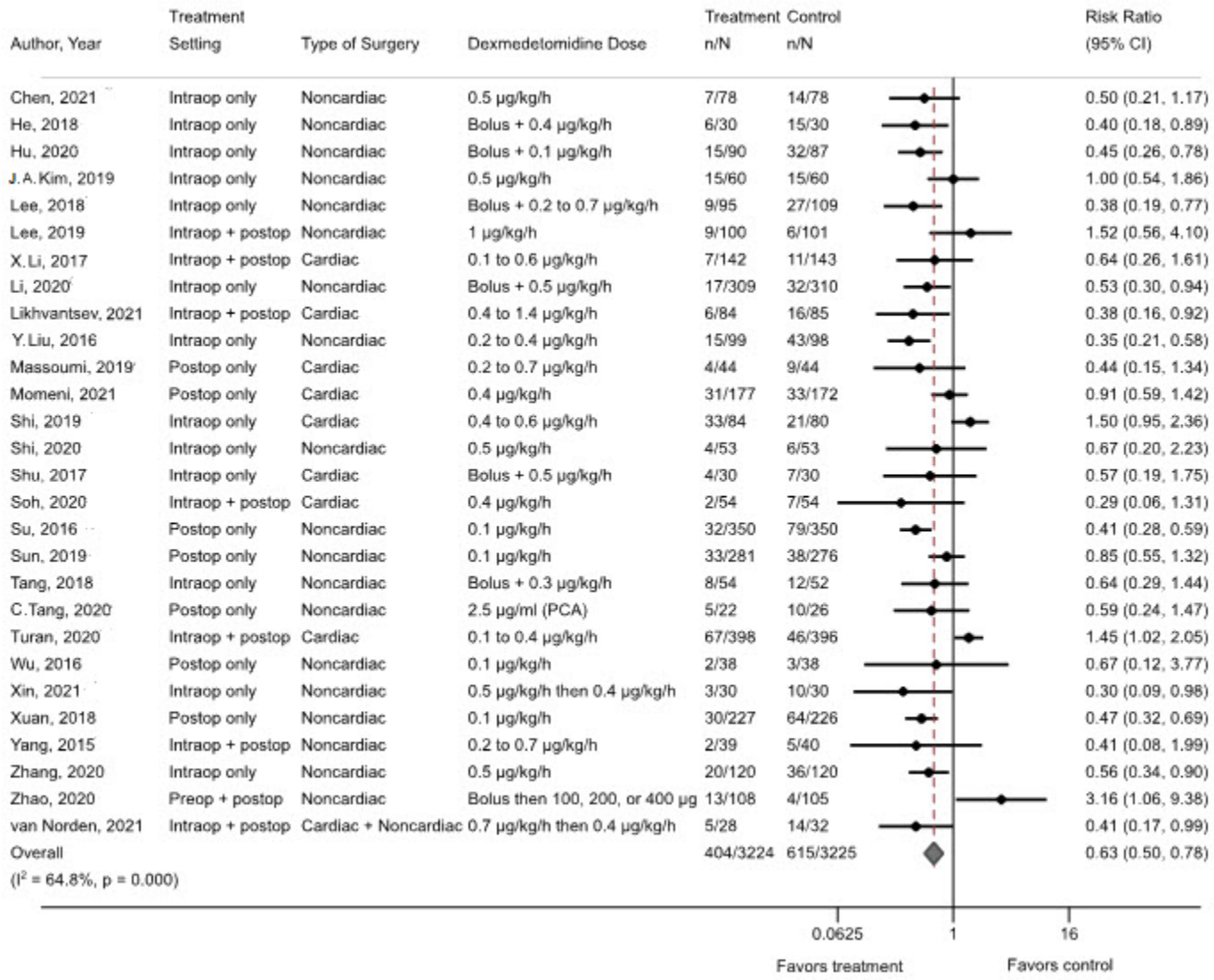
Regarding incidence of delirium in post-surgical patients, the pooled analysis of dexmedetomidine versus saline or usual care favored dexmedetomidine in the prevention of delirium (28 trials, N=6,449; 12.5% vs. 19.1%, RR 0.63, 95% CI 0.50–0.78, $I^2$=64.8%) (see Figure C-7)[1]. The effect of dexmedetomidine

[1] Pooled analysis conducted as part of the Pacific Northwest Evidence-Based Practice Center's systematic review included two studies (Shi et al. 2019; Sun et al. 2019) that were subsequently retracted.

was also significant when trials limited enrollment to noncardiac patients (19 trials, N=4,372; 11.2% vs. 20.6%, RR 0.56, 95% CI 0.46–0.69, $I^2$=42.3%) and when administration of dexmedetomidine was limited to either intra-operative or post-operative administration only (13 trials, N=2,269, 13.8% vs. 23.7%, RR 0.57, 95% CI 0.42–0.76, $I^2$=57.2%; 7 trials, N=2,271, 12.0% vs. 20.8%, RR 0.68, 95% CI 0.47–0.99, $I^2$=49.2%, respectively). One trial (N=346), not included in the pooled analysis due to lack of reporting overall incidence data, reported a lower incidence of delirium with dexmedetomidine on post-operative days 1 through 5 ($P$<0.05 each day) versus normal saline with no incident delirium on post-operative days 6 and 7 (Huyan et al. 2019).

Two trials compared dexmedetomidine with placebo in ICU patients (1 also including a comparison with haloperidol as discussed in the Overview of Study Characteristics section [Abdelgalel 2016]). Delirium incidence was significantly lower with treatment, and the magnitude of effect was large (16% vs. 45%, RR 0.38, 95% CI 0.22–0.65, $I^2$=0% [Abdelgalel 2016; Skrobik et al. 2018]).

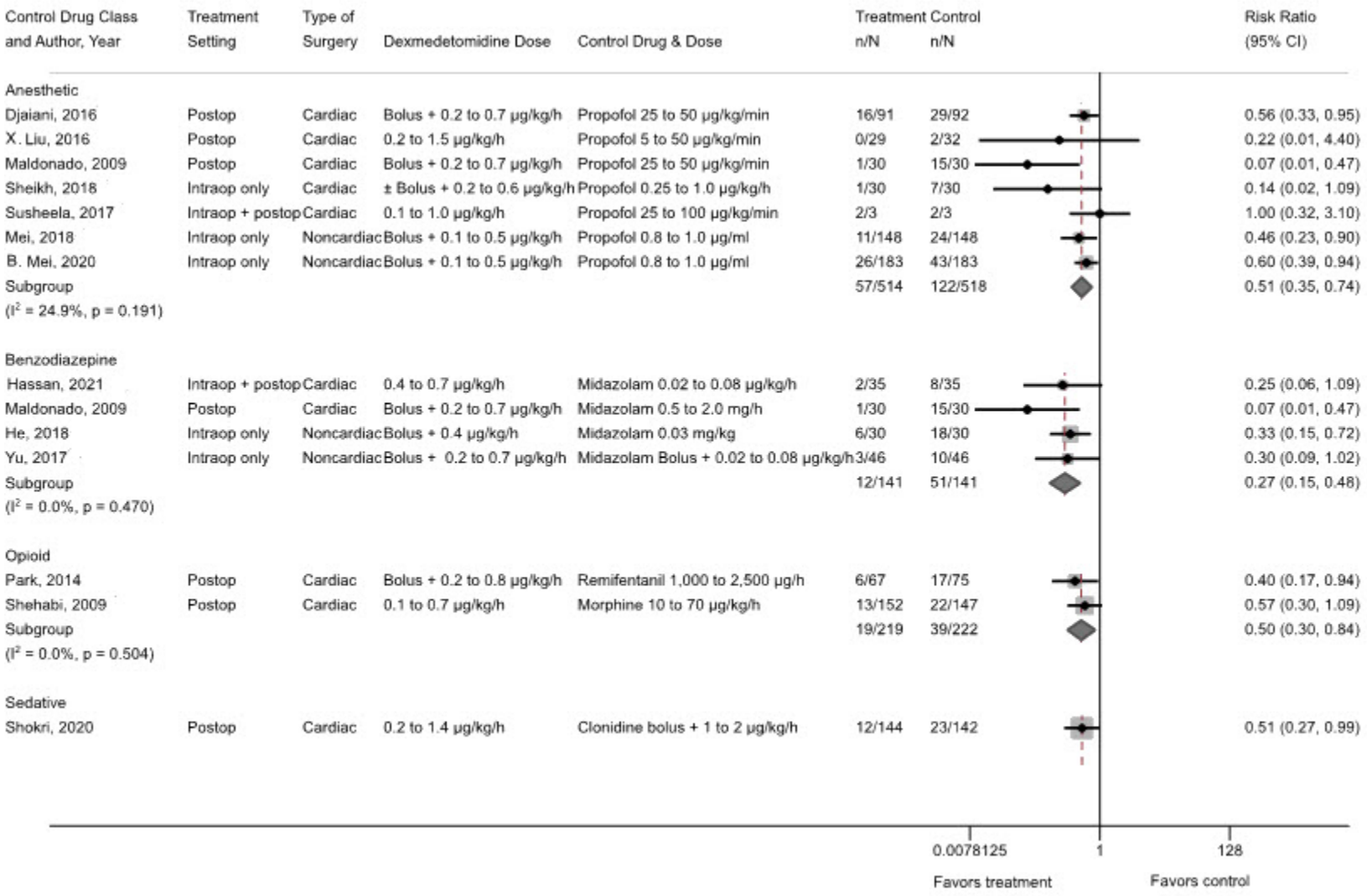
2344 Figure C-7. Delirium incidence with dexmedetomidine versus usual care or normal saline in surgical patients post-operatively.



*Note.* Pooled analysis conducted as part of the Pacific Northwest Evidence-Based Practice Center's systematic review included two studies (Shi et al. 2019; Sun et al. 2019) that were subsequently retracted.
*Abbreviations*. CI=confidence interval; h=hour; intraop=intra-operative; n/N=number; PCA=patient-controlled anesthesia; postop=post-operative.
*Source*. Chen et al. 2021; He et al. 2018; Hu et al. 2020; J.A. Kim et al. 2019; Lee et al. 2018, 2019; X. Li et al. 2017; Li et al. 2020; Likhvantsev et al. 2021; Y. Liu et al. 2016; Massoumi et al. 2019; Momeni et al. 2021; Shi et al. 2019, 2020; Shu et al. 2017; Soh et al. 2020; Su et al. 2016; Sun et al. 2019; Tang et al. 2018; C. Tang et al. 2020; Turan et al. 2020; van Norden et al. 2021; Wu et al. 2016; Xin et al. 2021; Xuan et al. 2018; Yang et al. 2015; Zhang et al. 2020; Zhao et al. 2020.

In head-to-head trials in post-operative patients (see Figure C-8), treatment with dexmedetomidine resulted in a significantly lower incidence of delirium than propofol when added to each trial's standard anesthesia medications (7 studies, N=1,032; 11.1% vs. 23.6%, RR 0.51, 95% CI 0.35–0.74, $I^2$=25% [Djaiani et al. 2016; X. Liu et al. 2016; Maldonado et al. 2009; Mei et al. 2018; B. Mei et al. 2020; Sheikh et al. 2018; Susheela et al. 2017]), midazolam (4 trials, N=282; 8.5% vs. 36.2%, RR 0.27, 95% CI 0.15–0.48, $I^2$=0% [Hassan et al. 2021; He et al. 2018; Maldonado et al. 2009; Yu et al. 2017]), an opioid (2 studies, N=441; 10.2% vs. 23%, RR 0.50, 95% CI, 0.30–0.84, $I^2$=0% [Park et al. 2014; Shehabi et al. 2009]), or clonidine (1 study, N=286; 8.3% vs. 16.2%, RR 0.51, 95% CI 0.27–0.99 [Shokri and Ali 2020]).

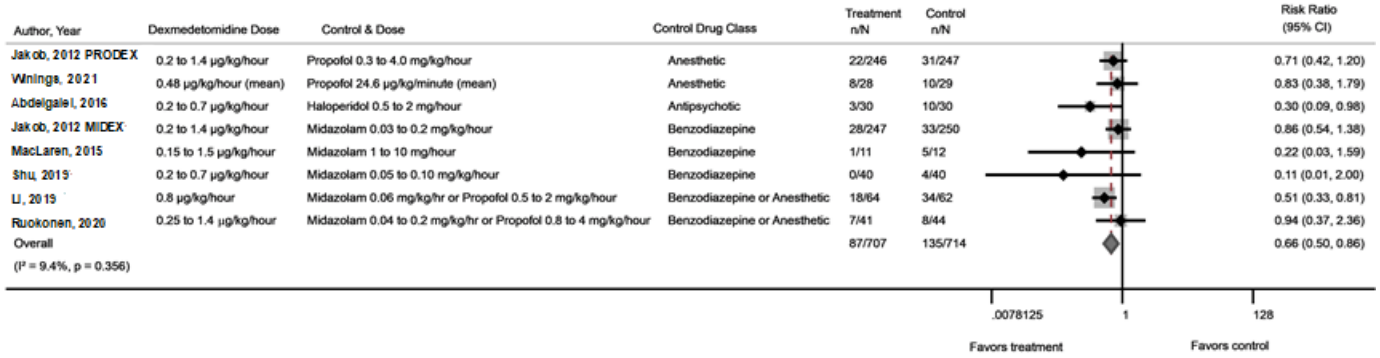
Figure C-8. Delirium incidence with dexmedetomidine versus propofol, midazolam, and opioids in surgical patients post-operatively.



*Abbreviations*. CI=confidence interval; h=hour; intraop=intra-operative; min=minute; n/N=number; postop=post-operative.
*Source*. Djaiani et al. 2016; Hassan et al. 2021; He et al. 2018; X. Liu et al. 2016; Maldonado et al. 2009; Mei et al. 2018; B. Mei et al. 2020; Park et al. 2014; Shehabi et al. 2009; Sheikh et al. 2018; Shokri and Ali 2020; Susheela et al. 2017; Yu et al. 2017.

Head-to-head comparisons in eight trials in ICU patients (see Figure C-9) showed a significantly lower incidence of delirium with dexmedetomidine treatment, with a moderate magnitude of effect (12% vs. 19%, RR 0.66, 95% CI 0.50–0.86, $I^2$=9.4% [Abdelgalel 2016; Jakob et al. 2012; Li et al. 2019; MacLaren et al. 2015; Ruokonen et al. 2009; Shu et al. 2019; Winings et al. 2021]). The specific comparator, whether haloperidol, midazolam, or propofol, did not have a statistically significant effect on this result (*P*=0.51 for interaction). Only two relatively small individual studies showed a significant difference between medications, one of haloperidol (Abdelgalel 2016) and the other of midazolam (Li et al. 2019). The study comparing sedation with midazolam and propofol did not show a significant difference in delirium incidence between the medications (17% vs. 13%, *P*=0.61 [Chen 2020]).

Figure C-9. Delirium incidence with dexmedetomidine versus other drugs in intensive care unit patients.




*Abbreviations*. CI=confidence interval; MIDEX=midazolam vs. dexmedetomidine; PRODEX=propofol vs. dexmedetomidine.
*Source*. Abdelgalel 2016; Jakob et al. 2012; Li et al. 2019; MacLaren et al. 2015; Ruokonen et al. 2009; Shu et al. 2019; Winings et al. 2021.

### Effect of dexmedetomidine on delirium duration

Among post-operative patients who developed delirium, the use of dexmedetomidine was associated with a shorter duration of symptoms compared with no dexmedetomidine (7 trials, N=240; MD -0.44 days, 95% CI -0.80 to -0.08, $I^2$=42.9%). There was no indication of publication bias based on funnel plot analysis. In one placebo-controlled trial of dexmedetomidine in ICU patients, the duration of patients' first delirium episode was similar with or without dexmedetomidine (median 2.0 days vs. 2.2 days, *P*=0.73 [Skrobik et al. 2018]).

In head-to-head trials in post-operative patients, a pooled analysis found a significantly shorter duration of delirium with dexmedetomidine than with propofol (2 trials, N=105; MD -0.78 days, 95% CI -1.30 to -0.26, $I^2$=0% [Djaiani et al. 2016; Maldonado et al. 2009]). In a single study each, dexmedetomidine also resulted in significantly shorter delirium duration than midazolam (N=60; MD -3.40 days, 95% CI -6.74 to -0.06 [Maldonado et al. 2009]) and clonidine (N=35; MD -2.31, 95% CI -2.79 to -1.83 [Shokri and Ali 2020]). However, a pooled analysis of two trials that compared dexmedetomidine versus the opioids remifentanil (N=23 [Park et al. 2014]) and morphine (N=35 [Shehabi et al. 2009]) did not find a significant difference in duration of delirium between the medications (MD 0.88 days, 95% CI -2.17–3.93, $I^2$=40%).

### Effect of dexmedetomidine on delirium severity

The vast majority of studies in post-operative or ICU patients did not report information on the severity of delirium. One study assessed the severity of delirium using the Intensive Care Delirium Screening Checklist (ICDSC) and found no difference in maximum scores in post-operative patients treated with dexmedetomidine as compared to usual care (*P*=0.24 [Likhvantsev et al. 2021]).

### Effect of dexmedetomidine on length of stay

Dexmedetomidine tended to be associated with shorter length of stay in the ICU and the hospital in post-operative patients, although in ICU patients, this effect was mixed. For example, a large, significant decrease in ICU length of stay was observed when compared with haloperidol, but outcomes were inconsistent when comparing dexmedetomidine with propofol or midazolam.

A pooled analysis of 13 trials (N=3,685)[2] in post-operative patients showed that dexmedetomidine resulted in a significant but very small difference in ICU stays (1.9 hours) compared with usual care or normal saline (MD -0.08 days, 95% CI, -0.13 to -0.02, $I^2$=69.1% [Chen et al. 2021; Lee et al. 2019; X. Li et al. 2017; Li et al. 2020; Likhvantsev et al. 2021; Massoumi et al. 2019; Momeni et al. 2021; Shi et al. 2019; Soh et al. 2020; Su et al. 2016; Turan et al. 2020; van Norden et al. 2021; Wu et al. 2016]). A subgroup analysis by the timing of the intervention (i.e., post-operative vs. intra-operative) or type of surgery (cardiac vs. noncardiac) did not explain the statistical heterogeneity. However, heterogeneity was greatest in the pooled analysis of cardiac trials ($I^2$=81.9%) based on the subgroup analysis. A pooled analysis of 15 trials[3] in post-operative patients found significantly shorter hospital stay with

[2] Pooled analysis conducted as part of the Pacific Northwest Evidence-Based Practice Center's systematic review included one study (Shi et al. 2019) that was subsequently retracted.
[3] Pooled analysis conducted as part of the Pacific Northwest Evidence-Based Practice Center's systematic review included two studies (Shi et al. 2019; Sun et al. 2019) that were subsequently retracted.

dexmedetomidine than with usual care or normal saline (N=5,053; MD -0.96 days, 95% CI -1.56 to -0.37, $I^2$=95.4% [Chen et al. 2021; Huyan et al. 2019; Lee et al. 2019; X. Li et al. 2017; Li et al. 2020; Likhvantsev et al. 2021; Momeni et al. 2021; Shi et al. 2019; Soh et al. 2020; Su et al. 2016; Sun et al. 2019; Turan et al. 2020; van Norden et al. 2021; Wu et al. 2016; Xuan et al. 2018]). Stratified analyses by the timing of the intervention and by surgery type did not explain the statistical heterogeneity.

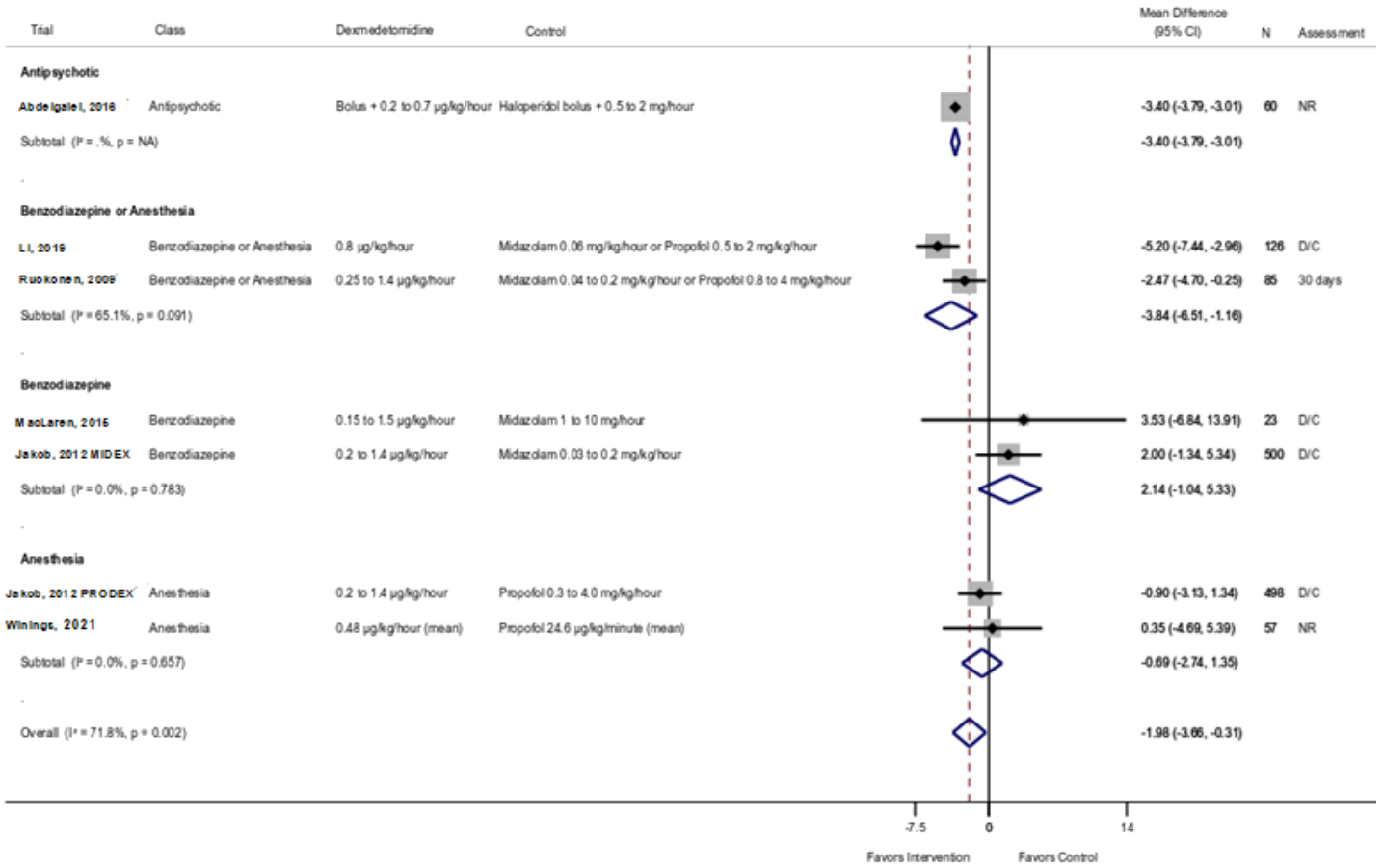
A pooled analysis of three trials of dexmedetomidine versus propofol in post-operative patients found shorter ICU stays with dexmedetomidine (N=303; MD -2.93 days, 95% CI -5.36 to -0.51, $I^2$=94% [Djaiani et al. 2016; Maldonado et al. 2009; Sheikh et al. 2018]). ICU stays were also shorter with dexmedetomidine compared with clonidine (N=286; MD -0.30, 95% CI -0.42 to -0.18) based on a single trial in cardiac surgery (Shokri and Ali 2020). When dexmedetomidine was compared with the opioids, remifentanil (Park et al. 2014) or morphine (Shehabi et al. 2009), the differences were very small and not significantly different (N=441; MD 0.11 days, 95% CI -0.23–0.46, $I^2$=46%). There was also no difference in length of ICU stay between post-operative dexmedetomidine and midazolam based on one cardiac surgery trial (N=60; MD -1.10 days, 95% CI -2.22–0.02 [Maldonado et al. 2009]).

The difference in pooled length of hospital stay in post-operative patients was large and favored dexmedetomidine versus propofol (N=605; MD -3.14 days, 95% CI -8.95 to -0.30, $I^2$=95% [Chang et al. 2018; Djaiani et al. 2016; Maldonado et al. 2009; Mei et al. 2018; Susheela et al. 2017]). As with the finding for ICU length of stay, a pooled analysis of the two opioid trials found a very small, non-significant difference in hospital stay compared with dexmedetomidine (N=441; MD 0.06 days, 95% CI -0.60–0.73, $I^2$=0% [Park et al. 2014; Shehabi et al. 2009]). There was also no difference between dexmedetomidine and midazolam on hospital stay based on one small trial (N=60; MD -1.80 days, 95% CI -3.61–0.01). One small trial also compared dexmedetomidine plus IV acetaminophen with propofol plus IV acetaminophen, and although the absolute difference in length of hospital stay was large, it was not statistically significant (N=12; 10.33 days vs. 5.33 days, $P$>0.05 [Susheela et al. 2017]).

All nine trials of dexmedetomidine in non-post-operative ICU patients reported ICU length of stay. Compared with other medications (antipsychotic, benzodiazepine, or anesthetic), dexmedetomidine was associated with shorter ICU stays; however, the magnitude of effect was small, and statistical heterogeneity was high (7 trials; MD -1.98 days, 95% CI -3.66–0.31, $I^2$=72%) (see Figure C-10). However, separating these analyses by comparator medication resulted in different findings depending on which medication was being compared with dexmedetomidine. There was a large, significant decrease in ICU length of stay with dexmedetomidine compared with haloperidol in a low risk of bias study of 60 patients (MD -3.40 days, 95% CI -3.79 to -3.01 [Abdelgalel 2016]). Comparisons of dexmedetomidine with propofol or midazolam resulted in different findings, depending on study size and risk of bias. In two smaller trials (N=211) with moderate risk of bias, comparing dexmedetomidine with either propofol or midazolam, dexmedetomidine showed a large, significant benefit (MD -3.84 days, 95% CI -6.51 to -1.16 [Li et al. 2019; Ruokonen et al. 2009]). However, the larger PRODEX and MIDEX trials (N=998) with low risk of bias (Jakob et al. 2012), and two additional trials (MacLaren et al. 2015; Winings et al. 2021) did not show statistically significant differences between dexmedetomidine and midazolam (MD 2.14 days, 95% CI -1.04–5.33) or propofol (MD -0.69, 95% CI -2.74–1.35). The two placebo-controlled trials (Abdelgalel 2016; Skrobik et al. 2018) suggested a moderate decrease in ICU stay with dexmedetomidine

treatment, but the difference was not statistically significant (MD -2.02, 95% CI -6.56–2.53). A trial comparing midazolam to propofol found that ICU length of stay was similar between groups (5.7 days vs 5.6 days, *P*=0.75 [Chen 2020]).

2454 Figure C-10. Length of intensive care unit stay with dexmedetomidine versus other drugs in intensive care unit patients.




2455 *Abbreviations*. CI=confidence interval; D/C=discharge; NA=not applicable; NR=not reported.
2456 *Source*. Abdelgalel 2016; Jakob et al. 2012; Li et al. 2019; MacLaren et al. 2015; Ruokonen et al. 2009; Winings et al. 2021.

For hospital length of stay, the PRODEX and MIDEX trials found no difference between dexmedetomidine and either midazolam or propofol (Jakob et al. 2012). In PRODEX, patients given dexmedetomidine stayed for a median 25 days compared with 28 days for propofol (*P*=0.76), whereas in MIDEX it was 35 days for dexmedetomidine and 27 days for midazolam (*P*=0.37). A small trial with high risk of bias showed no difference in hospital stays between dexmedetomidine and propofol (18 days vs. 17 days, *P*=0.63 [Winings et al. 2021]). Another small trial with low risk of bias found shorter hospital stays with dexmedetomidine than with haloperidol (6.2 days vs. 13.5 days, *P*<0.001 [Abdelgalel 2016]). The placebo-controlled trials (both with low risk of bias) had conflicting findings, with one reporting a statistically significant decrease in hospital stay with dexmedetomidine treatment (N=60; mean 6.2 days vs. 15.5 days, *P*<0.05 [Abdelgalel 2016]), whereas another reported no difference (N=100; median 27 days vs. 29 days, *P*=0.48 [Skrobik et al. 2018]).

### Effect of dexmedetomidine on mortality and adverse events

Mortality outcomes did not differ based on administration of dexmedetomidine versus placebo or a medication comparator.

Regarding mortality in post-surgical populations, a pooled analysis[4] indicated that mortality was not affected by dexmedetomidine when compared with normal saline (12 trials, N=4,107; 0.9% vs. 2.0%, RR 0.59, 95% CI 0.33–1.03, $I^2$=0% [Chen et al. 2021; Lee et al. 2019; X. Li et al. 2017; Li et al. 2020; Likhvantsev et al. 2021; Massoumi et al. 2019; Momeni et al. 2021; Soh et al. 2020; Su et al. 2016; Sun et al. 2019; Turan et al. 2020; van Norden et al. 2021]), propofol (2 trials, N=479; 0.8% vs. 0.4%, RR 1.61, 95% CI 0.20–12.98, $I^2$=0% [Djaiani et al. 2016; Mei et al. 2018]), an opioid (1 trial, N=299; 1.3% vs. 2.7%, RR 0.48, 95% CI 0.09–2.60 [Shehabi et al. 2009]), or clonidine (1 trial, N=286; 1.4% vs. 5.6%, RR 0.25, 95% CI 0.05–1.14 [Shokri and Ali 2020]).

In ICU patients, mortality across seven trials also did not differ between dexmedetomidine and other treatments (20% vs. 18%, RR 1.12, 95% CI 0.89–1.39, $I^2$=0%), and the specific medication comparison did not affect this finding (*P*=0.62 for interaction [Abdelgalel 2016; Jakob et al. 2012; Li et al. 2019; MacLaren et al. 2015; Ruokonen et al. 2009; Winings et al. 2021]). Results were similar for dexmedetomidine compared with placebo (19% vs. 18%, RR 1.09, 95% CI 0.57–2.08, $I^2$=0% [Abdelgalel 2016; Skrobik et al. 2018]).

In terms of other adverse events in post-operative patients, dexmedetomidine as compared with normal saline was associated with an increased risk of hypotension requiring treatment (10 trials[4], N=4,004; 23.1% vs. 15.4%, RR 1.50, 95% CI 1.32–1.70, $I^2$=0% [Hu et al. 2020; Lee et al. 2019; Shi et al. 2020; Su et al. 2016; Sun et al. 2019; Turan et al. 2020; Wu et al. 2016; Xuan et al. 2018; Yang et al. 2015; Zhang et al. 2020]). Post-operative bradycardia requiring treatment was not increased, based on nine trials[4] (N=3,038; 6.5% vs. 5.6%, RR 1.27, 95% CI 0.83–1.95, $I^2$=35% [Lee et al. 2019; X. Li et al. 2017; Shi et al. 2020; Su et al. 2016; Sun et al. 2019; Turan et al. 2020; Wu et al. 2016; Yang et al. 2015; Zhang et al. 2020]).

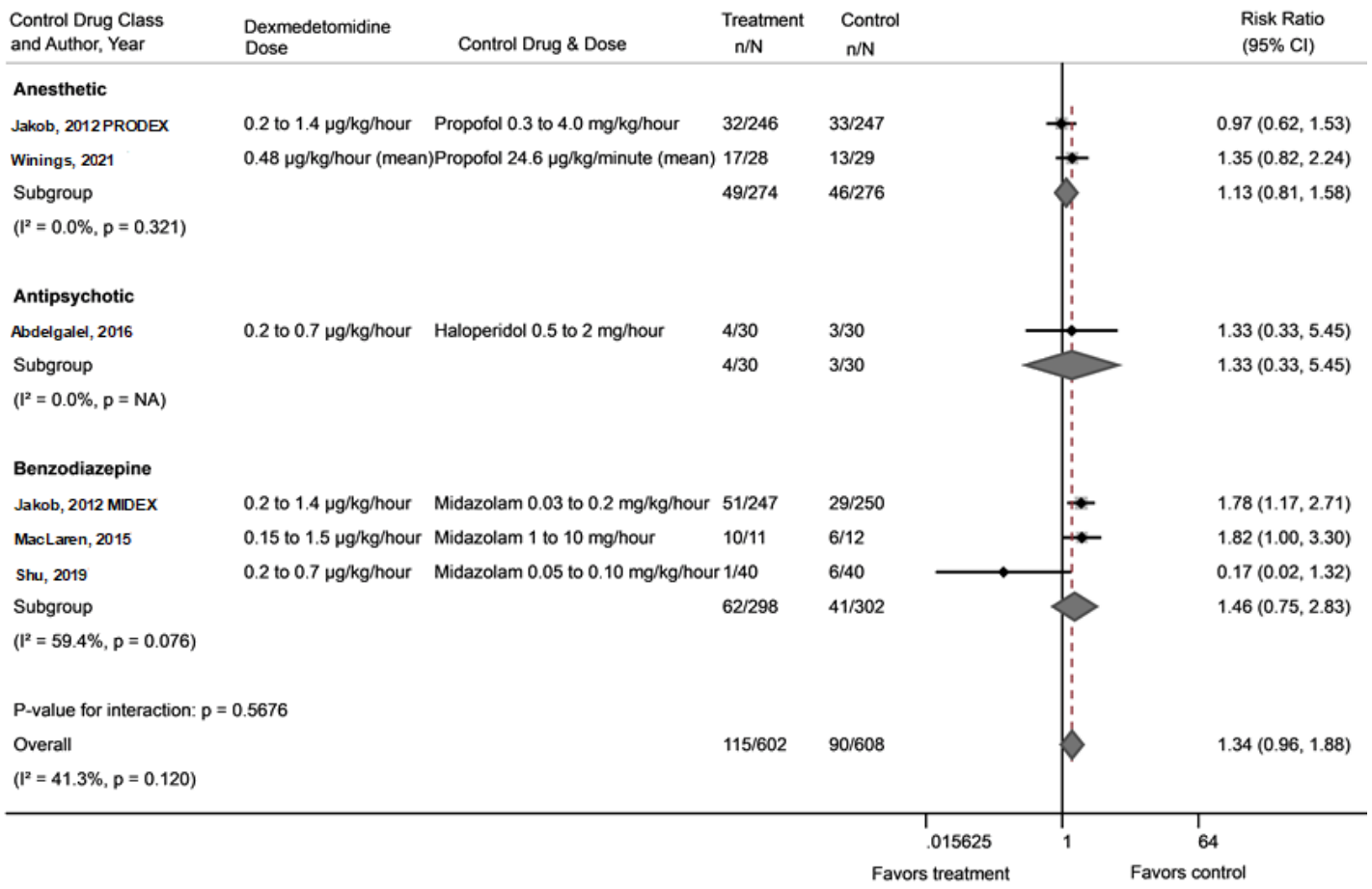
[4] Pooled analysis conducted as part of the Pacific Northwest Evidence-Based Practice Center's systematic review included one study (Sun et al. 2019) that was subsequently retracted.

A pooled analysis of two trials found no difference in risk of post-operative bradycardia or hypotension between dexmedetomidine and propofol (N=123; 15% vs. 4.8%, RR 2.87, 95% CI 0.80–10.34, $I^2$=0%; 18.3% vs. 19.0%, RR 1.02, 95% CI 0.51–2.04, $I^2$=0%; respectively [Chang et al. 2018; X. Liu et al. 2016]). However, a pooled analysis of two opioid trials (N=441 [Park et al. 2014; Shehabi et al. 2009]) found an increased risk of post-operative bradycardia (16.0% vs. 7.7%, RR 2.03, 95% CI 1.08–3.83, $I^2$=22%) but a decreased risk of hypotension (21.5% vs. 35.1%, RR 0.61, 95% CI 0.45–0.83, $I^2$=0%) with dexmedetomidine as compared with opioids (i.e., remifentanil, morphine).

Two post-operative trials, one of dexmedetomidine compared to placebo (van Norden et al. 2021) and the other of dexmedetomidine compared to sufentanil (Zhao et al. 2020), reported no difference between groups in post-operative bradycardia episodes; it was unclear if treatment was required for these episodes. Another trial reported that the total number of neurological complications was less with dexmedetomidine (26.3% vs. 43.8%, *P*=0.031), although there was no difference in severe neurological complications (11.3% vs. 20.0%, *P*=0.191 [Chen et al. 2021]).

Most trials of dexmedetomidine in ICU patients (see Figure C-11) reported hypotension and bradycardia, although some trials did not define these terms. Taken together, six trials (N=1,210) did not show a statistically significant difference in hypotension between dexmedetomidine and midazolam (Jakob et al. 2012; MacLaren et al. 2015; Shu et al. 2019), propofol (Jakob et al. 2012), or haloperidol (Abdelgalel 2016) (19% vs. 15%, RR 1.34, 95% CI 0.96–1.88, $I^2$=41%), but findings were inconsistent across the three midazolam trials. The MIDEX trial (Jakob et al. 2012), with low risk of bias, found a higher risk of hypotension (not defined) with dexmedetomidine than midazolam (N=497; 21% vs. 12%, RR 1.78, 95% CI 1.17–2.71), whereas smaller trials with moderate risk of bias did not.

2516 Figure C-11. Hypotension incidence with dexmedetomidine versus other drugs in intensive care unit patients.




2517 *Abbreviations*. CI=confidence interval; MIDEX=midazolam vs. dexmedetomidine; n/N=number; NA=not applicable; PRODEX=propofol vs. dexmedetomidine.
2518 *Source*. Abdelgalel 2016; Jakob et al. 2012; MacLaren et al. 2015; Shu et al. 2019; Winings et al. 2021.

The pattern was similar for bradycardia: MIDEX showed a higher risk with dexmedetomidine than midazolam (degree of bradycardia was not defined), but a pooled estimate across any comparator (midazolam, propofol, or haloperidol) did not show a difference (14% vs. 8.6%, RR 1.51, 95% CI 0.88–2.59, $I^2$=50%). In both MIDEX and PRODEX, the frequency of serious adverse events was comparable among the treatment groups (Jakob et al. 2012), and withdrawals due to adverse events did not differ between dexmedetomidine and midazolam or propofol (10% vs. 9.5%, RR 1.06, 95% CI 0.74–1.53, $I^2$=0% [Jakob et al. 2012; Ruokonen et al. 2009]).

Hypotension, bradycardia, and 28-day mortality were infrequent in the trial comparing midazolam and propofol and did not show a significant difference between groups (Chen 2020). One small placebo-controlled trial (N=60) reported a large, statistically significant increase in bradycardia with dexmedetomidine (27% vs. 3%, *P*<0.05), defined as a heart rate of 50 beats per minute or less, 60 or less if it required intervention (Abdelgalel 2016). Authors also noted a decrease in respiratory tract infections (6.7% vs. 33%, *P*<0.05). The study used noninvasive ventilation (NIV), and authors attributed the increase in respiratory infections in the placebo arm to more frequent NIV failure, requiring intubation that increased the risk of hospital-acquired infections. The other placebo-controlled trial reported bradycardia and hypotension only if they required interrupting treatment and found no differences between patients given dexmedetomidine and placebo (Skrobik et al. 2018).

### Effect of dexmedetomidine on other outcomes

Regarding other miscellaneous outcomes in post-surgical patients, a pooled analysis of three post-operative trials (N=989 [Lee et al. 2019; Massoumi et al. 2019; Su et al. 2016]) found no significant differences in antipsychotic use between dexmedetomidine and normal saline (2.0% vs. 2.8%, RR 0.68, 95% CI 0.14–3.41, $I^2$=0%), but dexmedetomidine was associated with significantly less antipsychotic use post-operatively than propofol (2 trials, N=213; 9.9% vs. 22.1%, RR 0.48, 95% CI 0.26–0.88, $I^2$=0% [Djaiani et al. 2016; Maldonado et al. 2009]). One trial (N=79; Yang et al. 2015) reported significantly less agitation post-operatively with dexmedetomidine compared with normal saline (10.3% vs. 30%, *P*=0.029), whereas another trial (N=108) reported less acute kidney injury with dexmedetomidine versus normal saline (14% vs. 32%, RR 0.41, 95% CI 0.19–0.91 [Soh et al. 2020]).

In ICU patients in the PRODEX trial, the number of people receiving rescue sedation was higher with dexmedetomidine than propofol, with borderline statistical significance (73% vs. 64%, *P*=0.05). The MIDEX trial showed no difference in rescue sedation between dexmedetomidine and midazolam (44% vs. 45%, *P*=0.72). A third small trial with high risk of bias did not show a statistically significant difference compared with propofol (Winings et al. 2021), whereas a fourth with low risk of bias showed less rescue sedation with dexmedetomidine than with haloperidol (Abdelgalel 2016).

### Grading of the Overall Supporting Body of Research Evidence for Use of Dexmedetomidine in the Prevention of Delirium

- Magnitude of effect: Variable. In post-operative patients, there was a small effect of dexmedetomidine relative to placebo in reducing the incidence of delirium whereas in ICU patients, typically receiving mechanical ventilation, there was a large effect of dexmedetomidine relative to placebo. When compared to other sedating medications, dexmedetomidine had a moderate to large

effect in reducing delirium incidence in post-operative patients but a small magnitude of effect in ICU patients. Duration of delirium was less often studied, and the magnitude of effect was minimal.

- Risk of bias: Moderate. Approximately half of the studies had a moderate risk of bias, with all but one of the remaining studies having a low risk of bias. Factors that most often influenced the risk of bias were inadequate reporting of information on allocation concealment and masking.

- Applicability: Studies were conducted in a wide range of countries with a substantial number conducted in China. Only a small proportion of the studies were conducted in the United Sates or Canada, which may limit applicability. Approximately half of the studies included older adults whereas the other studies included adults of all ages. Although many of the studies included comparable proportions of men and women, other studies had a preponderance of men enrolled. Race and ethnicity were rarely reported, which makes it difficult to determine whether study demographic characteristics were representative of usual clinical populations. Studies were done in post-operative patients and ICU settings, which is consistent with the settings in which dexmedetomidine would be used clinically.

- Directness: Direct. The studies provided direct information on delirium related outcomes including incidence and duration as well as on adverse events including mortality.

- Consistency: Consistent. For the key outcome, the finding of a reduced incidence of delirium was consistent in both post-operative and ICU patients and in placebo-controlled and head-to-head comparisons.

- Precision: Variable. For the key outcome of delirium incidence, the findings were precise in post-operative comparisons with placebo and with other sedating medications. For other outcomes, findings were imprecise.

- Dose-response relationship: No available information.

- Confounding factors (including likely direction of effect): The data may be confounded by variations in delirium assessment due to rater training. Individuals with hypoactive delirium may have been less likely to be identified than those with hyperactive delirium and the response to sedating treatments may differ. However, the direction of effect from these potential confounding factors is not clear.

- Publication bias: Not identified. For the outcome of delirium incidence in post-operative patients who received dexmedetomidine or placebo, there was no evidence of publication bias.

- Overall strength of research evidence: Moderate. The strength of the research evidence was moderate for the key outcome of delirium incidence. Pooled analyses were based on a large number of trials and a large total number of participants. Findings were generally consistent in both post-operative and ICU patients and in placebo-controlled and head-to-head comparisons, increasing the confidence in the strength of evidence.

### *Statement 12 – Dexmedetomidine in Patients with Delirium*

APA suggests **(2C)** that when patients with delirium are sedated for mechanical ventilation in a critical care setting, dexmedetomidine be used rather than other sedating agents.

Evidence for this statement comes from three studies that examined the effects of dexmedetomidine and other sedating agents in patients with delirium, each of which had 100 patients or fewer (Bakri et al. 2015; Liu et al. 2018; Yapici et al. 2011). However, all reported results favoring dexmedetomidine in terms of faster delirium resolution and fewer days with delirium. A very small trial of clonidine, which is also an $\alpha_2$-adrenergic receptor agonist, showed no difference from placebo (Hov et al. 2019). Indirect evidence for this statement is provided by studies of dexmedetomidine on reducing the incidence and duration of delirium (see Statement 11).

#### Overview of study characteristics

Three trials conducted in post-operative patients compared the effects of different sedating medications to treat delirium (Bakri et al. 2015; Liu et al. 2018; Yapici et al. 2011). One low risk of bias study that was conducted in China compared dexmedetomidine, sufentanil, and the combination given as a bolus followed by 2 dose-groups for maintenance of sufentanil (Liu et al. 2018). The population was young patients (N=100; age 20–40 years, mean 31 years, race/ethnicity not reported) who developed delirium post-operatively (surgical types not reported). The study reported outcomes only up to 8 hours after initiation of treatment (Liu et al. 2018). A second study with a moderate risk of bias was conducted in Turkey and compared dexmedetomidine with midazolam in patients (N=72) who had delirium and had failed extubation attempts following cardiac surgery (Yapici et al. 2011). Patients in this study had a mean age 60, and 62.5% were female. No information was given on race, ethnicity, or presence of dementia. A third trial, conducted in Saudi Arabia, enrolled patients who had undergone trauma surgery and required ICU admission (Bakri et al. 2015). This study had a moderate risk of bias and compared continuous infusion of dexmedetomidine (n=32), ondansetron (n=32), and haloperidol (n=32). Patients in this study had a mean age 31, and 9% were female; race and ethnicity were not reported.

Two trials conducted in ICU patients compared the effects of different sedating medications to treat delirium (Liu et al. 2021; Reade et al. 2016). One trial with a low risk of bias was done in Australia in patients (N=71) with agitated delirium and compared dexmedetomidine treatment with placebo (Reade et al. 2016). The median age of this sample was 57 years, and 24% were female. Race and ethnicity were not reported, and participants with dementia were excluded. One retrospective cohort study, with a moderate risk of bias, was conducted in China and compared dexmedetomidine (n=118) to olanzapine (n=145) in patients who were age ≥75 (Liu et al. 2021). Race and ethnicity were not reported, but 23% of the sample was female and 10.6% had dementia.

#### Effect of dexmedetomidine on delirium response

A study of post-operative patients compared dexmedetomidine, sufentanil, and the combination of dexmedetomidine and sufentanil using two different doses of sufentanil (Liu et al. 2018). Sufentanil alone and the two combination groups had significantly fewer patients with a response at 8 hours compared with dexmedetomidine alone (64% vs. 84% vs. 92% vs. 84%, $P<0.05$) (Liu et al. 2018). In patients who had undergone trauma surgery and had a subsequent ICU admission, there was no

significant difference in the proportion of patients with delirium in the dexmedetomidine group as compared to the ondansetron or haloperidol groups (Bakri et al. 2015). Also, in the ICU study of patient with agitated delirium, baseline delirium resolved more quickly in patients who received dexmedetomidine as compared to placebo (median 23 hours vs. 40 hours, *P*=0.01), and they had fewer study days with delirium present (median 1 day vs. 3 days, *P*=0.02) (Reade et al. 2016).

### Effect of dexmedetomidine on length of stay

Only one study examined effects of dexmedetomidine on length of stay in patients with delirium. Although the median length of stay was shorter in ICU patients treated with dexmedetomidine as compared to placebo, the difference was not significant for either the ICU stay (median 2.9 days vs. 4.1 days after randomization, *P*=0.09) or hospital stay (median 8.5 days vs. 9.5 days, *P*=0.96) (Reade et al. 2016). In ICU patients age ≥75, hospital LOS was greater in patients treated with dexmedetomidine as compared to those treated with olanzapine (mean 9.30 [SD 4.90] vs. 8.83 [SD 3.34], *P*<0.001) (Liu et al. 2021).

### Effect of dexmedetomidine on mortality and adverse events

Limited information was available from these studies on adverse events, including mortality. In the study of post-operative patients who received dexmedetomidine, sufentanil, or the combination, an increase in respiratory distress was noted in the combination groups (8% vs. 32% vs. 64% vs. 36%, *P*<0.05) (Liu et al. 2018). In the study of agitated patients in an ICU setting, rates of bradycardia and agitation did not differ significantly between groups (Reade et al. 2016). In terms of mortality, no patient died after receiving placebo, whereas one treated patient died in the ICU (*P*>0.99) and two in the hospital (*P*=0.50) (Reade et al. 2016). Cause of death and association with treatment were not reported. In ICU patients ≥75 years, there was no significant difference found in mortality between patients who received olanzapine and those who received dexmedetomidine (24.5% vs. 21.4%) (Liu et al. 2021).

### Effect of dexmedetomidine on other outcomes

In terms of other outcomes, the trial that compared dexmedetomidine with midazolam in patients following cardiac surgery found that, at 2.5 days post-operation, the proportion of patients who were able to be weaned from mechanical ventilation was significantly greater in the dexmedetomidine group (97% vs. 79%, RR 1.17, 95% CI 1.01–1.36) (Yapici et al. 2011). In post-operative trauma patients, a greater proportion of patients needed "rescue" treatment with haloperidol in the ondansetron group as compared to those who received haloperidol (11% vs. 3%; *P*=0.03) (Bakri et al. 2015). Dexmedetomidine and haloperidol groups did not differ in the amount of rescue haloperidol that was needed (*P*=0.07) (Bakri et al. 2015).

### Grading of the Overall Supporting Body of Research Evidence for Use of Dexmedetomidine in the Treatment of Delirium

- Magnitude of effect: Low to moderate. The magnitude of effect of varied with the outcome and the comparison condition but was clinically significant in terms of response of delirium and in the proportion of patients who were able to be weaned from mechanical ventilation in one study.

- Risk of bias: Low to moderate. The risk of bias was low in two studies and moderate in one study. In one study, there was insufficient description of randomization and masking procedures, and it was unclear whether the groups were comparable at baseline.

- Applicability: Studies were done in various countries, but none were done in the United States or Canada, which may limit applicability. In addition, the study populations were younger than typical patients with delirium. The proportion of women was low in most of the studies, but other demographic features were not well delineated. Studies were done in post-operative patients and ICU settings, which is consistent with the settings in which dexmedetomidine would be used clinically.

- Directness: Direct. The studies provided direct information on delirium related outcomes including response as well as providing limited information on adverse events including mortality.

- Consistency: Consistent. The finding of a better response of delirium and/or better outcome with dexmedetomidine compared to placebo or other sedating medications was consistent in both post-operative and ICU patients.

- Precision: Imprecise. The studies used proportions for a number of the measures and there was significant imprecision in terms of optimal information sizes.

- Dose-response relationship: No available information.

- Confounding factors (including likely direction of effect): The data may be confounded by variations in delirium assessment due to rater training. Although one study was limited to agitated patients, in the other studies, individuals with hypoactive delirium may have been less likely to be identified than those with hyperactive delirium. However, the direction of effect from these potential confounding factors is not clear.

- Publication bias: Not identified. Publication bias was not able to be assessed due to the small number of trials and differences in comparators.

- Overall strength of research evidence: Low. The studies had a low to moderate risk of bias and were generally consistent in their findings; however, only a small number of studies were available, and they had significant variations in design and outcome measures that were used.

*Statement 13 – Melatonin and Ramelteon*

APA suggests **(2C)** that melatonin and ramelteon not be used to prevent or treat delirium.

This recommendation is based on a systematic literature review conducted by the Pacific Northwest EPC, which focused on pharmacological approaches to prevention and treatment of delirium. The literature review mostly included prevention studies, which generally reported small or no effect of melatonin or ramelteon on delirium incidence or related outcomes (e.g., duration of delirium, severity of illness). A subsequent systematic review was consistent with a lack of effectiveness of ramelteon in prevention of delirium (Dang et al. 2023). The two treatment studies identified in the Pacific Northwest EPC review also failed to show that melatonin or ramelteon effectively treat delirium in terms of time to

delirium resolution, delirium severity, mortality, adverse events, rescue medication, and use of restraints (Lange et al. 2021; Thom et al. 2019). A subsequent systematic review (Beaucage-Charron et al. 2023) also suggested that further evidence was needed before using these medications to treat delirium.

### Overview of study characteristics

Eighteen studies (N=2,293; range 50 to 452) assessed effects of sleep-related medications in the prevention of delirium (Abbasi et al. 2018; Azuma et al. 2018; Bellapart et al. 2020; de Jonghe et al. 2014; Ford et al. 2020; Gandolfi et al. 2020; Gupta et al. 2019; Hatta et al. 2014b, 2017; Jaiswal et al. 2018, 2019; Javaherforoosh Zadeh et al. 2021; Lawlor et al. 2020; Mahrose et al. 2021; Nishikimi et al. 2018; E.S. Oh et al. 2021; Sharaf et al. 2018; Sultan 2010). There was a low risk of bias in five studies, a moderate risk of bias in eleven studies, and a high risk of bias in two studies. Studies were conducted in various countries including four trials in Japan, three trials each in Egypt and the United States, two trials each in Australia and Iran, and one trial each in Brazil, Canada, India, and The Netherlands. Seven of the studies limited enrollment to individuals age 65 or older, and eleven studies had a mean or median age greater than 65 years, whereas other studies included a broader range of adult participants. Six studies had a predominance of men, two studies had a predominance of women, nine studies had similar numbers of men and women, and one study did not report on the sex of participants. The majority of studies (15) did not report information on race or ethnicity. One study included 92% White participants, another included 74% White and 15% Black participants, and, in a third trial, all participants were Asian. In seven studies, individuals with delirium at baseline were excluded, whereas information on delirium at baseline was not described in the other eleven studies. Six studies excluded individuals with dementia, three studies included individuals with dementia (range 6.7% to 25% of the sample), and nine studies did not report this information.

In post-operative patients, nine trials (N=1,190) compared a sleep-related medication with placebo or no treatment, with four trials of melatonin 3 mg/day (de Jonghe et al. 2014; Ford et al. 2020; Javaherforoosh Zadeh et al. 2021; Sharaf et al. 2018), one of 5 mg/day (Mahrose et al. 2021), one of 5 mg the night before surgery and 5 mg pre-operatively (Sultan 2010), and three of ramelteon 8 mg/day (Gupta et al. 2019; Jaiswal et al. 2019; E.S. Oh et al. 2021). Six trials began treatment prior to surgery and continued for 2 to 7 days after (de Jonghe et al. 2014; Ford et al. 2020; Jaiswal et al. 2019; Javaherforoosh Zadeh et al. 2021; Mahrose et al. 2021; E.S. Oh et al. 2021), whereas two trials gave 2 pre-operative doses only (the night before or 12 hours before surgery, and then 90 or 60 minutes prior to surgery, respectively [Gupta et al. 2019; Sultan 2010]). One study enrolled older adults undergoing any type of surgery requiring more than one hour of anesthesia (Gupta et al. 2019), three enrolled older adults undergoing orthopedic surgeries (de Jonghe et al. 2014; E.S. Oh et al. 2021; Sultan 2010), and three enrolled patients undergoing elective cardiac or pulmonary surgeries requiring an ICU admission post-operatively (Ford et al. 2020; Jaiswal et al. 2019; Sharaf et al. 2018). One of the studies (of older patients undergoing hip arthroplasty under spinal anesthesia) also compared melatonin with midazolam 7.5 mg oral and 100 mcg clonidine given twice pre-operatively with no post-operative administration (Sultan 2010). A subsequent RCT, which was not included in the Pacific Northwest EPC meta-analysis, compared ramelteon (8 mg orally) or placebo for six nights (1 pre-operative night and 5 consecutive

post-operative nights) in patients age 65 or older who were undergoing elective surgery under general anesthesia (Kinouchi et al. 2023).

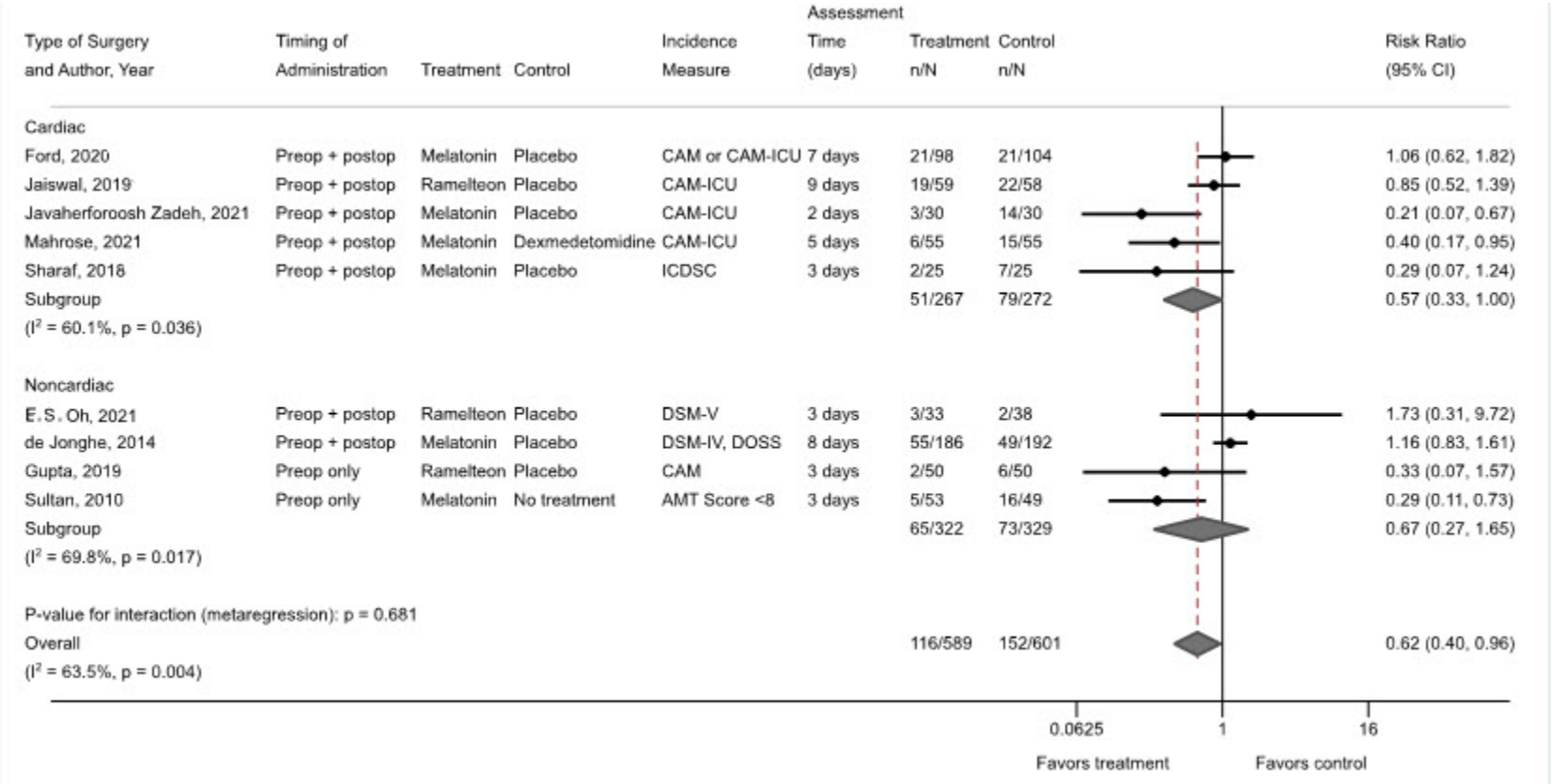
Regarding ICU populations, five trials (N=531) compared the effect of a sleep-related medication with placebo or usual care in preventing development of delirium, with three trials of melatonin (3–10 mg/day [Abbasi et al. 2018; Bellapart et al. 2020; Gandolfi et al. 2020]), one of ramelteon 8 mg/day (Nishikimi et al. 2018), and one of suvorexant 15 to 20 mg/day (Azuma et al. 2018). A subsequent Australian multicenter RCT, which was not included in the Pacific Northwest EPC meta-analysis, compared melatonin 4 mg to placebo for 14 consecutive nights or until discharge (Wibrow et al. 2022). In ICU patients with a diagnosis of delirium, one retrospective cohort study compared 77 ICU patients treated with ramelteon to 245 patients not given a sleep-related medications (Thom et al. 2019).

In mixed inpatient samples, one trial (N=69) compared the effect of 3 mg of melatonin nightly to placebo in individuals age 65 or older (Jaiswal et al. 2018). Another RCT (N=67) compared the effect of up to 7 days of 8 mg of ramelteon nightly to placebo in patients age 65 to 89 (Hatta et al. 2014b). A third trial (N=72), also in patients age 65 to 89, compared 15 mg of suvorexant every night for 3 days to placebo (Hatta et al. 2017). Among palliative care patients, one trial randomized 60 patients with advanced cancer to 3 mg/day of melatonin or placebo for up to 28 days (Lawlor et al. 2020).

### Effect of sleep-related medications on delirium incidence

All nine trials in post-operative patients reported delirium incidence, with four trials using the CAM-ICU instrument, three using the CAM, one the DOSS with DSM-5, and one using the Abbreviated Mental Test (score >8). Assessment time was 3 to 9 days after surgery. A pooled analysis of incidence of delirium found a small, but significant difference for sleep-related medications compared with placebo (N=1,190; RR 0.62, 95% CI 0.40–0.96, $I^2$=63.5%) (see Figure C-12). A subgroup analysis by type of surgery (cardiac vs. noncardiac) did not indicate significant effects. However, a subgroup analysis by specific medication (melatonin vs. ramelteon) showed a statistically significant difference for melatonin (6 trials, N=902; RR 0.53, 95% CI 0.29–0.97, $I^2$=75%) but not ramelteon (4 trials, N=288; RR 0.82, 95% CI 0.51–1.32). A subgroup analysis by whether the medication was given only pre-operatively or continued post-operatively again found no significant effect for continuing post-operatively (7 trials, N=988; 22% vs. 25%, RR 0.73, 95% CI 0.48–1.13, $I^2$=60%) but did find a significant reduction for the pre-operatively-only group (7% vs. 22%, RR 0.30, 95% CI 0.14–0.66, $I^2$=0%). However, the *P*-value for the subgroup interaction was not statistically significant (*P*=0.177). A subsequent placebo-controlled trial of ramelteon showed no significant difference in the likelihood of delirium between the groups (Cox proportional HR 1.40, 95% CI 0.40–4.85, $\chi^2$=0.29, df=1, P=0.60 [Kinouchi et al. 2023]). In addition to these placebo-controlled trials, a trial of older patients undergoing hip arthroplasty under spinal anesthesia (Sultan 2010) also compared melatonin with midazolam and clonidine, finding that significantly fewer patients developed delirium by day 3 in the melatonin group compared with all of the other groups (9.4% vs. 44% midazolam vs. 37% clonidine).

2779 Figure C-12. Delirium incidence with sleep-related medications in surgical patients post-operatively.



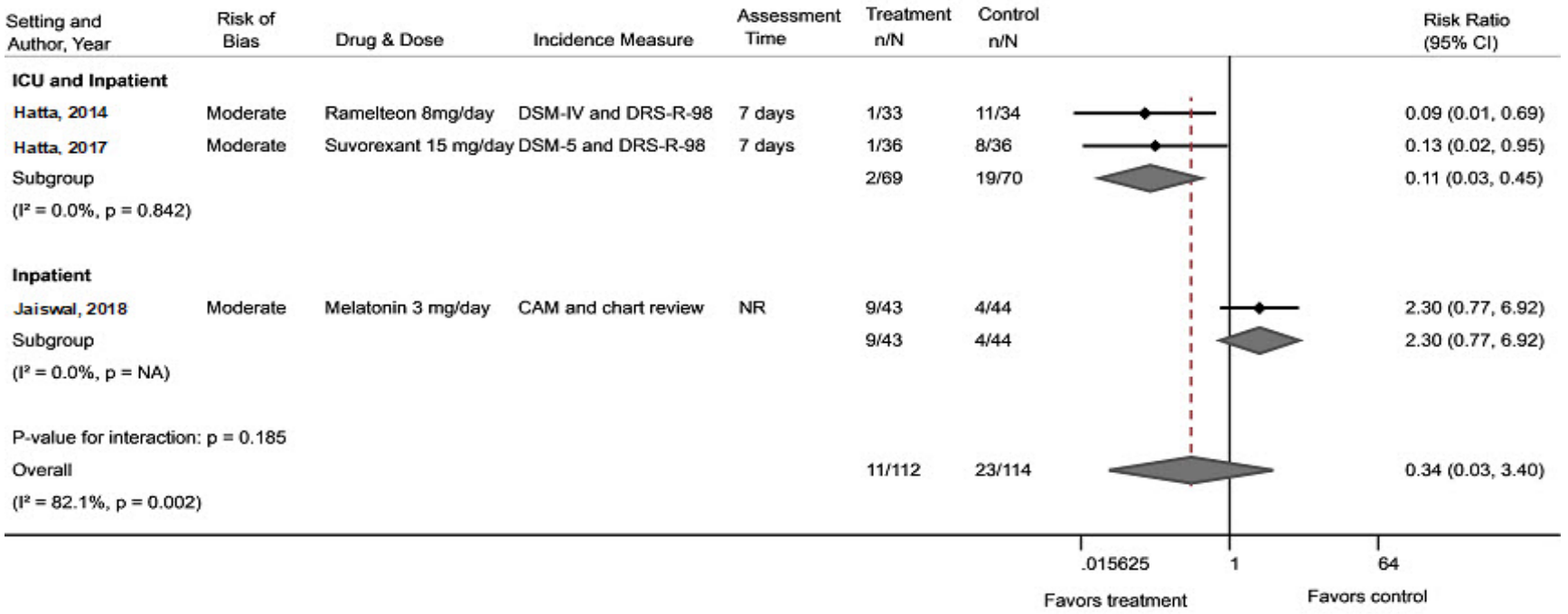

2780 *Abbreviations*. AMT=Abbreviated Mental Test; CAM=Confusion Assessment Method; CAM-ICU=Confusion Assessment Method for the Intensive Care Unit;
2781 CI=confidence interval; DOSS=Delirium Observation Screening Scale; DSM-IV=*Diagnostic and Statistical Manual of Mental Disorders,* 4th Edition;
2782 ICDSC=Intensive Care Delirium Screening Checklist; n/N=number; preop=pre-operative; postop=post-operative.
2783 *Source*. de Jonghe et al. 2014; Ford et al. 2020; Gupta et al. 2019; Jaiswal et al. 2019; Javaherforoosh Zadeh et al. 2021; Mahrose et al. 2021; E.S. Oh et al. 2021;
2784 Sharaf et al. 2018; Sultan 2010.

Three trials of sleep-related medications in ICU patients reported delirium incidence, with a large, but not statistically significant difference favoring active treatment (13% vs. 22%, RR 0.56, 95% CI 0.30–1.05, $I^2$=22% [Abbasi et al. 2018; Azuma et al. 2018; Nishikimi et al. 2018]). Ramelteon was the only individual medication for which the effect on delirium incidence was statistically significant, and again the magnitude of difference was large (24% vs. 47% for placebo, RR 0.53, 95% CI 0.29–0.96). A subsequent large (N=841) RCT of prophylactic melatonin in ICU patients showed no difference in delirium-free assessments compared to placebo (79.2% vs. 80% respectively, *P*=0.547) (Wibrow et al. 2022).

In general inpatient populations, the effect of sleep-related medications on delirium incidence was not statistically significant in the pooled analysis, but the absolute difference was moderate, and statistical heterogeneity was high (9.8% vs. 20%, RR 0.34, 95% CI 0.03–3.40, $I^2$=82%) (see Figure C-13). A subgroup analysis of the two trials with mixed inpatient and ICU patients resulted in a very different estimate of effect than the study that was limited to inpatients. The two trials with mixed inpatient and ICU patient samples assessed ramelteon and suvorexant and showed a large, significant reduction in delirium incidence (2.9% vs. 27%, RR 0.11, 95% CI 0.03–0.45, $I^2$=0% [Hatta et al. 2014b, 2017]). The study with only inpatients found a moderate but non-significant increase in incidence with melatonin (21% vs. 9.1%, RR 2.30, 95% CI 0.77–6.92 [Jaiswal et al. 2018]). The suvorexant trial (Hatta et al. 2017) reported a subgroup analysis, which found no effect on delirium incidence in patients with a Clinical Dementia Rating score of 0.5 or higher. However, the trial was underpowered to make this comparison, including just 18 patients with mild cognitive impairment by this definition.

Among palliative care patients, a trial of melatonin as compared with placebo did not show a statistically significant difference in the incidence of delirium (37% vs. 33%, *P*=0.79) (Lawlor et al. 2020).

Figure C-13. Delirium incidence with sleep-related medications versus placebo in inpatients.




*Abbreviations*. CAM=Confusion Assessment Method; CI=confidence interval; DRS-R-98=Delirium Rating Scale-Revised-98; DSM=*Diagnostic and Statistical Manual of Mental Disorders*; ICU=intensive care unit; NR=not reported.

*Source*. Hatta et al. 2014b, 2017; Jaiswal et al. 2018.

### Effect of sleep-related medications on delirium duration

The duration of delirium in surgical patients was reported in four trials, all of which continued the medication post-operatively (de Jonghe et al. 2014; Ford et al. 2020; Jaiswal et al. 2019; E.S. Oh et al. 2021). The duration of delirium had a range of 1 to 3 days in the sleep-related medication groups, and 1 to 2 days in the placebo groups, with a pooled MD of 0.18 days (95% CI -0.23–0.59, $I^2$=13%). Subgroup analyses of specific medication and risk of bias were not significant.

In ICU patients treated with sleep-related medications to prevent delirium, the duration of delirium did not differ between treated and untreated patients in the three trials, with a pooled MD of -0.86 days (95% CI -1.88–0.16 days, $I^2$=0%). The other two studies did not report data needed to pool, and individually they did not show differences in delirium outcomes between melatonin and placebo (Bellapart et al. 2020; Gandolfi et al. 2020). In ICU patients with a diagnosis of delirium, treatment did not shorten time to resolution of delirium and coma (adjusted HR 1.05, 95% CI 0.54–2.01) (Thom et al. 2019).

### Effect of sleep-related medications on delirium severity

Two trials in post-operative populations reported on the severity of delirium with no significant differences between groups, but the data were too heterogeneous to pool. In cardiac surgery patients the median MDAS score was 9 (IQR 3–26, with possible score values of 0 to 30) in the melatonin group, and 8.5 (IQR 3–22) in the placebo group (*P*=0.22 [Ford et al. 2020]). The proportion of patients who experienced episodes of severe delirium (MDAS>13) was not significantly different between groups (43% vs. 29%, *P*=0.33 [Ford et al. 2020]). A study in older orthopedic patients found similar DRS-R-98 scores between participants treated with ramelteon as compared with placebo (19.7 vs. 19.0, *P*=0.56 [E.S. Oh et al. 2021]). One trial reported severity of delirium was statistically significantly different (*P*=0.003), but the data were not shown (Javaherforoosh Zadeh et al. 2021). Another trial reported duration of delirium was significantly shorter in the group that received melatonin plus dexmedetomidine as compared to those that received dexmedetomidine alone (24.5 hours vs. 48.0 hours, *P*=0.001 [Mahrose et al. 2021]).

In general medical inpatients with delirium as determined by the CAM, improvement in MDAS scores, between baseline and the mean of 5 daily posttreatment scores, did not differ between melatonin and placebo (2.5 points vs. 2.2 points on a 30-point scale, *P*=0.41), nor did the number of CAM-positive days (4.5 days vs. 5 days, *P*=0.18) (Lange et al. 2021).

Among palliative care patients treated with melatonin as compared to placebo, there was no difference in delirium severity measured by the Nu-DESC scale over 3 days (*P*=0.19) (Lawlor et al. 2020).

### Effect of sleep-related medications on length of stay

Length of ICU stay was reported in two trials of post-operative patients. One trial reported a statistically significantly shorter length of ICU stay with melatonin versus placebo (mean of 3.83 days vs. 4.00 days, *P*=0.04 [Javaherforoosh Zadeh et al. 2021]). Another trial showed no differences between groups (median of 4 days each, *P*=0.349 [Jaiswal et al. 2019]).

Length of hospital stay was reported in three trials of post-operative patients (de Jonghe et al. 2014; Ford et al. 2020; Jaiswal et al. 2019). The length of stay was significantly shorter in one trial of melatonin in older patients undergoing hip surgery (de Jonghe et al. 2014), significantly longer with melatonin in adult cardiac surgery patients (Ford et al. 2020), and not significantly different in a trial of ramelteon in patients undergoing pulmonary thromboendarterectomy (Jaiswal et al. 2019). The pooled estimate did not find a significant difference (MD 0.11 days, 95% CI -1.40–1.62, $I^2$=82%). A subgroup analysis by medication did not find a significant effect. A subgroup analysis by type of surgery (cardiac/pulmonary vs. orthopedic) found a significant reduction in the orthopedic trial (MD -1.50 days, 95% CI -2.82 to -0.18) and a significant increase in the cardiac/pulmonary trials (MD 0.94 days, 95% C -1.40–1.62, $I^2$=0%). However, the *P*-value for the interaction was not statistically significant (*P*=0.187).

Taken together, four studies of sleep-related medications did not show an effect of treatment on the length of stay in ICU patients, but the pooled effect showed substantial heterogeneity (MD -0.79 days, 95% CI, -2.72–1.14, $I^2$=90% [Abbasi et al. 2018; Azuma et al. 2018; Gandolfi et al. 2020; Nishikimi et al. 2018]). Ramelteon differed from the other medications, showing a significant effect on ICU length of stay for treatment compared with placebo (median 4.6 days vs. 5.9 days, *P*=0.028 in a multivariate model [Nishikimi et al. 2018]). A subsequent large study of melatonin showed no effect on ICU length of stay (median: 5 days vs 5 days, *P*=0.135) or hospital length of stay (median: 14 days vs 12 days, *P*=0816) (Wibrow et al. 2022). Another study of 137 ICU patients (Abbasi et al. 2018) showed no effect of melatonin treatment on time spent in the hospital compared to placebo (18.1 days vs. 18.6 days, *P*=0.85).

### Effect of sleep-related medications on mortality and adverse events

Three trials in post-operative patients reported on mortality during hospitalization (de Jonghe et al. 2014; Ford et al. 2020; Jaiswal et al. 2019), and one also reported 90-day mortality (de Jonghe et al. 2014). Overall, mortality was not different between the groups either during hospitalization (5% vs. 7%, RR 0.98, 95% CI 0.38–2.54, $I^2$=0%) or at 90 days (21% vs. 21%, RR 0.98, 95% CI 0.67–1.45) (de Jonghe et al. 2014).

Among 428 ICU patients, three trials reported deaths—two trials using melatonin (Abbasi et al. 2018; Gandolfi et al. 2020) and one ramelteon (Nishikimi et al. 2018). The trials showed no effect of sleep-related medications on mortality (9.8% vs. 9.8%, RR 1.01, 95% CI 0.57–1.79, $I^2$=0%). In a subsequent trial of melatonin compared to placebo, there was no significant difference in mortality at 90 days (15.5% vs 15.6%, *P*=0.948 [Wibrow et al. 2022]). In addition, in ICU patients with a diagnosis of delirium, there was no statistically significant effect on mortality, and the estimate was imprecise (adjusted HR 0.31, 95% CI 0.07–1.32 [Thom et al. 2019]).

In terms of mortality in inpatients, the suvorexant trial included 72 patients, none of whom died in either group (Hatta et al. 2017).

Only one of the post-operative trials reported adverse events related to the study medications: nausea (5 ramelteon vs. 2 placebo), hypotension (2 ramelteon vs. 1 placebo), and dizziness (1 ramelteon vs. 2

placebo [E.S. Oh et al. 2021]). Logistic regression analysis for risk of any adverse event as a function of assignment to ramelteon was not significant (*P*=0.95).

One trial in 203 ICU patients did not show a significant difference in adverse events between melatonin and placebo (27% vs 35%, *P*=0.27 [Gandolfi et al. 2020]).

In terms of adverse outcomes, one adverse event occurred in the melatonin trial, in a treated patient who withdrew because of nausea [Jaiswal et al. 2018]). In another trial that compared melatonin to placebo in ICU patients, no serious adverse events were reported in either group (Wibrow et al. 2022). In general medical inpatients with delirium as determined by the CAM, adverse events were similar between melatonin-treated and untreated patients (Lange et al. 2021). The ramelteon trial (Hatta et al. 2014b) reported no adverse events in any patient in a mixed group of ICU and general inpatients.

One trial of suvorexant in ICU patients reported that no patient in either group had an adverse event that investigators judged was attributable to the study drug (Azuma et al. 2018). There were no serious adverse events and no statistically significant differences in somnolence, headache, or dizziness between suvorexant and placebo in a mixed group of ICU and general inpatients, but events were few (0 to 6 per outcome [Hatta et al. 2017]).

Serious adverse events occurred in 67% of palliative care patients given melatonin and 57% given placebo (*P*=0.43), but these were not considered related to study medications (Lawlor et al. 2020).

### Effect of sleep-related medications on other outcomes

Two trials of melatonin in post-operative patients reported on outcomes related to cognition, with no difference in cognitive decline (defined as Telephone Interview for Cognitive Status-Modified score <32) at discharge (1 trial [Ford et al. 2020]) or at 90 days post discharge (2 trials [de Jonghe et al. 2014; Ford et al. 2020]). One of these also reported on Katz Index of Independent in Activities of Daily Living scores at 90 days, again finding no difference between groups (de Jonghe et al. 2014). One of these trials also reported that anxiety and depression scores did not differ between groups.

Several trials reported on use of rescue medication in trials of sleep-related medications. Two trials in post-operative patients, one of melatonin and one of ramelteon, reported on use of other medications such as antipsychotics and benzodiazepines and found no differences between groups (de Jonghe et al. 2014; Jaiswal et al. 2019).

In ICU patients, the mean cumulative dose of rescue haloperidol did not differ between individual who were given melatonin and those given placebo, according to an analysis adjusted for baseline characteristics in one trial (Abbasi et al. 2018). The other melatonin trial did not show differences in the use of rescue sedatives, antipsychotics, or $\alpha_2$ agonists (Gandolfi et al. 2020). An additional trial in ICU patients showed no effect of suvorexant on rescue dexmedetomidine dose (Azuma et al. 2018).

In general medical inpatients with delirium, rates of rescue medication and restraint use were comparable between patients treated with melatonin and untreated patients (Lange et al. 2021).

### Grading of the Overall Supporting Body of Research Evidence for Use of Melatonin or Ramelteon in the Prevention or Treatment of Delirium

- Magnitude of effect: Minimal to small. Most outcomes showed no effect of melatonin or ramelteon. For some subgroup analyses, a small effect was present but typically did not reach statistical significance and was not consistent in other outcomes or patient groups.

- Risk of bias: Moderate. The majority of studies (11) had a moderate risk of bias with five studies having a low risk of bias and two with a high risk of bias. The predominant reasons for an increased risk of bias were related to inadequate allocation concealment and masking as well as problems with attrition and differences in treatment groups at baseline.

- Applicability: Studies were conducted in a wide range of countries, with only four trials conducted in the United States or Canada. Approximately half of the studies were limited to older individuals, but the remaining studies included a range of adult ages. A mix of men and women were represented in the studies, but few studies reported information on race or ethnicity. Individuals with delirium at baseline were excluded in about half of studies, but the others did not describe whether delirium was present at baseline. In terms of co-occurring dementia, half of studies did not report this information and of the remaining studies, only one-third included patients with dementia. The majority of studies were in post-operative patients with a smaller number of studies in ICU or inpatient samples.

- Directness: Direct. The studies provided direct information on delirium related outcomes including incidence as well as providing limited information on adverse events including mortality.

- Consistency: Consistent. The majority of studies show minimal to no effect of melatonin or ramelteon on prevention or treatment of delirium.

- Precision: Imprecise. Many of the studies were small with sizable confidence intervals and there was significant imprecision in terms of optimal information sizes.

- Dose-response relationship: No available information.

- Confounding factors (including likely direction of effect): The data may be confounded by variations in delirium assessment due to rater training. Several of the studies had differences in the treatment and control groups at baseline as well as evidence of differential attrition. However, the direction of effect from these potential confounding factors is not clear.

- Publication bias: Not identified. Publication bias was not able to be assessed due to the small number of trials and differences in comparators.

- Overall strength of research evidence: Low. The studies had a moderate risk of bias and were generally consistent in their findings; however, many of the studies were small and several studies had differences in the treatment and control groups at baseline as well as evidence of differential attrition. Only a few studies were available that assessed the effects of melatonin or ramelteon on treatment of delirium.

## Transitions of Care

### *Statement 14 – Medication Review at Transitions of Care*

APA recommends **(1C)** that, in patients with delirium or who are at risk for delirium, a detailed medication review, medication reconciliation, and reassessment of the indications for medications, including psychotropic medications, be conducted at transitions of care within the hospital.

This recommendation is based on a targeted review of the literature on the impact of medication interventions during transitions of care for patients with or at risk for delirium.

Medication review, reconciliation, and reassessment are critical because inappropriate short- or long-term psychotropic medication use may lead to unnecessary exposure to potential adverse effects of medications (e.g., increased mortality, development and worsening of cardiometabolic abnormalities, risk of falls), polypharmacy, and increased healthcare spending (Johnson et al. 2017; Lambert et al. 2021). Additionally, adults ages 65 and older are highly vulnerable to adverse effects from psychotropic medications (Ćurković et al. 2016). For instance, antipsychotic use in older adults has been linked to an increased risk of mortality, hip fracture, falls, urinary infections, cerebrovascular events (e.g., stroke, seizures), and pneumonia (Ćurković et al. 2016; Johnson et al 2017). This is especially concerning considering a recent review found that healthcare professionals perceive antipsychotics as effective for delirium but do not perceive them as having enough of a risk to limit their prescribing practices (Jaworksa et al. 2022).

Approximately one-quarter to one-half of ICU patients who received an antipsychotic medication for delirium were continued on the medication with transition to a lower acuity setting of care (Dixit et al., 2021; Flurie et al. 2015; Lambert et al. 2021). The highest rate of antipsychotic continuation was among patients in a community hospital of mixed ICU patients, whereas the lowest rate was among patients in a surgical ICU. In one study of the patients who continued on antipsychotics following transfer from the ICU, 61% were assessed for inappropriate antipsychotic continuation and almost two-thirds of this group (64%) were determined to have been continued on the medication inappropriately (Flurie et al. 2015).

A small number of trials were conducted at transitions of care and assessed the effects of multi-component pharmacological interventions, such as medication review, medication reconciliation, and reassessment of the need for psychotropic medication. Findings support the use of medication-related interventions in this context. One trial conducted in the Netherlands assessed the effects of medication review on length of delirium, length of stay, mortality, and discharge destination among 93 patients (van Velthuijsen et al 2018). Duration of delirium in patients who underwent medication review was shorter than in controls (8.56 days vs 15.47 days). Patients who were taking up to 6 medications and who had a medication review had significantly shorter episodes of delirium than controls (MD 15.46 days, $P<0.001$). There were no differences between medication review patients and controls for length of stay, in-hospital mortality, or discharge destination (van Velthuijsen et al 2018).

In patients 70 years and older hospitalized for trauma, an individual pharmacotherapy management program appeared to effectively prevent complicating delirium, which the authors defined as “delirium

necessitating further investigations as laboratory parameters, cranial computed tomography or magnetic resonance imaging, and/or psychiatric consultation" (N=404; Drewas et al. 2022). The pharmacotherapy management program was largely comprised of an electronic medication review and individualized recommendations based on identified medication risks and interdisciplinary consensus. Use of the intervention was associated with a 90% reduction in risk of complicating delirium (OR 0.09, 95% CI 0.01–0.7, *P*=0.03). A Cochrane review of multi-component non-pharmacological interventions for delirium in non-ICU hospitalized patients (Burton et al. 2021) also found a small but favorable effect of medication review on reducing the risk of delirium (OR 0.81, 95% CI 0.21–3.02).

Several other intervention trials did not look at delirium-related outcomes but did report significant improvements in unnecessary exposure to psychotropic medication. One trial explored the use of a multi-component intervention to reduce high-risk medications in adults ages 70 and older (N=70) in acute medical care or surgical units who were at risk for delirium (Adeola et al. 2018). The intervention included technology-assisted medication review as well as formulary and policy changes, best practice alerts, and prescriber education. Medication review included the use of electronic pharmacy surveillance and alerts for pharmacist review of high-risk medications, which were to be followed by dose reduction, medication discontinuation, medication switching, or (when appropriate) continuation of the medication after conducting a risk-benefit assessment with the prescribing healthcare professional. High-risk medications targeted for intervention were zolpidem, diphenhydramine, lorazepam, methocarbamol, hydroxyzine, diazepam, cyclobenzaprine, carisoprodol, and meperidine. Investigators found the proportion of patients who received at least one high-risk medication decreased from 45.6% to 31.3%, and mean number of doses decreased for seven of the nine high-risk medications. Of the 6,645 electronic pharmacy surveillance alerts that were triggered and responded to, 31% resulted in a change to the medication (i.e., a discontinuation, dose reduction, or switch). The intervention also included discharge reconciliation, in which 21,956 best practice alerts were generated—38% of which resulted in the high-risk medication being discontinued.

A quality improvement trial designed to reduce inappropriate continuation of second-generation antipsychotics among patients with delirium discharged from the ICU (N=358) found that use of an electronic medication review and handoff tool was associated with reduced antipsychotic continuation at ICU discharge (78.7% continued pre-intervention vs 66.7% post-intervention, *P*=0.012 [Kram et al. 2019]). Finally, one study included medical ICU patients who had been prescribed antipsychotics for delirium and assessed antipsychotic continuation before and after introduction of a medication tapering bundle intervention (D'Angelo et al. 2019). The bundle intervention, which included medication education and an antipsychotic discontinuation algorithm, was associated with a significant decrease in antipsychotic continuation (27.9% vs 17.7%, OR 0.56, 95% CI 0.31–0.99, *P*<0.05) and lower odds of antipsychotic continuation (OR 0.47, 95% CI 0.26–0.86, *P*=0.014) at ICU discharge (D'Angelo et al. 2019).

### Grading of the Overall Supporting Body of Research Evidence for Medication Review at Transitions of Care

In the absence of a detailed systematic review on the medication review at transitions of care for patients with delirium, no grading of the body of research evidence is possible.

### *Statement 15 – Follow-up Planning at Transitions of Care*

APA recommends **(1C)** that, when patients with delirium are transferred to another setting of care, plans for follow-up include:

- continued assessments for persistence of delirium;
- detailed medication review, medication reconciliation, and reassessment of the indications for medications, including psychotropic medications;
- assessment of consequences of delirium (e.g., post-traumatic symptoms, cognitive impairment); and
- psychoeducation about delirium for patients and their care partners.

This recommendation is based on a targeted review of the literature on follow-up care for patients with delirium following transition to another care setting or discharge home.

#### Medication Review, Reconciliation, and Reassessment

As discussed in the evidence for Statement 14, a detailed medication review and medication reconciliation is important at transitions of care, including transfer of patients to other care settings. A systematic review of medication reconciliation studies showed reductions in drug discrepancies at transitions of care, although the quality of the evidence was low (Redmond et al. 2018). More recently, a cluster randomized trial in Canada examined the benefits of electronic retrieval of outpatient medication information in facilitating medication reconciliation in 3,491 discharged patients and also found a reduction in medication discrepancies (Tamblyn et al. 2019). Although studies have not found differences in other outcomes, such as risks of adverse drug effects, follow-up has usually been limited to 30 days of discharge (McDonald et al. 2022; Redmond et al. 2018; Tamblyn et al. 2019). Furthermore, other guidelines support reviewing medications to reduce those that are associated with higher risks of adverse effects in older individuals (American Geriatrics Society Beers Criteria® Update Expert Panel 2023).

Multiple retrospective studies suggest that a significant fraction of individuals with in-hospital delirium are discharged on an antipsychotic or sedative medication without receiving instructions to taper or discontinue the medication. In three studies of ICU patients who were on an antipsychotic medication for delirium when transitioned out of the ICU, 21% to 61% remained on the medication when discharged from the hospital (Boncyk et al. 2021; Dixit et al., 2021; Flurie et al. 2015). One retrospective chart review of 691 patients older than 65 who were prescribed an antipsychotic during hospital stay (i.e., ICU, general medical, and surgical patients) found approximately 30% were discharged on the antipsychotic (Johnson et al. 2017). Of those, 82% had a diagnosis of delirium. Only approximately 12% of patients with delirium who were discharged on an antipsychotic received instructions to discontinue the antipsychotic (Johnson et al. 2017). In another study about half of patients (49%) discharged from an ICU on an antipsychotic medication received instructions in their discharge letter regarding tapering their medication, following up with a neurologist, seeking a psychiatric consultation, or explaining conditions in which their antipsychotic dose should be increased (Lambert et al. 2021).

Detailed medication review, medication reconciliation, and reassessment of the need for psychotropics may be able to decrease patients' exposure to inappropriate continuation of medication after transitions of care (Adeola et al. 2018; D'Angelo et al. 2019; Kram et al 2019; Stuart et al. 2020; see Appendix C, Statement 14). Although use of an electronic medication review and handoff tool reduced prescribing of antipsychotic medications on transitioning from the ICU, it was not associated with a reduced odds of antipsychotic prescribing at hospital discharge (OR 0.97, 95% CI 0.57–1.65) in one study (Kram et al. 2019). In contrast, other studies show benefits of medication-related interventions at discharge. For example, a cluster randomized trial in Canada used a software product aimed at identifying deprescribing opportunities in 5,698 hospitalized participants ages 65 and older who were taking at least five medications per day (McDonald et al. 2022). Although the primary outcome of adverse drug effects after discharge was no different between groups, rates of deprescribing were greater for individuals in the intervention group when compared to medication reconciliation alone (55.4% vs. 29.8%) (McDonald et al. 2022). In another Canadian study that used an interrupted time series analysis in 15,932 patients ages 66 and older (18,405 hospital discharges), the proportion of patients who received a prescription for a benzodiazepine, antipsychotic, or gastric acid suppressant declined from 16.3% to 13.4% with implementation of electronic medication reconciliation (Welk et al. 2021). For patients newly treated in the hospital with a benzodiazepine or antipsychotic medication, there was a small but significant decline in the proportion who returned to the hospital with a fracture or fall within 90 days of discharge (Welk et al. 2021). A study of 158 ICU patients prescribed antipsychotics for delirium had a significant decrease in antipsychotic prescribing at hospital discharge (32.9% vs 7.6%, $P<0.001$) following a pharmacist-led antipsychotic discontinuation protocol for delirium (Stuart et al. 2020). A medication tapering bundle intervention (D'Angelo et al. 2019) was also associated with significantly lower odds of antipsychotic continuation at hospital discharge (OR 0.40, 95% CI .018–0.89, $P=0.024$).

### Continued Assessment for Persistence and Consequences of Delirium

In support of helping patients achieve better recovery, practice guidelines and consensus statements recommend continued assessment of cognitive and physical functioning at the next level of care following transition or at home/in the community following hospital discharge (Guthrie et al. 2018; Mikkelsen et al. 2020). Ongoing cognitive assessment for persistence of delirium after discharge is crucial because delirium is a powerful predictor of new-onset dementia compared with patients without delirium (OR 11.9, 95% CI 7.29–19.6, $P<0.001$ [Pereira et al. 2021]). In a prospective survey of ICU patients (median age 65), the 171 patients with delirium (18.7%) had higher scores on a questionnaire of cognitive failures at 18 months post-discharge compared to those without delirium (van den Boogaard et al. 2012). Of 821 adults with respiratory failure or shock in a medical or surgical ICU, persistent cognitive impairment occurred and persisted in at least one-third of patients (Pandharipande et al. 2013). In addition, global cognitive impairment and worse executive function were found in patients with longer durations of delirium ($P<0.05$ or less at 3 and 12 months for both measures) (Pandharipande et al. 2013). Persistence of delirium in the months following discharge is also associated with greater rates of emergency visits, hospitalization, or death (Cole et al. 2017). Further, a meta-analysis of 23 studies among surgical and nonsurgical populations found a significant association between delirium and cognitive decline at 3 or more months following the delirium episode (Hedges g=0.45, 95% CI 0.34–

0.57, *P*<0.001 [Goldberg et al. 2020]). Over the long term (e.g., 24 to 36 months), ongoing cognitive assessment may be useful for monitoring disease course and fluctuations in symptoms (Cole and McCusker 2016). Physically, patients who develop delirium during hospitalization are at risk of greater functional decline and disability than hospitalized patients without delirium (Wilson et al. 2020).

In addition to post-discharge assessment of cognition, other long-term consequences of delirium can include anxiety, depression, posttraumatic stress disorder (PTSD), and lower quality of life (Bolton et al. 2021; Ramnarain et al. 2023; Wilson et al. 2020). Assessing for PTSD is particularly important for ICU patients with delirium, who in some studies demonstrate an increased risk of PTSD for up to 1 year following ICU stay (Bolton et al. 2021). For example, in 556 adults (median age 62) who had been hospitalized in an ICU with respiratory failure and/or shock, depression occurred in 36% and PTSD in 5% at 3- and 12-months post-discharge (Rengel et al. 2021). In an observational multicenter study in Norway, univariate analysis suggested that adult ICU patients (N=273) were more likely to exhibit evidence of post-traumatic stress at 3 months (as measured by the Impact of Event Scale-Revised [IES-R]) if they experienced delirium during the ICU stay although this was no longer significant on multivariable analysis (Friberg et al. 2023). Delirium was also associated with an increased risk of PTSD symptoms (as measured by the PTSD checklist—civilian version) on univariate and multivariable analyses in 205 patients with a nontraumatic intracerebral hemorrhage (Griffin et al. 2023). An Australian prospective cohort study of 103 adults who were mechanically ventilated in an ICU found that the 36% of patients with delirium were more likely to have symptoms of PTSD at 12 months on the IES-R (Bulic et al. 2020). A study of 198 adult patients who had stayed at least 4 days in an ICU in South Wales and visited an ICU follow-up clinic found that increased rates of PTSD as measured by the UK-Post-Traumatic Stress Syndrome 14-Questions Inventory were associated with a diagnosis of delirium as well as lower age, lower illness severity, and pre-illness psychopathology (Battle et al. 2017). However, other studies do not show an increased risk of PTSD with delirium as compared to ICU patients without delirium, although both groups show increased rates of PTSD and other psychiatric symptoms after discharge (Weidman et al. 2022; Wolters et al. 2016). Collectively, this evidence underscores the need for continued assessment post discharge to monitor patients for changes in functioning and, where possible, inform the use of interventions to help slow physical, cognitive, and psychosocial decline.

Little research has examined the quality of documentation of patients with delirium at discharge. The impact of follow-up interventions after delirium or critical care hospitalization has also been insufficiently studied (Schofield-Robinson et al. 2018). One retrospective chart review among Canadian patients with probable or definite delirium during hospitalization (N=110; Chuen et al. 2021) found only about one-quarter (25.4%) included instructions for follow-up care (e.g., cognitive assessment, specialist appointment). Other studies also suggest significant gaps in documentation at discharge (Johnson et al. 2017; Lambert et al. 2021) in patients who have experienced delirium in the hospital. This suggests post discharge care may be suboptimal for many patients and could benefit from strategies to ensure that quality standards are met.

### Psychoeducation About Delirium

Caregivers and family could also help play a role in ensuring patients receive recovery-enhancing interventions. A recent literature review on interventions to support recovery from delirium found that

strategies increasing the chances of long-term recovery include physical activities, such as rehabilitation and exercise programs to improve functioning and reduce frailty; cognitive activities, such as reality orientation, memory exercises, and cognitive stimulation; and emotional strategies, such as discussing any negative emotions about their delirium experience with a trusted person (O'Rourke et al. 2021).

Caregiver and family education are a necessary aspect of quality post discharge care for patients with delirium. A recent systematic literature review found families often do not receive enough information about delirium from healthcare professionals but that they would like to be more informed and included in helping to recognize and monitor for delirium in their loved one (Shrestha and Fick 2020). Desired information includes content about delirium etiology, pathologies, treatments, disease course, and non-pharmacological interventions to prevent and manage illness (Shrestha and Fick 2020). Studies suggest that, when properly educated, families can be reliable informants and can accurately identify and describe in detail the patient's delirium symptoms (Shrestha and Fick, 2020).

Finally, a small randomized controlled feasibility trial (N=35) pilot tested a transition-to-home model of care for older adults with delirium and their caregivers (Khan et al. 2022). The model included a multi-component intervention that involved assessment for diagnosis of a cognitive disorder, medication review, patient and family education, assessment of functioning, and setting health goals. The intervention demonstrated feasibility but resulted in no differences in 30-day readmission or emergency department visits between intervention and control patients.

More research is needed to understand the effects of other caregiver- or family-led delirium interventions following release from the hospital. The TRAnsport and DElirium in older people (TRADE) project is currently being pilot tested in Germany and aims to determine the effects of a complex caregiver intervention both during hospital stay and after discharge (e.g., to home, to rehabilitation) on outcomes of delirium incidence and cognitive functioning (Leinert et al. 2021). Included in the intervention is education about non-pharmacologic intervention strategies that can be implemented by families at home, such as supporting orientation, adapting communication, and promoting exercise. Positive findings from this and similar studies could lead to increased efforts to incorporate caregivers and family in the dissemination of post discharge interventions.

### Grading of the Overall Supporting Body of Research Evidence for Follow-up Planning at Transitions of Care

In the absence of a detailed systematic review on follow-up planning at transitions of care for patients with delirium, no grading of the body of research evidence is possible.

# Appendix D. Evidence Tables for Individual Studies Supporting Guideline Statements

## Non-Pharmacological Interventions for Prevention of Delirium

### *Multi-Component Interventions*

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Abbasinia et al. (2021) | Design: RCT<br>Setting: ICU<br>Country: Iran<br>Funding: None | Randomized N: 60<br>Analyzed N: 60<br>Intervention (N=30): Video tutorial before surgery and HELP protocol after surgery; HELP consisted of reorientation, therapeutic activities, reduced use and doses of psychoactive drugs, early mobilization, promotion of sleep, maintenance of adequate hydration and nutrition, and provision of vision and hearing adaptations.<br>Control (N=30): Usual care<br>Duration: During ICU stay<br>Follow-up (days): 3, Discharge | Inclusion: ≥18 years, candidate for CABG, and alert at the time of admission<br>Exclusion: Being admitted due to infectious disease, deterioration of the patient's condition after surgery, or history of previous major surgery | Mean (SD) age: 57.7 (10.24)<br>Female %: 45<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: There were no significant differences in the rate of delirium episodes and mean scores of RASS between both groups in the 2nd (p=0.301, p=0.125) and 3rd days (p=0.389, p=0.057) after surgery, respectively. However, the mean duration of ICU stays after surgery was significantly lower in the intervention group compared with the control group (p=0.042).<br>Overall attrition: 0% | Moderate |
| Avendano-Cespedes et al. (2016); MID-Nurse-P | Design: RCT<br>Setting: Inpatient<br>Country: Spain<br>Funding: Government | Randomized N: 50<br>Analyzed N: 50<br>Intervention (N=21): Multi-component nurse-led intervention of risk factor analysis and interventions for identified risk factors; provided within first 24 hours of admission and daily until discharge<br>Control (N=29): Usual care<br>Duration: During hospitalization<br>Follow-up (days): 16 | Inclusion: ≥65 years hospitalized patients<br>Exclusion: Severe cognitive decline | Mean (SD) age: 86 (5.5)<br>Female %: 48<br>Race %: NR<br>Delirium %: 18<br>Pfeiffer's Short Portable Mental Status Questionnaire (0-10 errors) score: 4.5<br>Dementia %: "severe" cognitive decline excluded<br>Postop %: NR<br>Cancer %: NR | Main outcomes: Delirium prevalence (33.3% vs. 48.3%) and incidence (14.3% vs. 41.4%, p=0.039) were reduced in the intervention group vs. control. Total delirium severity was lower in the intervention group vs. control (35.0 vs. 65.0, p=0.040). Mortality was not different between groups (19.0% vs. 17.2%).<br>Overall attrition: 0% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Boockvar et al. (2020); HELP-LTC | Design: RCT<br>Setting: Nursing homes<br>Country: U.S.<br>Funding: Mixed | Randomized N: 219<br>Analyzed N: 219<br>Intervention (N=114): Long-term care facility adapted HELP; a multi-component intervention targeting delirium risk factors of cognitive impairment, immobility, dehydration, and malnutrition; delivered by certified nursing assistants<br>Control (N=105): Usual care<br>Duration: During acute illness<br>Follow-up (days): 7, 30 | Inclusion: Care homes residents who were suspected of having onset of acute illness or change in condition within the prior 24-48 hours<br>Exclusion: Receiving hospice care or not determined to have a change in condition after further screening | Mean (SD) age: 81.7 (1.1)<br>Female %: 65.3<br>Race %:<br>Caucasian: 33.3<br>Black/African American: 35.2<br>Asian: NR<br>Hispanic: 29.7<br>Other: 1.8<br>Delirium %: NR<br>Mean (SD) physical function, ADL score: 15.2 (0.7)<br>Non-Alzheimer's dementia %: 52.5<br>Alzheimer's disease %: 10.5<br>Postop %: NR<br>Cancer %: NR<br>Hospitalized in the past 12 months %: 60.7 | Main outcomes: Delirium symptoms declined over the course of the episode (mean CAM-S=3.63 at start vs. 3.27 at end). Overall, 33.8% of the total sample experienced incident delirium. After adjusting for baseline cognitive function, no significant differences were found in delirium or delirium severity (CAM-S=3.6 for the intervention group vs. 2.8 for the control group) between groups. Hospitalization was not significantly different between groups.<br>Attrition at follow-up: 11% vs. 21% | High |
| Boustani et al. (2012); Khan et al. (2013); e-CHAMPS trial | Design: RCT<br>Setting: Inpatient<br>Country: U.S.<br>Funding: Government | Randomized N: 424<br>Analyzed N: 424<br>Intervention (N=199): Clinical decision support system to alert physicians to the presence of cognitive impairment, recommend early referral to a geriatrician, and suggest discontinuation of the use of urinary catheters, physical restraints, and anticholinergic drugs<br>Control (N=225): Usual care<br>Duration: During hospitalization<br>Follow-up (days): Until discharge, 30 | Inclusion: ≥65 years, hospitalized, with cognitive impairment<br>Exclusion: Those with aphasia | Mean (SD) age: 77.2 (8.1)<br>Female %: 65.7<br>Race %:<br>Caucasian: NR<br>Black/African American: 59.5<br>Asian: NR<br>Other: NR<br>Delirium %: 30.6<br>Mean (SD) Charlson Comorbidity Index: 2.1 (1.9)<br>Dementia %: NR<br>Mean (SD) SPMSQ: 5.1 (2.7)<br>Postop %: NR<br>Cancer %: NR | Main outcomes: No difference was found in the incidence of delirium (33.7% vs. 31.1%, p=0.78). Similar results were found when analyzing those with delirium at baseline only (data NR).<br>Attrition: NR | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| Caplan et al. (2006); The REACH-OUT trial | Design: RCT<br>Setting: Inpatient<br>Country: Australia<br>Funding: Government | Randomized N: 104<br>Analyzed N: 70<br>Intervention (N=70): Home rehabilitation service provided by a hospital-based multidisciplinary outreach service made up of nurses, physiotherapists, occupational therapists, and doctors<br>Control (N=34): Usual care in geriatric rehabilitation ward in hospital<br>Intervention duration: Mean of 20 visits<br>Control duration: During hospitalization<br>Follow-up (days): 30, 182 | Inclusion: Patients with a LOS >6 days who were referred for geriatric rehabilitation, expected to return home, and lived reasonably independent after rehabilitation<br>Exclusion: Patients who lived in a nursing home | Mean (SD) age: 83.9 (7.55)<br>Female %: 62.5<br>Race %: NR<br>Delirium %: NR<br>Mean (SD) FIM: 76.44 (21.17)<br>Dementia %: 25<br>Postop %: NR<br>Cancer %: NR<br>Mean (SD) number of medications at baseline: 5.66 (3.22) | Main outcomes: Lower odds of delirium were found in the home rehabilitation group (OR 0.17, 95% CI 0.03 to 0.65).<br>Attrition: 24% vs. 26% | Moderate |
| Chen et al. (2011); mHELP | Design: Non-RCT<br>Setting: Inpatient<br>Country: Taiwan<br>Funding: Government | Randomized N: 189<br>Analyzed N: 179<br>Intervention (N=107): mHELP consisting of early mobilization, nutritional assistance, and therapeutic (cognitive) activities implemented by a trained nurse<br>Control (N=82): Usual care<br>Duration: Daily during hospitalization<br>Follow-up (days): Unclear | Inclusion: ≥65 years, admitted to the 36-bed GI ward, scheduled for elective abdominal surgery, and expected LOS of >6 days<br>Exclusion: Profound sensory impairment or aphasia, intubation or respiratory isolation, severe dementia, coma, or critical condition | Mean (SD) age: 73 (5.71)<br>Female %: 45<br>Race %: NR<br>Delirium %: NR<br>Mean (SD) MMSE (scale 0-30): 26.6 (4.05)<br>Dementia %: "severe" dementia excluded<br>Postop %: 100<br>Cancer %: 78<br>Mean (SD) duration of surgery minutes: 214.8 (82.2) | Main outcomes: Delirium rate was significantly lower in the mHELP group (0%) vs. the control group (16.7%) (p<0.001).<br>Attrition: 5% vs. 6% | Moderate |
| Chen et al. (2017); mHELP | Design: RCT<br>Setting: Postop, abdominal<br>Country: Taiwan | Randomized N: 377<br>Analyzed N: 375<br>Intervention (N=197): mHELP consisting of daily orienting communication, oral and nutritional assistance, and early mobilization<br>Control (N=180): Usual care | Inclusion: ≥65 years, admitted to 1 of two 36-bed GI wards of a single hospital, scheduled for elective abdominal surgery, and expected LOS >6 days | Mean (SD) age: 74 (5.9)<br>Female %: 44<br>Race %: NR<br>Delirium %: NR<br>Mean (SD) MMSE (scale 0-30): 26.9 (3.48)<br>Dementia %: NR | Main outcomes: POD occurred in 13/196 (6.6%) mHELP participants vs. 27/179 (15.1%) control individuals (RR 0.44 in the mHELP group) (95% CI 0.23 to 0.83, p=0.008). The | Moderate |

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| | Funding: Government | Duration: Daily during hospitalization<br>Follow-up (days): Unclear | Exclusion: NR | Postop %: 100<br>Cancer %: 91<br>Median (IQR) duration of surgery minutes: 195 (105) vs. 213 (98)* *Not reported overall or with means to be able to calculate | intervention group had a shorter median LOS (12.0 days) vs. control participants (14.0 days) (p=0.04).<br>Attrition: 3% vs. 2% | |
| Dong et al. (2020); mHELP | Design: RCT<br>Setting: Inpatient<br>Country: China<br>Funding: Government | Randomized N: 106<br>Analyzed N: 103<br>Intervention (N=53): mHELP including delirium and dementia improvement plans and multiple medication management plan; the assessment of delirium risk factors, delirium diagnosis, and multidisciplinary intervention for elderly patients with severe acute pancreatitis<br>Control (N=53): Usual care<br>Duration: During hospitalization<br>Follow-up (days): 14 | Inclusion: ≥70 years with severe acute pancreatitis and expected hospital stay >2 weeks<br>Exclusion: History of severe acute pancreatitis, coma, mental disorders, dementia, low immune function, or end-stage disease | Mean (SD) age: 76.1 (4.5)<br>Female %: 36<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: 0 (excluded)<br>Postop %: NR<br>Cancer %: NR | Main outcomes: The incidence of delirium was 4.00% in the intervention group and 16.98% in the control group; the difference was statistically significant (p=0.033).<br>Attrition: 6% vs. 0% | Moderate |
| Guo et al. (2016) | Design: RCT<br>Setting: Postop, cancer<br>Country: China<br>Funding: None | Randomized N: 182<br>Analyzed N: 160<br>Intervention (N=91): Multi-component, non-pharmacologic intervention focusing on general geriatric approaches and supportive nursing care; nursing staff received training and guidance from a geriatric specialist and pre-operatively provided this guidance to the patient. Tools (e.g., calendars, clocks, glasses, etc.) were repeatedly offered to accomplish time, place, and character orientation. For patients with endotracheal intubation or a tracheostomy, communication card and | Inclusion: Age 65-80 years undergoing tumor resection surgery with a duration of postop stay in the ICU ≥3 days<br>Exclusion: History of CNS disorder or mental illness or MMSE <24 or dementia | Mean (SD) age: 73.5 (5.6)<br>Female %: 59<br>Race %: NR<br>Delirium %: NR<br>Mean (SD) preop Charlson's Comorbidity Index: 1.6 (0.8)<br>Mean (SD) preop MMSE: 27.2 (1.9)<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: 100<br>Mean (SD) LOS minutes: 213 (68) | Main outcomes: Compared with usual care, the intervention group experienced less POD (incidence and duration, p<0.05).<br>Attrition: 11% vs. 13% | Moderate |

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| | | WordPad were created. Noise was decreased as much as possible, and measures were adopted to create a good sleep-wake cycle. Sleep mask and ear plugs were allocated. If possible, no restraints or indwelling catheters were applied. Bedside MP3 players were provided to play light music.; three times a day<br>Control (N=91): Usual care<br>Duration: During ICU stay<br>Follow-up (days): 1, 2, 3 | | | | |
| Hamzehpour et al. (2018) | Design: RCT<br>Setting: ICU<br>Country: Iran<br>Funding: University | Randomized N: 100<br>Analyzed N: 100<br>Intervention (N=50): Based on the Roy adaptation model for identifying and converting maladaptive behaviors (delirium) to adaptive behaviors in 7 physiological dimensions by increasing, decreasing, or adjusting each trigger<br>Control (N=50): Usual care<br>Duration: During ICU stay<br>Follow-up (days): 7 | Inclusion: ≥18 years, GCS >7, with no mental illness<br>Exclusion: Those who died during the study | Mean (SD) age: 47.7 (22.6)<br>Female %: 27<br>Race %: NR<br>Delirium %: NR<br>Mean GCS at baseline: 11.6<br>Dementia %: NR, but excluded mental illness<br>Postop %: 98<br>Cancer %: NR<br>Received MV %: 30 | Main outcomes: Mean Neecham score on 4$^{th}$ day was lower in the control group vs. intervention (17.40 vs. 20.58, p<0.028) as well as on the 4$^{th}$ night (16.78 vs. 21.35, p<0.001).<br>Overall attrition: 0% | Moderate |
| Hempenius et al. (2013; 2016); LIFE trial | Design: RCT<br>Setting: Postop, cancer<br>Country: The Netherlands<br>Funding: Government | Randomized N: 297<br>Analyzed N: 260<br>Intervention (N=148): Geriatric team delivered a multi-component intervention focused on best supportive care and the prevention of delirium; a preop checklist of medical history was completed, and an individual treatment plan was drawn up based on patient-related risk factors.; daily | Inclusion: ≥65 years, undergoing elective surgery for a solid tumor, and frail<br>Exclusion: Unable to complete the study protocol, follow-up schedule before inclusion, and fill in the questionnaires | Mean (SD) age: 77.54 (7.22)<br>Female %: 64<br>Race %: NR<br>Delirium %: NR<br>Mean (SD) SF-36 Physical Function Scale: 48.03 (30.53)<br>Dementia %: NR<br>Mean (SD) MMSE: 26.5 (3.47) | Main outcomes: Delirium occurred in 31/260 patients (11.9%), and there was no significant difference on the incidence of delirium between the intervention group and the usual care group (9.4% vs. 14.3%, OR 0.63, 95% CI 0.29 to 1.35). | Moderate |

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| | | Control (N=149): Usual care<br>Duration: During hospitalization<br>Follow-up (days): Until discharge | | Postop %: 100<br>Cancer %: 100 | There were no differences between the groups for any of the outcomes 3 months after discharge. The presence of POD was associated with an increased risk of decline in ADL functioning (OR 2.65, 95% CI 1.02 to 6.88), an increased use of supportive assistance (OR 2.45, 95% CI 1.02 to 5.87), and a decreased chance to return to the independent preop living situation (OR 0.18, 95% CI 0.07 to 0.49).<br>Attrition at follow-up: 14% vs. 11% | |
| Hosie et al. (2020); PRESERVE Pilot Study | Design: RCT<br>Setting: Palliative<br>Country: Australia<br>Funding: Mixed | Randomized N: 72<br>Analyzed N: 65<br>Intervention (N=20): Multi-component intervention consisting of 6 domains: eating and drinking, sleep, exercise, reorientation, vision and hearing, and family partnership<br>Intervention 2 (N=27): Waitlist<br>Control (N=25): No intervention<br>Duration: During admission<br>Follow-up (days): 7 | Inclusion: ≥18 years with advanced (stage 4) cancer and 1 of the 4-specialist palliative care inpatient units<br>Exclusion: NR | Mean (SD) age: 71.8 (12.9)<br>Female %: 44<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: 100 | Main outcomes: One-third of control site patients (8/25, 32%) became delirious within 7 days of admissions vs. one-fifth (4/20, 20%) at intervention and waitlist sites (p=0.5). Mean (SD) delirium severity (DRS-R-98) scores were 16.8 (12.0) control sites vs. 18.4 (8.2) (p=0.6) intervention and 18.7 (7.8) (p=0.5) waitlist sites. The intervention caused no adverse events.<br>Attrition: 0% vs. 26% vs. 0% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| Khan et al. (2013); Boustani et al. (2012); e-CHAMP trial | Design: Subgroup analysis of RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: Government | Randomized N: 60 (those transferred to the ICU for at least 1 day among the original 424 patients enrolled in the e-CHAMPS trial)<br>Analyzed N: 60<br>Intervention (N=30): Clinical decision support system to alert physicians to the presence of cognitive impairment, recommend early referral to a geriatrician, and suggest discontinuation of the use of urinary catheters, physical restraints, and anticholinergic drugs<br>Control (N=30): Usual care<br>Duration: During hospitalization<br>Follow-up (days): Until discharge, 30 | Inclusion: ≥65 years, enrolled in the e-CHAMPS trial, transferred to the ICU during hospital stay<br>Exclusion: Those who had previously been enrolled in any other study, were aphasic, or were unresponsive at the time of screening | Mean (SD) age: 74.6 (8.4)<br>Female %: 52<br>Race %:<br>Caucasian: NR<br>Black/African American: 45%<br>Asian: NR<br>Other: NR<br>Delirium %: 0% (excluded)<br>Mean (SD) Charlson Comorbidity Index: 2.3 (1.8)<br>Mean (SD) APS: 32.4 (17.6)<br>Mean (SD) SPMSQ: 5.0 (2.9)<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR<br>Received MV: 17% | Main outcomes: No difference was found in the incidence of delirium (intervention: 27% vs. usual care: 29%, p=0.85).<br>Attrition: NR | Moderate |
| Moon and Lee (2015) | Design: RCT<br>Setting: ICU<br>Country: South Korea<br>Funding: University | Randomized N: 134<br>Analyzed N: 123<br>Intervention (N=65): Multi-component intervention of delirium risk monitoring and screening cognitive, sensory, physical, and social changes; cognitive assessment and orientation; environment interventions; and early therapeutic interventions<br>Control (N=69): Usual care<br>Intervention duration: Daily for 7 days<br>Control duration: Daily during hospitalization<br>Follow-up (days): 7, 30 | Inclusion: ≥18 years, hospitalized for ≥48 hours in the ICU<br>Exclusion: Persistent score of -4 or -5 on RASS, MMSE-K score of ≤23, admission to isolation ward due to infection, or death or discharge on the day of admission | Mean (SD) age: 69.7 (13.1)<br>Female %: 51.2<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR<br>Ever used ventilator %: 21.1 | Main outcomes: Application of the intervention had no significant effect on delirium incidence, in-hospital mortality, re-admission to the ICU, or ICU LOS. Whereas the risk of 30-day in-hospital mortality was not significantly lower in the intervention than in the control group (OR 0.33, 95% CI 0.10 to 1.09), a significantly decreased 7-day in-hospital mortality was found in the intervention group (HR 0.09, 95% CI 0.01 to 0.72). | Moderate |

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| | | | | | Attrition: 8% vs. 9% | |
| Lapane et al. (2011); GRAM software | Design: RCT<br>Setting: Nursing homes<br>Country: U.S.<br>Funding: Government | Randomized N: Unclear<br>Analyzed N: 3,538<br>Intervention (N=1,769): GRAM software used to identify patients with risk factors for falls and delirium, and when identified, implementing a resident assessment protocol<br>Control (N=1,769): Usual care<br>Intervention duration: Within 24 hours of admission for new admissions and every 30 days for long-term residents<br>Control duration: Unclear<br>Follow-up (days): Unclear | Inclusion: ≥50 geriatric bed, Medicare and Medicaid certified nursing homes with few short-stay residents<br>Exclusion: NR | Mean age: 65-85<br>Female %: 70<br>Race %:<br>Caucasian: NR<br>Black/African American: NR<br>Asian: NR<br>Other: 14.5<br>Delirium %: 3<br>Moderate cognitive impairment %: 47<br>Severe cognitive impairment %: 24<br>Dementia %: 39<br>Postop %: NR<br>Cancer %: 10<br>Taking 6-9 medications at time of intervention %: 30.3<br>Taking ≥10 medications at time of intervention %: 56.3 | Main outcomes: Newly admitted residents in the intervention homes experienced a lower rate of potential delirium onset (adjusted HR 50.42, 95% CI 50.35 to 0.52), overall hospitalization (adjusted HR 50.89, 95% CI 50.72 to 1.09), and mortality (adjusted HR 50.88, 95% CI 50.66 to 1.16) than those in usual care homes. In longer stay residents, the effects of the intervention were attenuated.<br>Attrition: NR | High |
| Lundström et al. (2005) | Design: RCT<br>Setting: Inpatient<br>Country: Sweden<br>Funding: Mixed | Randomized N: 400<br>Analyzed N: 400<br>Intervention (N=200): Geriatric ward' staff education in delirium assessment, prevention, and treatment; re-organization from a task-allocation care system to a patient-allocation system with individualized care<br>Control (N=200): Usual care<br>Intervention duration: Daily until discharge | Inclusion: ≥70 years admitted to 2 wards over an 8-month period<br>Exclusion: NR | Mean (SD) age: 80.0 (5.9)<br>Female %: 55.7<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: 4.5<br>Mean (SD) MMSE: 25.2 (6)<br>Postop %: NR<br>Cancer %: NR | Main outcomes: Delirium was equally common on the day of admission at the 2 wards, but fewer patients remained delirious on day 7 on the intervention ward (19/63, 30.2%) vs. in the usual care group (37/62, 59.7%) (p=0.001).<br>Attrition: NR | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | Control duration: During hospitalization<br>Follow-up (days): Until discharge | | | | |
| Lundström et al. (2007); Stenvall et al. (2012) | Design: RCT<br>Setting: Postop, orthopedic<br>Country: Sweden<br>Funding: Government | Randomized N: 199<br>Analyzed N: 199<br>Intervention (N=102): Postop multi-factorial intervention program in a 24-bed geriatric unit specializing in geriatric orthopedic patients where the staff worked as a team, applying comprehensive geriatric assessment, management, and rehabilitation<br>Control (N=97): Usual care<br>Intervention duration: Daily until discharge<br>Control duration: During hospitalization<br>Follow-up (days): Until discharge | Inclusion: ≥70 years, with femoral neck fracture<br>Exclusion: Severe RA, hip osteoarthritis, and renal failure; pathological fracture; patients bedridden before the fracture | Mean (SD) age: 82.1 (6.1)<br>Female %: 74.4<br>Race %: NR<br>Delirium %: 26.3<br>Functioning: NR<br>Dementia %: 32<br>Postop %: 100<br>Cancer %: NR<br>Mean (SD) number of medications: 5.8 (3.7) | Main outcomes: Days with POD were fewer in the intervention group vs. control group (5.0 days [7.1] vs. 10.2 days [13.3], p=0.009). A lower proportion of the intervention patients was delirious post-operatively vs. controls (56/102 [54.9%] vs. 73/97 [75.3%], p=0.003). 18% in the intervention group vs. 52% controls were delirious after the postop day 7 (p<0.001). Intervention patients suffered from fewer complications, such as decubitus ulcers, urinary tract infections, nutritional complications, sleeping problems, and falls than controls.<br>Attrition: 6% vs. 7% | Moderate |
| Rice et al. (2017); mHELP | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: Non-profit | Randomized N: 134<br>Analyzed N: 125<br>Intervention (N=67): Multi-component intervention including all standardized stroke care; the intervention was also augmented by 1) therapeutic activities twice daily based on mHELP and 2) calculated anticholinergic burden and | Inclusion: ≥50 years admitted to a 32-bed neurological ICU or a 44-bed stroke unit<br>Exclusion: Delirium at baseline, aphasia, or LOS <48 hours | Mean (SD) age: 66 (10)<br>Female %: 43<br>Race %:<br>Caucasian: 48<br>Black/African American: 47<br>Asian: 1.6<br>Other: 3.2<br>Delirium %: 0 (excluded) | Main outcomes: Delirium incidence was 8% (10/125) with 3 subjects in the intervention group vs. 7 in the usual care group.<br>Attrition at follow-up: 12% vs. 1% | Moderate |

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| | | drug risk each day by clinical pharmacists, using AChB and ADS, to guide medication recommendations<br>Control (N=67): Usual care<br>Duration: Daily during hospitalization<br>Follow-up (days): Unclear | | Function: NR<br>Dementia %: NR<br>Mean (SD) NIHSS: 4.76 (4.91)<br>Mean (SD) MoCA: 20.4 (5.95)<br>Postop %: NR<br>Cancer %: NR | | |
| Rood et al. (2021); UNDERPIN-ICU study | Design: RCT<br>Setting: ICU<br>Country: the Netherlands<br>Funding: Government | Randomized N: 1,749<br>Analyzed N: 1,749<br>Intervention (N=924): Customized nursing interventions to reduce delirium aimed at visual and hearing impairment, orientation loss, sleep deprivation, cognitive impairment, and immobility<br>Control (N=825): Usual care<br>Duration: During ICU stay<br>Follow-up (days): 28 | Inclusion: ≥18 years, medical, surgical, and trauma critically ill patients that were at high-risk to develop delirium (E-PRE-DELIRIC score ≥35%), and delirium-free at time of ICU admission<br>Exclusion: Expected ICU stay <1 day or reliable assessment of delirium not possible (acute brain injury, sustained coma during completed ICU stay [RASS score ≤-3], audiovisual disorders, language problems, mental disability, or aphasia) | Mean (SD) age: 71 (10)<br>Female %: 40<br>Race %: NR<br>Delirium %: NR<br>Median (IQR) E-PRE-DELIRIC score %: 42 (37-49%)<br>Mean (SD) APACHE-IV score: 82 (30)<br>Dementia %: NR<br>-Documented history of cognitive impairment % (dementia, mild cognitive impairment, or delirium): 11.1<br>Postop %: 9.6<br>Cancer %: NR | Main outcomes: Patients in the intervention period had median 23 (IQR 4-27) delirium-free and coma-free days alive, compared to median 23 (IQR 5-27) days for patients in the control group (mean difference -1.21 days, 95% CI -2.84 to 0.42 days, p=0.15). Also, the number of delirium days was similar: median 2 days (IQR 1-4) (ratio of medians 0.90, 95% CI 0.75 to 1.09, p=0.27).<br>Overall attrition: 0% | Moderate |
| Siddiqi et al. (2016); Stop Delirium! | Design: RCT<br>Setting: Nursing homes<br>Country: U.K. | Randomized N: 215<br>Analyzed N: 160<br>Intervention (N=103): Stop Delirium!; a 16-month-enhanced educational package | Inclusion: Residents of included care homes<br>Exclusion: Those | Mean (SD) age: 84 (8.4)<br>Female %: 69<br>Race %: | Main outcomes: 1-month delirium prevalence was 4.0% in intervention vs. 7.1% in control homes. | High |

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| | Funding: Government | incorporating multiple strategies to support care home staff to address key delirium risk factors<br>Control (N=112): Usual care<br>Duration: Unclear<br>Follow-up (days): 480 | receiving end of life care | Caucasian: 99.5<br>Black/African American: 0.5<br>Asian: 0<br>Other: 0<br>Delirium %: 1.4<br>Cognitive impairment % (6-CIT score ≥8): 70<br>Median Charlson comorbidity score (scale 0-37): 1.0 (range 0-8)<br>Dementia %: 42<br>Postop %: NR<br>Cancer %: NR<br>End of life/palliative care %: 0 (excluded)<br>Mean (SD) number of medications taken at baseline: 7.3 (4.1) | Attrition: 27% vs. 24% | |
| Verloo et al. (2015) | Design: RCT<br>Setting: Home care<br>Country: Switzerland<br>Funding: Government and university | Randomized N: 114<br>Analyzed N: 103<br>Intervention (N=56): Multi-component person-centered nursing interventions consisting of assessment, detection, monitoring, support, dispensed care, health promotion, and education<br>Control (N=58): Usual care<br>Intervention 1 duration: Within 2 days of starting study, then again on days 3, 7, 14, and 21<br>Control duration: Mean (SD) of 2.28 (0.84) weekly visits per person<br>Follow-up (days): 30 | Inclusion: ≥65 years, recently discharged from hospital with a prescription for home health care<br>Exclusion: Those who had outpatient treatment within the hospital premises and a medical prescription for a single intervention of home health care and were outside the study reach | Mean age: 83<br>Female %: 65<br>Race %: NR<br>Delirium %: NR<br>Mean number of delirium symptoms at baseline (CAM 0-9): 2.5<br>Dementia %: NR<br>Mean MMSE: 23.88<br>Mean IQCODE: 3.68<br>Postop %: NR<br>Cancer %: NR | Main outcomes: There were no statistical differences regarding symptoms of delirium (p=0.085), cognitive impairment (p=0.151), and functional status (p=0.235) between the intervention and control groups at study entry and at 1 month. After adjustment, statistical differences were found in favor of the intervention group for symptoms of delirium (p=0.046), cognitive | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | | | | impairment (p=0.015), and functional status (p=0.033).<br>Attrition at follow-up: 9% vs. 10% | |
| Wang Y.Y. et al. (2020); t-HELP | Design: RCT<br>Setting: Postop, elective other<br>Country: China<br>Funding: Government | Randomized N: 281<br>Analyzed N: 281<br>Intervention (N=152): t-HELP consisting of 3 universal protocols and 8 targeted protocols; the universal protocols included orientation, therapeutic activities, and early mobilization protocol; the targeted protocols were tailored for each patient based on delirium-related risk factors.<br>Control (N=129): Usual care<br>Duration: Daily until POD 7 or discharge<br>Follow-up (days): 30 | Inclusion: ≥70 years, scheduled for an elective surgical procedure with expected LOS >2 days<br>Exclusion: Delirium at baseline or severe dementia | Mean (SD) age: 75.7 (5.2)<br>Female %: 39<br>Race %: NR<br>Delirium %: 0 (excluded)<br>Cognitive function intact %: 83<br>Median (IQR) APACHE II: 15 (12-20) vs. 14 (12-20)*<br>*Reported as median for each group, not overall<br>Dementia %: "severe" dementia excluded<br>Postop %: 100<br>Cancer %: 96 | Main outcomes: POD occurred in 4 participants (2.6%) in the intervention group vs. 25 (19.4%) in the control group (RR 0.14, 95% CI 0.05 to 0.38). NNT to prevent 1 case of POD was 5.9 (95% CI 4.2 to 11.1).<br>Attrition: 13% vs. 11% | Low |
| Watne et al. (2014); Oslo Orthogeriatric Trial | Design: RCT<br>Setting: Postop, orthopedic<br>Country: Norway<br>Funding: Mixed | Randomized N: 329<br>Analyzed N: 329<br>Intervention (N=163): Multi-component intervention in the acute geriatric ward; geriatric assessment by nurses, nursing assistants, physiotherapists, occupational therapists, nutritionists, and social workers and daily interdisciplinary meetings<br>Intervention 2 (N=166): Usual care in the orthopedic ward<br>Intervention 1 duration: Daily until discharge | Inclusion: Patients admitted acutely to the hospital with a hip fracture<br>Exclusion: Hip fracture was a part of a high energy trauma (defined as a fall from higher than 1 m) or if they were moribund on admission | Median age: 85<br>Female %: 75.7<br>Race %: NR<br>Delirium %: 29.5<br>Median (IQR) Charlson Comorbidity Index: 1 (0-2)<br>Mean (SD) APACHE II: 9.4 (2.7)<br>Median Barthel Index: 18<br>Dementia %: 49<br>Postop %: 100<br>Cancer %: NR | Main outcomes: No significant difference was found in delirium rates (49% intervention group vs. 53% usual care group, p=0.51) or 4-month mortality (17% vs. 15%, p=0.50) between the intervention and the control groups.<br>Attrition: 2% vs 1% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Control duration: During hospitalization<br>Follow-up (days): 5, until discharge, 120, 365 | | Median (IQR) medications used regularly: 4.5 (2-7) | | |
| Young et al. (2020) | Design: RCT<br>Setting: Inpatient<br>Country: U.K.<br>Funding: Mixed | Randomized N: 713<br>Analyzed N: 713<br>Intervention (N=343): Multi-component intervention consisting of actions centered on 10 risk factors associated with the development of delirium; interventions directly affect the patient experience of care and include optimizing hydration and nutrition, reducing environmental triggers (excessive noise, multiple moves), increasing orientation to time and place, improving communicative practices (personally meaningful interaction and cognitive stimulation), and supporting and/or encouraging mobility and better management of pain and infection.<br>Control (N=370): Usual care<br>Duration: During hospitalization<br>Follow-up (days): 10, 30, 90 | Inclusion: ≥65 years admitted to study wards<br>Exclusion: Delirium present on admission, discharge planned within 48 hours, delirium assessment not performed by a researcher within 24 hours of admission or preop, end of life care being provided, or under the care of another ward | Mean (SD) age: 82.8 (7.9)<br>Female %: 68.3<br>Race %:<br>Caucasian: 91.7<br>Black/African American: NR<br>Asian: NR<br>Other: NR<br>Delirium %: 0 (excluded)<br>Mean (SD) Charlson comorbidity index score: 1.7 (1.9)<br>Cognitive impairment and/or dementia %: 21<br>Postop %: NR<br>Cancer %: NR | Main outcomes: Rates of new-onset delirium were lower than expected and did not differ between groups (24 [7.0%] intervention group vs. 33 [8.9%] control group, OR 0.68, 95% CI 0.37 to 1.26, p=0.2225).<br>Attrition at 10-day follow-up: 8% vs. 6% | Moderate |

*Abbreviations.* AChB=Anticholinergic Cognitive Burden scale; ADL=activities of daily living; ADS=Anticholinergic Drug Scale; APACHE II=Acute Physiology and Chronic Health Evaluation II; APACHE-IV=Acute Physiology and Chronic Health Evaluation-IV; APS=Acute Physiology Score; CABG=coronary artery bypass graf; CAM=Confusion Assessment Method; CAM-S=Confusion Assessment Method-Severity; CI=confidence interval; 6-CIT=6 item cognitive impairment test; CNS=central nervous system; DRS-R-98=Delirium Rating Scale-Revised-1998; e-CHAMPS=enhanced Care for Hospitalized older Adults with Memory Problems; E-PRE-DELIRIC=Early Prediction of Delirium in ICU Patients; FIM=functional independence measure; GCS=Glasgow Coma Scale; GI=gastrointestinal; GRAM=Geriatric Risk Assessment MedGuide; HELP=Hospital Elder Life Program; HELP-LTC=Hospital Elder Life Program-Long Term Care; HR=hazard ratio; ICU=intensive care unit; IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly; IQR=interquartile range; LIFE=Liaison Intervention in Frail Elderly; LOS=length of stay; mHELP=modified Hospital Elder Life Program; MID-Nurse-P=preventive multi-component non-pharmacologic nurse-led intervention randomized clinical trial; MMSE=Mini-Mental State Examination; MMSE-K=Mini-Mental State Examination-Korean version; MoCA=Montreal Cognitive Assessment; MV=medical ventilation; N=number; NIHSS=National Institutes of Health Stroke Scale; NNT=number needed to treat; NR=not reported; OR=odds ratio; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RA=rheumatoid arthritis; RASS=Richmond Agitation Sedation Scale; RCT=randomized controlled trial; REACH-OUT=Rehabilitation Of Elderly And Care At Home Or Usual Treatment; RR=relative risk; SD=standard deviation; SF-36=Short Form-36; t-HELP=Tailored, Family-Involved Hospital Elder Life Program; SPMSQ=Short Portable Mental Status Questionnaire; UNDERPIN-ICU=Nursing Delirium Preventive Interventions in the Intensive Care Unit.

3194 *Single-Component Interventions*

3195 Family Member Interventions

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Eghbali-Babadi et al. (2017) | Design: RCT<br>Setting: Postop, cardiac<br>Country: Iran<br>Funding: University | Randomized N: 68<br>Analyzed N: 68<br>Intervention (N=34): Family member education about delirium and were permitted to attend by the patient for 30-40 minutes and communicated based on the education; received twice a day<br>Control (N=34): Usual care<br>Duration: During ICU stay<br>Follow-up (days): 2, 3 | Inclusion: Age 18-70 years<br>Exclusion: Delirium, consciousness level disorder, mental diseases, history of blindness or deafness, intubated with a tracheal tube, or death during the study | Mean (SD) age: 55 (12.11)<br>Female %: 59<br>Race %: NR<br>Delirium %: 0 (excluded)<br>Cognitive status: NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR<br>Mean (SD) length of surgery hours: 4.5 (1.26) | Main outcomes: Incidence of delirium in the morning after surgery (2nd day) was 11.76% in intervention group vs. 23.53% in control group, p=0.04; for the 3rd day, 8.83% vs. 20.58%, p=0.03. In the control group, the incidence of delirium in the evening was 32.35%, which was more than that in the morning, p=0.004.<br>Attrition: NR | Moderate |
| Martinez et al. (2012) | Design: RCT<br>Setting: Inpatient<br>Country: Chile<br>Funding: None reported | Randomized N: 287<br>Analyzed N: 287<br>Intervention (N=144): Family member education about delirium; a clock and calendar available for the patient; sensory deprivation avoided (glasses, dentures, and hearing aids available); presence of familiar objects in the room (photographs, cushions, and radio); reorientation (current date and time, recent events) by family members; and extended visitation times (5 hours daily)<br>Control (N=143): Usual care<br>Duration: Daily during hospitalization<br>Follow-up (days): Until discharge | Inclusion: Older adults hospitalized and at risk for delirium<br>Exclusion: Those with delirium on admission and in a room with ≥2 beds | Mean (SD) age: 78.2 (6.2)<br>Female %: 63.7* *The text says female and the table says males for this %<br>Race %: NR<br>Delirium %: 0 (excluded)<br>Previous Delirium %: 3.8<br>Median Charlson Comorbidity Index: 2<br>Mild cognitive impairment %: 8<br>Dementia %: 5.9<br>Postop %: NR<br>Cancer %: 17.7<br>Started on risky medications: 5.2 | Main outcomes: Delirium occurred during the hospitalization in 5.6% of the patients in the intervention group and in 13.3% of the patients in the control group (RR 0.41, 95% CI 0.19 to 0.92, p=0.027).<br>Attrition: 3% vs. 6% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | | | Received anticholinergics %: 1<br>Received opioids %: 0.3 | | |
| Mitchell et al. (2017) | Design: RCT<br>Setting: ICU<br>Country: Australia<br>Funding: University | Randomized N: 61<br>Analyzed N: 61<br>Intervention (N=29): Family member delivered intervention containing orientation (memory clues), therapeutic engagement (engage patient), and if applicable sensory (making sure glasses are on and hearing aids in place/working)<br>Control (N=32): Usual care<br>Intervention 1 duration: Daily during ICU stay<br>Control duration: Daily for up to 30 days<br>Follow-up (days): Unclear | Inclusion: ≥16 years, expected to be in ICU ≥4 days<br>Exclusion: Unable to communicate in both written and spoken English | Mean (SD) age: 56.2 (26.8)<br>Female %: 65.5<br>Race %: NR<br>Delirium %: NR<br>Functioning: NR<br>Dementia %: NR<br>Postop %: 18.0<br>Cancer %: NR<br>On MV in ICU %: 98.4<br>Median (IQR) days on MV in ICU: 9.0 (7) intervention vs. 10.0 (10) control | Main outcomes: No significant differences between groups were found on outcomes of delirium.<br>Attrition: 0% vs. 3% | Moderate |
| Munro et al. (2017) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: NR | Randomized N: 30<br>Analyzed N: 30<br>Intervention 1 (N=10): Family member recorded messages to reorient the patient about being in the ICU and their condition there<br>Intervention 2 (N=10): Generic female recorded messages to reorient the patient about being in the ICU and their condition there<br>Control (N=10): Usual care<br>Duration: Daily during ICU stay<br>Follow-up (days): 3 | Inclusion: ≥18 years, within 24 hours of ICU admission<br>Exclusion: Expected imminent patient death | Mean (SD) age: 59.5 (17)<br>Female %: 36.7<br>Race %:<br>Caucasian: 83.3<br>Black/African American: 16.7<br>Asian: NR<br>Other: NR<br>Delirium %: 13.3<br>Mean (SD) APACHE score: 63.6 (20.7)<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR | Main outcomes: The family voice group had more delirium free days than the non-family voice group, and significantly more delirium free days (p=0.0437) than the control group.<br>Attrition: 70% vs. 50% vs. 40% | Moderate |
| Rosa et al. | Design: RCT<br>Setting: ICU | Randomized N: 1,685<br>Analyzed N: 1,685 | Inclusion: ≥18 years, admitted to participating ICUs | Mean (SD) age: 58.5 (18.2)<br>Female %: 47.2 | Main outcomes: Incidence of delirium during ICU stay was | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| (2019) | Country: Brazil<br>Funding: Government | Intervention (N=837): Flexible family visitation schedule for up to 12 hours per day, along with education about the ICU environment, common procedures, multidisciplinary work, infection control, palliative care, and delirium<br>Control (N=848): Usual care; restricted visitation (median 1.5 hours/day)<br>Duration: Daily during ICU stay<br>Follow-up (days): 30 or until discharge | Exclusion: Coma for ≥96 hours, presence of delirium, brain death, exclusive palliative care, expected ICU stay of <48 hours, or prisoners | Race %: NR<br>Delirium %: 0 (excluded)<br>Median (IQR) Charlson Comorbidity Index: 1.0 (0-2)<br>Dementia %: 0.9<br>Postop %: 42.6<br>Cancer %: NR<br>Hazardous alcohol consumption %: 7.1<br>Taking opioids %: 18.7<br>Taking vasopressors %: 27.0<br>Taking corticosteroids %: 18.7<br>Taking parenteral sedatives %: 14.2<br>Taking benzodiazepines %: 12.7 | not significantly different between flexible and restricted visitation (18.9% vs. 20.1%, adjusted difference −1.7%, 95% CI −6.1% to 2.7%, p=0.44). For family members, median anxiety (6.0 vs. 7.0, adjusted difference −1.6, 95% CI −2.3 to −0.9, p<0.001) and depression scores (4.0 vs. 5.0, adjusted difference −1.2, 95% CI −2.0 to −0.4, p=0.003) were significantly better with flexible visitation.<br>Overall attrition: 0%; no lost to follow-up but primary outcome data were not available for 9 patients (6 vs. 3). | |

*Abbreviations.* APACHE=Acute Physiology and Chronic Health Evaluation; CI=confidence interval; ICU=intensive care unit; MV=medical ventilation; N=number; NR=not reported; postop=post-operative; RCT=randomized controlled trial; RR=relative risk; SD=standard deviation.

## Individualized Education

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Chevillon et al. (2015) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: None | Randomized N: 132<br>Analyzed N: 129<br>Intervention (N=63): Individualized | Inclusion: ≥18 years with no prior pulmonary thromboendarterectomy<br>Exclusion: History of | Mean age: 54<br>Female %: 55<br>Race %: | Main outcomes: The 2 groups did not differ significantly in anxiety, | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | education<br>Control (N=69): Usual care<br>Duration: Preop<br>Follow-up (days): Until discharge | Alzheimer disease, dementia, or inability to give consent | Caucasian: 67<br>Black/African American: 19<br>Hispanic: 8<br>Asian: 2<br>Other: 3<br>Delirium %: NR<br>Function: NR<br>Dementia %: 0 (excluded)<br>Postop %: NR<br>Cancer %: NR | incidence of delirium, or ICU days.<br>Attrition: 3% vs. 1% | |
| Fahimi et al. (2020) | Design: RCT<br>Setting: Postop, cardiac<br>Country: Iran<br>Funding: None | Randomized N: 110<br>Analyzed N: 110<br>Intervention (N=55): Multimedia education consisting of 3 videos on the nature of the surgery, respiratory exercises, and prior patients' experiences<br>Control (N=55): Usual care<br>Intervention duration: Preop<br>Control duration: During hospitalization<br>Follow-up (days): Until discharge | Inclusion: Undergoing CABG for the first time and non-development of postop cardiogenic shock or myocardial rupture<br>Exclusion: Not willing to continue the study and died during the intervention | Mean (SD) age: 58 (12.21)<br>Female %: 50<br>Race %: NR<br>Delirium %: 0 (excluded)<br>Baseline scale of function: NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Considering the lower incidence of POD in patients who experienced multimedia education than the control group, the use of this non-pharmaceutical method is recommended to prevent delirium in such patients.<br>Overall attrition: 0% | Moderate |
| Xue et al. (2020) | Design: RCT<br>Setting: Postop, cardiac<br>Country: China<br>Funding: Non-profit | Randomized N: 156<br>Analyzed N: 133<br>Intervention (N=67): Individualized education based on patient's age, gender, education level, and surgery type, along with leaflets given to the patient and family, and a tour<br>Control (N=66): Routine preop education | Inclusion: ≥18 years who received routine elective CPB surgery<br>Exclusion: Cognitive impairment, serious organ dysfunction relying on mechanical support, or undergone cardiothoracic surgery before | Mean (SD) age: 58.0 (16.2)<br>Female %: 54.9<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR, cognitive impairment excluded | Main outcomes: The incidence of delirium in the intervention group was significantly lower than that in the control group (10.4% vs. 24.2%, p=0.038).<br>Overall attrition: 15% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Duration: 3 days prior to surgery<br>Follow-up (days): Until discharge | | Postop %: 100<br>Cancer %: NR | | |

*Abbreviations.* CABG=coronary artery bypass graf; CPB=cardiopulmonary bypass; ICU=intensive care unit; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; SD=standard deviation.

## Exercise/Mobilization

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Jeffs et al. (2013) | Design: RCT<br>Setting: Inpatient<br>Country: Australia<br>Funding: University, government | Randomized N: 649<br>Analyzed N: 648<br>Intervention (N=305): A program of progressive resistance exercise, mobilization, and orientation in addition to usual care, delivered twice daily by ward staff until discharge<br>Control (N=344): Usual care<br>Duration: During hospital stay (median 5.5 days)<br>Follow-up: Every 2 days until discharge (median 5.5 days) | Inclusion: ≥65 years in hospital for <48 hours<br>Exclusion: Severe dysphasia, isolation for infection control, death expected within 24 hours, contraindication to mobilization, or admission to stroke unit or ICU | Mean (SD) age: 79 (7.7)<br>Female %: 48<br>Race %: NR<br>Delirium %: 0 (excluded)<br>Median (IQR) Barthel Index: 90 (71-100)<br>Median (IQR) IADL: 6 (3-8)<br>Premorbid cognitive impairment %: 14<br>Median (IQR) MMSE score: 26 (19-28)<br>Mean (SD) APACHE II score: 14 (5)<br>Median (IQR) Charlson score: 2 (1-3)<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR | Main outcomes: 4.9% (95% CI 2.3 to 7.3) intervention group vs. 5.9% (95% CI 3.8 to 9.2) usual care group had delirium. There was no difference between the groups (p=0.5).<br>Attrition: 6% vs. 6% | Moderate |
| Karadas and Ozdemir (2016) | Design: RCT<br>Setting: ICU<br>Country: Turkey | Randomized N: 94<br>Analyzed N: 94<br>Intervention (N=47): Range of motion exercises were performed once a day until the patients were | Inclusion: ≥65 years, no previous delirium, and ICU stay ≥24 hours<br>Exclusion: Amputated extremity, undergoing invasive MV and procedures limiting mobility, a RASS | Mean (SD) age: 74 (7.2)<br>Female %: 53<br>Race %: NR<br>Delirium %: 0 (excluded)<br>Functioning: NR | Main outcomes: Although delirium incidence and duration decreased by 2.5-fold in the intervention group | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Funding: Unclear | discharged<br>Control (N=47): Usual care<br>Duration: Duration of hospital stay (median 5 days)<br>Follow-up (days): Until discharge | score of -4 and -5, advanced osteoporosis, terminal illness, increased intracranial pressure, active gastrointestinal system bleeding, or arrhythmia and active myocardial ischemia | Dementia %: 0 (excluded)<br>Postop %: NR<br>Cancer %: NR | vs. the control group, there was no significant relationship between the intervention and control groups.<br>Attrition: NR | |
| Martinez-Velilla et al. (2019) | Design: RCT<br>Setting: Inpatient<br>Country: Spain<br>Funding: Government | Randomized N: 370<br>Analyzed N: 370<br>Intervention (N=185): Exercise sessions, with morning sessions including individualized supervised progressive resistance, balance, and walking training exercises; and evening sessions including functional unsupervised exercises using light loads<br>Control (N=185): Usual care<br>Intervention duration: 2 sessions daily for 5-7 consecutive days<br>Control duration: During hospitalization<br>Follow-up (days): Until discharge | Inclusion: ≥75 years, Barthel Index score ≥60, and admitted to 1 of the ACE units<br>Exclusion: Expected LOS <6 days, very severe cognitive decline, terminal illness, uncontrolled arrhythmias, acute pulmonary embolism, recent MI, recent major surgery, or extremity bone fracture in the past 3 months | Mean (SD) age: 87.4 (4.9)<br>Female %: 56.5<br>Race %: NR<br>Delirium %: 14.3<br>Mean (SD) MMSE: 22 (4)<br>Mean (SD) Barthel Index: 83.5 (17)<br>Dementia %: NR, severe cognitive decline excluded<br>Cancer %: NR<br>Postop %: NR<br>Mean (SD) number of diseases/person: 9 (6) | Main outcomes: No significant differences between groups were found in incident delirium (p>0.10).<br>Attrition: 17% vs. 15% | Moderate |
| Morris et al. (2016) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: Government | Randomized N: 300<br>Analyzed N: 300<br>Intervention (N=150): Passive range of motion, PT, and progressive resistance exercise administered as 3 separate sessions every day<br>Control (N=150): Usual care<br>Intervention duration: Daily until discharge | Inclusion: ≥18 years admitted to a medical ICU, MV via endotracheal tube or noninvasive ventilation by mask, and PaO2/FIO2 ratio <300<br>Exclusion: Inability to walk without assistance prior to the acute ICU illness, cognitive impairment prior to acute ICU illness, acute stroke, BMI >50, neuromuscular disease impairing weaning from MV, acute hip fracture, unstable cervical spine or pathologic | Mean (SD) age: 56 (15)<br>Female %: 55.3<br>Race %:<br>Caucasian: 77.3<br>Black/African American: 21.3<br>Hispanic or Latino: 1.3<br>Asian: NR<br>Other: NR<br>Delirium %: NR<br>Mean (SD) APACHE II: 76 (27) | Main outcomes: No differences in CAM positive days were found between intervention and control groups.<br>Attrition at discharge: 13% vs. 16% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Control duration: During hospitalization<br>Follow-up (days): Discharge, 60, 120, 180 | fracture, MV >80 hours or current hospitalization >7 days, orders for do not intubate on admission, or considered to be moribund | Dementia %: NR, cognitive impairment excluded<br>Postop %: NR<br>Cancer %: NR | | |
| Nydahl et al. (2020) | Design: RCT<br>Setting: ICU<br>Country: Germany<br>Funding: NR | Randomized N: 274<br>Analyzed N: 272<br>Intervention (N=122): Mobilization<br>Control (N=152): Usual care<br>Intervention duration: Each day during hospitalization<br>Control duration: During hospitalization<br>Follow-up (days): Discharge, 28 | Inclusion: ≥18 years and order for mobilization<br>Exclusion: Palliative state, immobility order, or not documented mobilization | Median age: 70 vs. 74<br>Female %: 44.8<br>Race %: NR<br>Delirium %: NR<br>Median (IQR) RASS: 0 (-1-0)<br>Frailty index ≥5 %: 36.3<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR | Main outcomes: Secondary outcomes, such as days with MV, delirium, and in ICU and hospital stay, did not significantly differ.<br>Attrition: 2% vs. 0% | Moderate |
| Nydahl et al. (2022) | Design: RCT<br>Setting: ICU<br>Country: Germany<br>Funding: Government | Randomized N: 53<br>Analyzed N: 46<br>Intervention (N=122): Evening mobilization ranging from 3 minutes to 2 hours a session based on tolerability by the patient<br>Control (N=122): Usual care<br>Intervention duration: Each evening for 3 days<br>Control duration: NR<br>Follow-up (days): 3, discharge | Inclusion: ≥18 years, RASS ≥ -3 and responsive, were able to be mobilized out of bed according to local policies, and expected to spend ≥1 night in ICU<br>Exclusion: Expectation of death within 72 hours, pre-existing immobility, delirium already present before recruitment, or not possible to assess for delirium | Mean (SD) age: 62.5 (14.5)<br>Female %: 28.3<br>Race %: NR<br>Delirium %: 0 (excluded)<br>Median (IQR) Charlson Comorbidity Index: 4 (3-6)<br>Dementia %: 0<br>Postop %: NR<br>Cancer %: NR | Main outcomes: There was less delirium in the intervention group (not significant).<br>Overall attrition: 13% | Moderate |
| Schweickert et al. (2009) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: Unclear | Randomized N: 104<br>Analyzed N: 104<br>Intervention (N=49): Exercise and mobilization<br>Control (N=55): Standard care with physical and occupational therapy as ordered by primary | Inclusion: ≥18 years on MV <72 hours and expected to continue ≥24 hours; excluded patients not functionally independent<br>Exclusion: Rapidly developing neuromuscular disease, | Median age: 56<br>Female %: 50<br>Race %:<br>Caucasian: NR<br>Black/African American: 58.7<br>Asian: NR | Main outcomes: Patients in the intervention group experienced fewer delirium days than in the control group (median 4 vs. 2, p=0.02) and less | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | care<br>Duration: During MV<br>Follow-up (days): Until discharge | cardiopulmonary arrest, irreversible disorders with 6-month mortality estimated at >50%, raised intracranial pressure, absent limbs, or enrollment in another trial | Other: NR<br>Delirium %: NR<br>APACHE II: 19.5<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: 2.9 | time in ICU with delirium (33% vs. 57%, p=0.02).<br>Overall attrition: 0% | |
| Shirvani et al. (2020) | Design: RCT<br>Setting: Postop, cardiac<br>Country: Iran<br>Funding: None | Randomized N: 92<br>Analyzed N: 90<br>Intervention (N=46): Early planned mobilization<br>Control (N=46): Usual care<br>Intervention duration: Daily during ICU stay<br>Control duration: During ICU stay<br>Follow-up (days): Discharge, 30, 180 | Inclusion: Patients who underwent elective CABG, had GCS score of 15, no neurological and movement disorders, and were conscious<br>Exclusion: Undergoing emergency CABG or any physiologic or hemodynamic instability after surgery | Mean (SD) age: 60.4 (8.6)<br>Female %: 17.8<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: The intervention group had significantly higher Neecham scores on postop day 2 (22.49 [2.03] vs. 26.82 [2.10], p=0.001). Multivariable analysis showed significant associations between Neecham score and age (p=0.022), ejection fraction (p=0.015), myocardial infarction (p=0.016), systolic pressure (p=0.009), and diastolic pressure (p=0.008).<br>Attrition at follow-up: 2% vs. 2% | High |

*Abbreviations.* ACE=acute care of elderly; APACHE II=Acute Physiology and Chronic Health Evaluation II; BMI=body mass index; CABG=coronary artery bypass graf; CAM=Confusion Assessment Method; CI=confidence interval; GCS=Glasgow Coma Scale; IADL=independent activities of daily living; ICU=intensive care unit; IQR=interquartile range; LOS=length of stay; MI=myocardial infarction; MMSE=Mini-Mental State Examination; MV=medical ventilation; N=number; NR=not reported; postop=post-operative; PT=physical therapy; RASS=Richmond Agitation Sedation Scale; RCT=randomized controlled trial; SD=standard deviation.

## Bright Light Therapy/Light Therapy

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Ono et al. (2011) | Design: RCT<br>Setting: Postop, esophageal cancer<br>Country: Japan<br>Funding: None | Randomized N: 26<br>Analyzed N: 22<br>Intervention (N=10): Bright light therapy<br>Control (N=12): Usual care<br>Intervention duration: 2 hours/day starting POD 2 for 4 days<br>Control duration: During hospitalization<br>Follow-up (days): 6 | Inclusion: ≥18 years scheduled to undergo surgical resection and reconstruction through a right thoracotomy for the treatment of thoracic esophageal cancer<br>Exclusion: NR | Mean (SD) age: 63.6 (8.7)<br>Female %: 0<br>Race %: NR<br>Delirium %: NR<br>Mean (SD) APACHE II: 8.2 (2.3)<br>Dementia %: NR<br>Cancer %: 100<br>Postop %: 100<br>Mean (SD) operation time minutes: 444 (80) | Main outcomes: The occurrence rate of POD tended to be lower in the light exposure group (1/10 vs. 5/12), but there was no significant difference.<br>Attrition: 23% vs. 8% | Moderate |
| Potharajaroen et al. (2018) | Design: RCT<br>Setting: Postop, mixed<br>Country: Thailand<br>Funding: University | Randomized N: 62<br>Analyzed N: 62<br>Intervention (N=31): Bright light therapy plus usual care<br>Control (N=31): Usual care<br>Intervention duration: Started by POD 1-3<br>Control duration: Postop<br>Follow-up (days): 3 | Inclusion: ≥50 years, postop patients' admittance to SICU, and APACHE II score ≥8<br>Exclusion: Alzheimer's, Parkinson's, multiple sclerosis, psychiatric illness, couldn't sit in a 30-45° position, due to c-spine injury, or eye problems | Mean (SD) age: 68.2 (11.47)<br>Female %: 56<br>Race %: NR<br>Delirium %: NR<br>APACHE II: 14.4 (3.9) vs. 16.4 (4.9)<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR<br>Mean number of medications taken at baseline: NR (11% taking hypnotics) | Main outcomes: 2 subjects in the intervention group (2/31) vs. 11 controls (11/31) had a delirium diagnosis at the endpoint. Generalized estimating equations analysis showed a significant preventive effect of bright light therapy on delirium, which was independent of risk or treatment factors.<br>Attrition: 3% vs. 0% | Moderate |
| Simons et al. (2016) | Design: RCT<br>Setting: ICU<br>Country: The Netherlands | Randomized N: 734<br>Analyzed N: 734<br>Intervention (N=361): Dynamic lighting to achieve 800-1000 lux bluish-white | Inclusion: ≥18 years in the ICU longer than 24 hours and could be assessed for delirium<br>Exclusion: Life expectancy <48 hours or who could not be | Mean (SD) age: 65.33 (13.26)<br>Female %: 41.5<br>Race %: NR<br>Delirium %: NR<br>PRE-DELIRIC mean (SD): 58.8 | Main outcomes: Delirium occurred in 137/361 (38%) dynamic lighting patients and 123/373 (33%) control | High |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Funding: None; "Philips supplied the lighting system for the study but had no role in the study design or conduct." | light<br>Control (N=373): Usual care<br>Duration: During hospitalization<br>Follow-up (days): 28 | assessed for delirium (e.g., severe hearing or visual impairment, unable to understand Dutch, or severe mental impairment) | (31.8) vs. 55.4 (30.6)<br>APACHE II score: 22.7 (8.6) vs. 22.4 (8.1)<br>Dementia %: NR<br>Postop %: 25<br>Cancer %: NR<br>Mean number of medications taken at baseline: NR | patients (OR 1.24, 95% CI 0.92 to 1.68, p=0.16). No adverse events were noted in patients or staff.<br>Attrition: 2% vs. 3% | |
| Taguchi et al. (2007) | Design: RCT<br>Setting: Postop, esophageal cancer<br>Country: Japan<br>Funding: Unclear | Randomized N: 15<br>Analyzed N: 11<br>Intervention (N=8): Bright light therapy<br>Control (N=7): Usual care<br>Intervention duration: 3 days after surgery<br>Control duration: Postop<br>Follow-up (days): 5 | Inclusion: Age 29-68 years, middle-aged or aged patients with no mental or ophthalmologic disorders<br>Exclusion: Reintubation, medical complications, or deterioration of the condition* *Excluded post randomization | Mean (SD) age: 57.6 (12.8)<br>Female %: 0<br>Race %:<br>Caucasian: NR<br>Black/African American: NR<br>Asian: 100<br>Other: NR<br>Delirium %: NR (implies 0%)<br>Baseline scale of function: NR*<br>*circadian rhythm, sleep-awake rhythm: NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: 100, esophageal<br>Mean number of medications taken at baseline: NR | Main outcomes: A significant difference was observed in the delirium score on the morning of day 3 of the bright light therapy (p=0.014).<br>Attrition: 25% vs. 29% | High |
| Zhang K.S. et al. (2021) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: Non-profit | Randomized N: 108<br>Analyzed N: 78<br>Intervention (N=54): Bright light therapy with peaks of 10,000 lux white light<br>Control (N=54): Standard light of 150 lux<br>Intervention duration: Started at 7:30am and | Inclusion: ≥18 years and expected ICU stay of ≥24 hours<br>Exclusion: Confirmed psychiatric history of bipolar disorder | Median age: 63.5 vs. 64<br>Female %: 42.3<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR<br>Past neurological or behavioral impairment %: 51.3 | Main outcomes: Daily morning 10,000 lux bright light therapy of 30-minute duration alone was not associated with a significant decrease in ICU-acquired delirium incidence or duration compared to | High |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | lasted for 30 minutes during ICU stay<br>Control duration: During ICU stay<br>Follow-up (days): NR | | Postop %: 17.9<br>Cancer %: NR | standard hospital lighting.<br>Attrition: 30% vs. 26% | |

*Abbreviations*. APACHE II=Acute Physiology and Chronic Health Evaluation II; CI=confidence interval; ICU=intensive care unit; N=number; NR=not reported; OR=odds ratio; postop=post-operative; POD= post-operative delirium; PRE-DELIRIC=Prediction of Delirium in ICU Patients; RCT=randomized controlled trial; SD=standard deviation; SICU=surgical intensive care unit.

## Ear Plugs/Eye Mask

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Arttawejkul et al. (2020) | Design: RCT<br>Setting: ICU<br>Country: Thailand<br>Funding: Non-profit | Randomized N: 17<br>Analyzed N: 17<br>Intervention (N=8): Earplugs and eye masks<br>Control (N=9): Usual care<br>Intervention duration: During the night while in the ICU<br>Control duration: During ICU stay<br>Follow-up (days): NR | Inclusion: ≥18 years admitted to a medical ICU, expected to remain in the ICU for >24 hours, GCS score ≥13, RASS -1 to +1, and did not require medication or intervention to facilitate sleep<br>Exclusion: Bilateral deafness, bilateral blindness, severe encephalopathy, severe dementia, hepatic encephalopathy, uremic encephalopathy, encephalitis, increased intracranial pressure, metabolic derangements, severe hemodynamic instability, high vasopressure requirement, or severe respiratory failure | Mean (SD) age: 71.8 (28.9)<br>Female %: 35.3<br>Race %: NR<br>Delirium %: NR<br>Mean (SD) APACHE II: 14.5 (4.9)<br>Dementia %: NR, severe dementia excluded<br>Postop %: NR<br>Cancer %: NR | Main outcomes: The prevalence of delirium, the use of sedation, duration of ICU stay, and duration of MV were not different between the groups.<br>Overall attrition: 0% | Moderate |
| Leong et al. (2021) | Design: RCT<br>Setting: Postop, colorectal<br>Country: Singapore<br>Funding: Non-profit | Randomized N: 100<br>Analyzed N: 93<br>Intervention (N=51): Earplugs and eye mask<br>Control (N=49): No intervention | Inclusion: >21 years undergoing elective major colorectal surgery and with a GCS of ≥10 post-operatively in the study<br>Exclusion: Known hearing impairment, dementia, confusion, delirium, pre-existing tracheostomy, or who returned post-operatively to the ward after 22.00 | Median age: 67 vs. 60<br>Female %: 45.2<br>Race %:<br>Chinese: 83.9<br>Malay: 5.4<br>Indian: 8.6<br>Others: 2.1 | Main outcomes: There were no differences in patient satisfaction, reduction in frequency of nursing demands, or incidence of delirium on | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Intervention duration: Nightly until POD 3<br>Control duration: NR<br>Follow-up (days): 1, 2, 3 | | Delirium %: 0 (excluded)<br>ASA I %: 2.1<br>ASA II %: 65.6<br>ASA III %: 31.2<br>Dementia %: 0 (excluded)<br>Postop %: 100, colorectal Cancer %: NR | postop days 1-3 after major abdominal surgery.<br>Attrition: 6% vs. 8% | |
| Obanor et al. (2021) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: NR, but no conflicts reported | Randomized N: 90<br>Analyzed N: 87<br>Intervention (N=44): Earplugs and eye mask<br>Control (N=43): Usual care<br>Intervention duration: Each night during ICU stay<br>Control duration: During ICU stay<br>Follow-up (days): Discharge | Inclusion: ≥18 years and female patients admitted to the ICU following plastic surgical breast free flap procedures requiring hourly postop assessments<br>Exclusion: Current incarceration and diagnosis of sleep apnea, insomnia, or other sleep disturbance | Mean (SD) age: 51.05 (9.01)<br>Female %: 100<br>Race %:<br>White: 72.4<br>Black: 19.5<br>Hispanic: 4.6<br>Unknown/NR: 3.4<br>Delirium %: NR<br>ASA I %: 3.4<br>ASA II %: 77.0<br>ASA III %: 19.5<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: There were no significant group differences for CAM for the ICU scores.<br>Overall attrition: 3% | Moderate |
| Van Rompaey et al. (2012) | Design: RCT<br>Setting: ICU<br>Country: Belgium<br>Funding: None | Randomized N: 136<br>Analyzed N: 136<br>Intervention (N=69): Sleeping with earplugs during the night<br>Control (N=67): Usual care<br>Duration: At night during ICU stay<br>Follow-up (days): 5 | Inclusion: ≥18 years with expected ICU stay of ≥24 hours and GCS ≥10<br>Exclusion: Dementia, confusion or delirium, or receiving sedation | Mean (SD) age: 59<br>Female %: 44<br>Race %: NR<br>Delirium %: 0 (excluded)<br>Functioning: NR<br>Dementia %: 0 (excluded)<br>Postop %: 74.3<br>Cancer %: NR<br>≥1 comorbidity %: 72 | Main outcomes: The patients in the earplug group showed 15% mild confusion vs. 40% in the control group. A HR for delirium or mild confusion with earplugs was 0.47 (95% CI 0.27 to 0.82).<br>Attrition: NR | Moderate |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; ASA=American Society of Anesthesiologists; CAM=Confusion Assessment Method; CI=confidence interval; GCS=Glasgow Coma Scale; HR=hazard ratio; ICU=intensive care unit; MV=medical ventilation; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; RASS=Richmond Agitation Sedation Scale; RCT=randomized controlled trial; SD=standard deviation.

## Listening to Music

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Browning et al. (2020) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: None | Randomized N: 6<br>Analyzed N: 6<br>Intervention (N=3): Therapeutic music listening in 1-hour increments; twice a day from 10-11am and 9-10pm<br>Control (N=3): Usual care<br>Duration: During ICU stay<br>Follow-up (days): Discharge from ICU | Inclusion: Patients in the medical ICU who were on MV<br>Exclusion: Hard of hearing or hearing impaired, baseline cognitive dysfunction, prisoners, moribund, receiving comfort or end-of-life care, or no family or friend present | Mean (SD) age: 67.5 (9.7)<br>Female %: 66.6<br>Race %: NR<br>Delirium %: NR (but cognitive dysfunction at baseline excluded)<br>Function: NR<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR | Main outcomes: Although no statistical significance was established relative to the small sample size, the pilot study results indicated the music group experienced less proportion of time CAM+ (the presence of ICU delirium) (33%) than the control group did (67%).<br>Attrition: NR | High |
| Johnson et al. (2018) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: None | Randomized N: 40<br>Analyzed N: 40<br>Intervention (N=20): Listening to music for 60 minutes; 2 times per day<br>Control (N=20): Usual care<br>Duration: During hospitalization for 3 days<br>Follow-up (days): 3 | Inclusion: >55 years and oriented to person, time, and place on admission<br>Exclusion: Not able to pass the Whisper Test, intubated patients, or CAM-ICU positive | Mean (SD) age: 72 (9.2)<br>Female %: 85<br>Race %:<br>Caucasian: 85<br>Black/African American: 0.025<br>Asian: 0.025<br>Other: 10<br>Delirium %: 0 (excluded)<br>Functioning: NR<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR | Main outcomes: The CAM-ICU for both groups remained negative at each data collection time point.<br>Attrition: No patients withdrew from the study, but it appears some patients missed doses. | High |
| Khan et al. (2020) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: Unclear | Randomized N: 52<br>Analyzed N: 52<br>Intervention 1 (N=17): Personalized music playlist; two 1-hour sessions per day | Inclusion: ≥18 years and admitted to the ICU and receiving MV ≥24 hours but ≤48 hours<br>Exclusion: Neurological injury, | Mean age:<br>18-49: 23%<br>50-64: 52%<br>>64: 25% | Main outcomes: The median number (IQR) of delirium/coma-free days by day 7 was 1 (1-6) for personalized music, 3 (1-6) for | High |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | Intervention 2 (N=17): Relaxing slow-tempo music playlist; two 1-hour sessions per day<br>Intervention 3 (N=18): Attention control (audiobook); two 1-hour sessions per day<br>Duration: During hospitalization for up to 7 days<br>Follow-up (days): Up to 7 days | chronic neurologic disease, uncorrected hearing or vision impairments, were in a coma after cardiac arrest, or incarcerated | Female %: 52<br>Race %:<br>Caucasian: 56<br>Black/African American: 40<br>Asian: NR<br>Other: 4<br>Delirium %: NR<br>ADL index: Median 6 (3 to 6)<br>IQCODE: Median 3 (3.0-3.1)<br>Dementia %: NR<br>Postop %: 27<br>Cancer %: NR<br>Carlson comorbidity index: Median 1 (0-3) | slow tempo music, and 2 (0-3) for attention control (p=0.32).<br>Median delirium severity was 5.5 (1-7) vs. 3.5 (0-7) vs. 4 (1-6.5) (p-0.78).<br>Attrition: 6% vs. 6% vs. 6% | |

*Abbreviations.* ADL=activities of daily living; CAM-ICU=Confusion Assessment Method for the ICU; ICU=intensive care unit; IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly; IQR=interquartile range; MV=medical ventilation; NR=not reported; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

## Cognitive Therapy Plus Physical Therapy

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Brummel et al. (2014) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: None | Randomized N: 87<br>Analyzed N: 87<br>Intervention 1 (N=43): Cognitive therapy + PT<br>Intervention 2 (N=22): PT only<br>Control (N=22): Usual care<br><br>Intervention 1, Intervention 2: Daily during ICU stay<br>Control: During ICU stay<br><br>Follow-up (days): 90 | Inclusion: ≥18 years being treated for respiratory failure and/or septic, cardiogenic, or hemorrhagic shock<br>Exclusion: Been critically ill for >72 hours since the opportunity to administer early cognitive and physical therapy had passed, been in the ICU >5 days in the previous 30 days, unlikely to benefit from the rehabilitation targeting acute declines in cognitive or functional status due to the moribund status, severe pre-existing dementia or physical | Median age:62 vs. 62 vs. 60<br>Female %: 43.7<br>Race %: NR<br>Delirium %: NR<br>Median APACHE II: 27 vs. 21.5 vs. 25<br>Dementia %: NR, severe pre-existing dementia excluded<br>Postop %: 18.4<br>Cancer %: NR | Main outcomes: Cognitive, functional, and health-related quality of life outcomes did not differ between groups at 3-month follow-up.<br>Attrition: 35% vs. 27% vs. 27% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | | disability in ADLs, or unlikely to continue in outpatient setting | | | |

*Abbreviations.* ADL=activities of daily living; APACHE II=Acute Physiology and Chronic Health Evaluation II; ICU=intensive care unit; N=number; NR=not reported; postop=post-operative; PT=physical therapy; RCT=randomized controlled trial.

## Cognitive Exercises or Test

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Dai et al. (2021) | Design: RCT<br>Setting: ICU<br>Country: China<br>Funding: None | Randomized N: 76<br>Analyzed N: 76<br>Intervention (N=38): Cognitive function training<br>Control (N=38): Usual care<br>Duration: During ICU stay<br>Follow-up (days): 7 | Inclusion: >18 years ICU patients without delirium, expected to be treated for >1 week, and had a family member who agreed to participate<br>Exclusion: Patients in deteriorated condition, patients who couldn't express their ideas, missing relevant data, other malignant tumor, or experienced delirium during their hospitalization before the study | Mean (SD) age: 41.8 (14.01)<br>Female %: 48.7<br>Race %: NR<br>Delirium %: 0 (excluded)<br>Mean (SD) Barthel Index: 45.44 (6.51)<br>Mean (SD) MMSE: 18.7 (3.2)<br>Postop %: NR<br>Cancer %: NR | Main outcomes: After 1 week of treatment, the incidences of delirium in the intervention group were significantly lower than they were in the control group (23.68% vs. 42.11%, p<0.05).<br>Attrition: NR, but 2 deaths vs. 1 death | High |
| Humeidan et al. (2021) | Design: RCT<br>Setting: Preop, mixed<br>Country: U.S.<br>Funding: University | Randomized N: 268<br>Analyzed N: 251<br>Intervention (N=134): Cognitive exercises for a total of 10 hours<br>Control (N=134): Usual care<br>Intervention duration: The days prior to surgery (suggested 1 hour a day | Inclusion: ≥60 years undergoing major noncardiac or nonneurological surgery under general anesthesia with an anticipated hospital stay of ≥72 hours and immediate postop extubation<br>Exclusion: Cognitive impairment on the modified MMSE (score, <26 of 30 or <24 of 30 if the patient's education level was less | Median (IQR) age: 67 (63-71)<br>Female %: 64.9<br>Race %: NR<br>Delirium %: NR<br>ASA I-II %: 14.3<br>ASA III %: 81.3<br>ASA IV %: 4.4<br>Median (IQR) Charlson Comorbidity Index: 2 (1-3)<br>Median (IQR) MMSE: 29 (28-30) | Main outcomes: The delirium rate among control participants was 23.0% (29/126). With intention-to-treat analysis, the delirium rate in the intervention group was 14.4% (18/125, p=0.08).<br>Attrition: 7% vs. 6% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | for 10 days, but was at patient's discretion)<br>Control duration: Prior to surgery<br>Follow-up (days): 7, discharge | than high school) or evidence of active depression (GDS; score >9 of 15) during their visit | Postop %: 100<br>-General %: 37.5<br>-Orthopedic %: 47.0<br>-Gynecologic %: 4.0<br>-Thoracic %: 2.4<br>-Urology %: 3.6<br>-Plastic %: 4.4<br>-Other %: 1.2<br>Cancer %: NR | | |
| O'Gara et al. (2020); PEaPoD study | Design: RCT<br>Setting: Postop, cardiac<br>Country: U.S.<br>Funding: University | Randomized N: 45<br>Analyzed N: 40<br>Intervention (N=22): Cognitive training software used to train users in the cognitive domains of memory, attention, problem solving, flexibility, and processing speed<br>Control (N=23): Usual care<br>Intervention duration: Trained for 2 separate 15-minute sessions per day, from the day of enrollment until 4 weeks after surgery including the immediate postop period<br>Control duration: During hospitalization<br>Follow-up (days): 28 | Inclusion: Age 60-90 years scheduled to undergo cardiac surgery ≥10 days from enrollment<br>Exclusion: History of psychiatric illness that increased risk of POD, other forms of cognitive decline, and score <10 on MoCA (indicating severe cognitive impairment) | Mean (SD) age: 69.5 (6.5)<br>Female %: 27.5<br>Race %: NR<br>Delirium %: NR<br>Functioning: NR<br>Dementia %: NR, severe cognitive impairment excluded<br>Solid tumor nonmetastatic %: 30<br>Solid tumor metastatic %: 2.5<br>Postop %: 100 | Main outcomes: Incidence of POD was not statistically significant (cognitive training group 5/20 [25%] vs. control 3/20 [15%], p=0.69).<br>Attrition: 9% vs. 13% vs. 11% | Moderate |
| Vlisides et al. (2019) | Design: RCT<br>Setting: Postop, mixed | Randomized N: 61<br>Analyzed N: 52<br>Intervention (N=30): Computer-based cognitive | Inclusion: ≥60 years, scheduled noncardiac, non-major vascular, or nonintracranial surgery, and | Mean (SD) age: 67 (5.2)<br>Female %: 48<br>Race %: NR | Main outcomes: POD incidence was 6/23 (26%) in the intervention group vs. | High |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Country: U.S.<br>Funding: University | training battery that specifically targets executive function, attention, working memory, and visuospatial processing<br>Control (N=31): Usual care<br>Intervention duration: ~20-minute sessions, every day for 7 days prior to surgery<br>Control duration: Unclear<br>Follow-up (days): 3 | daily access to computer and internet use before surgery<br>Exclusion: Preop delirium, mild cognitive impairment, or dementia | Delirium %: 0 (excluded)<br>Functioning: NR<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR | 5/29 (17%) in the control group (p=0.507).<br>Attrition: 23% vs. 6% | |

*Abbreviations.* ASA=American Society of Anesthesiologists; GDS=Geriatric Depression Score; ICU=intensive care unit; IQR=interquartile range; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; N=number; NR=not reported; PEaPoD=Prevention of Early Post-operative Decline; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RASS=Richmond Agitation Sedation Scale; RCT=randomized controlled trial; SD=standard deviation.

## Massage

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Fazlollah et al. (2021) | Design: RCT<br>Setting: Postop, cardiac<br>Country: Iran<br>Funding: Non-profit | Randomized N: 60<br>Analyzed N: 60<br>Intervention (N=30): Foot reflexology massage for 20 minutes<br>Control (N=30): No intervention<br>Intervention duration: Once a day for 2 days<br>Control duration: None<br>Follow-up (days): 2 | Inclusion: Age 35-70 years, ejection fraction >40%, non-emergency surgery, negative history of stroke or other severe neurologic disorders, healthy feet, and non-redo surgery<br>Exclusion: Drainage of >400 mL at first 4 hours after surgery, hemodynamic instability, loss of consciousness, and requiring MV >24 hours after the surgery | Mean (SD) age: 64.3 (7.2)<br>Female %: 52<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Delirium occurred in 8 (26.7%) and 7 (23.3%) of patients in the intervention and control groups, respectively (p>0.05). The pain intensity was decreased in the intervention group (p<0.001).<br>Overall attrition: 0% | Moderate |

*Abbreviations.* MV=medical ventilation; N=number; NR=not reported; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

## Occupational Therapy

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Alvarez et al. (2017) | Design: RCT<br><br>Setting: ICU<br>Country: Chile<br>Funding: Government | Randomized N: 140<br>Analyzed N: 140<br>Intervention (N=70): Occupational therapy (early and intensive), with standard non-pharmacologic prevention; twice a day, once in the morning, once in the evening for consecutive 5 days<br>Control (N=70): Usual care<br><br>Duration: During hospitalization within 24 hours of ICU admission<br>Follow-up (days): 5, Discharge | Inclusion: ≥60 years, non-intubated, and hospitalized within 24 hours in the ICU<br>Exclusion: CAM positive patients with cognitive decline, severe communication disorders, delirium before ICU admission, or a requirement for invasive MV | Median age: 68 vs. 71<br>Female %: 50<br>Race %: NR<br>Delirium %: 0 (excluded)<br>Baseline PRE-DELIRIC %: 16.5<br>Median (range) APACHE II: 10 (9-12) vs. 11 (8-12)<br>Dementia %: 0<br>SIU %: 64<br>Cancer %: 16<br>Medications taken at baseline: NR | Main outcomes: The intervention group had lower duration (risk incidence ratios 0.15 [95% CI 0.12 to 0.19, p=0.000] vs. 6.6 [95% CI 5.23 to 8.3, p=0.000]) and incidence of delirium (3% vs 20%, p=0.001), and had higher scores in Motor Functional Independence Measure (59 points vs. 40 points, p=0.0001), cognitive state (MMSE: 28 points vs 26 points, p=0.05), and grip strength in the dominant hand (26 kg vs. 18 kg, p=0.05), compared with the control group.<br><br>Attrition: 7% vs. 9% | Low |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; CAM=Confusion Assessment Method; CI=confidence interval; ICU=intensive care unit; MMSE=Mini-Mental State Examination; MV=medical ventilation; N=number; NR=not reported; PRE-DELIRIC=Prediction of Delirium in ICU Patients; RCT=randomized controlled trial; SIU=Surgical Intermediate Unit.

## Use of Mirrors

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Giraud et al. (2016) | Design: RCT<br>Setting: ICU<br>Country: U.K.<br>Funding: Non-profit | Randomized N: 223<br>Analyzed N: 223<br>Intervention (N=115): Structured mirrors intervention to support mental status and attention, physical mobilization, and multisensory feedback integration | Inclusion: ≥70 years and admitted to ICU after elective or urgent cardiac surgery<br>Exclusion: Severe visual impairment, | Mean (SD) age: 77 (4.9)<br>Female %: 24<br>Race %: NR<br>Delirium %: NR<br>Baseline scale of function: NR<br>Dementia %: NR | Main outcomes: The intervention did not significantly reduce ICU delirium incidence (mirrors: 20/115 [17%] vs. usual care: 17/108 [16%]) or duration | Moderate |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | administered by nursing and physiotherapy teams; timing of intervention followed change in patient's mental status<br>Control (N=108): Usual care<br>Duration: During hospitalization; median ICU stay of 2 days<br>Follow-up (days): 84 | physical or communication barriers, severe mental disability, or history of psychiatric illness previously requiring hospitalization | Postop %: 100<br>Cancer %: NR | (mirrors: 1 [1-3]) vs. usual care: 2 [1-8]).<br>Attrition: 10% vs. 0% | |

*Abbreviations.* ICU=intensive care unit; N=number; NR=not reported; RCT=randomized controlled trial; SD=standard deviation.

## Non-Pharmacological Interventions for Treatment of Delirium

### *Multi-Component Interventions*

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Cole et al. (1994) | Design: RCT<br>Setting: Inpatient<br>Country: Canada<br>Funding: Non-profit | Randomized N: 88<br>Analyzed N: 88<br>Intervention (N=42): Geriatric internist or psychiatrist performed consultations to determine probable predisposing, precipitating, and perpetuating factors of delirium and resulted in management recommendations that were carried out by study nurses following an intervention protocol<br>Control (N=46): Usual care<br>Duration: Daily until discharge<br>Follow-up (days): Until discharge, 56 | Inclusion: ≥75 years admitted to the hospital and diagnosed with delirium<br>Exclusion: Those admitted to the ICU or cardiac monitoring unit | Mean (SD) age: 86.1 (6.1)<br>Female %: 65<br>Race %: NR<br>Delirium %: 100<br>Mean (SD) CGBRS: 33.0 (8.8)<br>Mean (SD) SPMSQ: 8.8 (1.7)<br>Postop %: NR<br>Cancer %: NR | Main outcomes: Delirium was diagnosed in 16% of the control cases. 28% in the treatment group had delirium alone, 56% had delirium superimposed on dementia (Alzheimer's disease in most cases), and 16% had delirium superimposed on another psychiatric disorder. The delirium was attributed to drugs (n=1), cardiovascular disease (n=1), infection (n=4), other causes (n=7), or a combination of factors (n=16). The cause was not determined in 10 cases.<br>Attrition: 7% vs. NR (14/46 received a consultation by a geriatrician or geriatric psychiatrist) | Moderate |
| Cole et al. (2002) | Design: RCT<br>Setting: Inpatient<br>Country: | Randomized N: 227<br>Analyzed N: 218<br>Intervention (N=113): Geriatric internist or psychiatrist performed | Inclusion: ≥65 years admitted to the hospital with prevalent or incident delirium within | Mean (SD) age: 82.3 (7.3)<br>Female %: 54<br>Race %: NR<br>Prevalent Delirium %: 81 | Main outcomes: 48% in intervention group vs. 45% in control group had their delirium improved. HR for shorter time to improvement was | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Canada<br>Funding: Government | consultations to determine probable predisposing, precipitating, and perpetuating factors of delirium and resulted in management recommendations that were carried out by study nurses following an intervention protocol<br>Control (N=114): Usual care<br>Duration: Daily until discharge<br>Follow-up (days): Until discharge, 56 | 1 week of admission<br>Exclusion: Those with a primary diagnosis of stroke, ICU LOS, or cardiac monitoring unit >48 hours | Incident Delirium %: 19<br>Mean (SD) Charlson Comorbidity Index: 3.2 (2.1)<br>Mean (SD) clinical severity of illness (scale of 1=mild to 9=moribund): 5.8 (1.2)<br>Suspected Dementia %: 58<br>Postop %: NR<br>Cancer %: NR | 1.10 (95% CI 0.74 to 1.63), outcomes between the 2 groups did not differ statistically significantly for patients without dementia (HR 1.54, 95% CI 0.80 to 2.97), for those who had less comorbidity (HR 1.36, 95% CI 0.75 to 2.46), or for those with prevalent delirium (HR 1.15, 95% CI 0.48 to 2.79).<br>Attrition: 6% vs. 2% | |
| Khalifezadeh et al. (2011) | Design: RCT<br>Setting: Postop, neurosurgery<br>Country: Iran<br>Funding: None | Randomized N: 40<br>Analyzed N: 40<br>Intervention (N=20): Multi-component nurse-led intervention of clear information, effective communication, assurance, and emotional support from the researcher, his partners, and the nurses. The patients' families in the intervention group were allowed to have regular daily visits twice a day; once in the morning shift and once in the afternoon for 45 minutes<br>Control (N=20): Usual care<br>Duration: During ICU stay<br>Follow-up (days): 5 | Inclusion: Age 17-70 years, ≥9 for level of consciousness, and 6 on GCS<br>Exclusion: Dementia and those who died before the 5th day after delirium diagnosis | Mean age: Range: 17-70<br>Female %: NR<br>Race %: NR<br>Delirium %: 100<br>RASS score of +1: 100<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: There was significant difference in irritability and delirium severity status on the 1st day of admission and the 5th day which indicated the reduction in the irritability severity, which was higher in the intervention group vs. control group. The number of subjects with delirium in both groups reduced on the 5th day vs. the 1st day of admission with a significant difference between these 2 days. The number of samples without delirium in the intervention group was almost two times higher vs. the control group on the 5th day.<br>Attrition: NR | High |
| Kolanowski et al. (2011) | Design: RCT<br>Setting: Rehab<br>Country: U.S. | Randomized N: 16<br>Analyzed N: 16<br>Intervention (N=11): Cognitive stimulation delivered using simple recreational activities that were | Inclusion: ≥65 years, with mild to moderate stage dementia, and presence of delirium | Mean (SD) age: 86.5 (4.3)<br>Female %: 58.5<br>Race %:<br>Caucasian: 100<br>Black/African American: 0 | Main outcomes: Delirium, severity of delirium, attention approached significance, and improvement over time favored the intervention group. Although not statistically significant, | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Funding: University | increasingly challenging, mentally stimulating, and tailored to each person's interests and functional ability; the recreational activities target cognitive domains affected by delirium: attention, orientation, memory, abstract thinking, and executive functioning; <30 (mean 26.1, SD 8) minutes each time<br>Control (N=5): Usual care<br>Duration: Daily for up to 30 days<br>Follow-up (days): 30 | Exclusion: Neurological or neurosurgical disease associated with cognitive impairment other than dementia, nonverbal, severe hearing or vision impairment, or no family or caregiver to interview | Asian: 0<br>Other: 0<br>Delirium %: 100<br>Mean (SD) CDR: 1.1 (0.3)<br>Dementia %: 100<br>Postop %: 100<br>Cancer %: NR | a difference in mean (7.0 vs. 3.27) and median (7.0 vs. 3.0) days with delirium was found, with the control group having more days of delirium.<br>Attrition: NR | |
| Kolanowski et al. (2016) | Design: RCT<br>Setting: Rehab<br>Country: U.S.<br>Funding: Government | Randomized N: 283<br>Analyzed N: 282<br>Intervention (N=141): Cognitive stimulation delivered using simple recreational activities that were increasingly challenging, mentally stimulating, and tailored to each person's interests and functional ability; the recreational activities target cognitive domains affected by delirium %: attention, orientation, memory, abstract thinking, and executive functioning; <30 minutes each day delivered 5 days a week<br>Control (N=142): Usual care<br>Duration: Daily for up to 30 days<br>Follow-up (days): 30 or discharge | Inclusion: ≥65 years, with mild to moderate stage dementia, and presence of delirium<br>Exclusion: Any neurological or neurosurgical disease associated with cognitive impairment, nonverbal, having a life expectancy of 6 months or less, acute major depression or psychosis, and severe hearing or vision impairment | Mean (SD) age: 85.78 (6.8)<br>Female %: 64.6<br>Race %:<br>Caucasian: 97.5<br>Black/African American: 2.4<br>Asian: NR<br>Other: NR<br>Delirium %: 100<br>Mean (SD) Charlson Comorbidity Index: 3.00 (1.93)<br>Mean (SD) CDR: 1.25 (0.5)<br>Dementia %: 100<br>Postop %: 100<br>Cancer %: NR<br>Mean (SD) number of medications: 15.38 (4.7)<br>Mean (SD) number of anticholinergic medications: 1.61 (1.1) | Main outcomes: Mean percentage of delirium-free days was similar between intervention vs. control (64.8% [95% CI 59.6 to 70.1] vs. 68.7% [95% CI 63.9 to 73.6], p=0.37, Wilcoxon's rank sums test). Delirium severity was similar between intervention and control (10.77 [95% CI 10.10 to 11.45] vs. 11.15 [95% CI 10.50 to 11.80]; a difference of 0.37, 95% CI 0.56 to 1.31, p=0.43).<br>Attrition: 1% vs. 4% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Marcantonio et al. (2001) | Design: RCT<br>Setting: Nursing homes<br>Country: U.S.<br>Funding: Government | Randomized N: 126<br>Analyzed N: 126<br>Intervention (N=62): Proactive geriatrics consultation; geriatrician's daily visits<br>Control (N=64): Usual care<br>Intervention duration: At admission; if negative, again when warranted<br>Control duration: At admission<br>Follow-up (days): Until discharge | Inclusion: ≥65 years, admitted directly from an acute medical or surgical hospitalization<br>Exclusion: End-stage dementia and those who had complete functional dependence before hospitalization | Mean (SD) age: 79 (8)<br>Female %: 79<br>Race %:<br>Caucasian: 90<br>Black/African American: NR<br>Asian: NR<br>Other: NR<br>Delirium %: 100<br>Charlson index ≥4 %: 36<br>Clinical Dementia %: 40<br>Postop %: 33<br>Cancer %: NR | Main outcomes: Delirium occurred in 20/62 (32%) intervention patients vs. 32/64 (50%) usual care patients (p=0.04, RR 0.64, 95% CI 0.37 to 0.98) for the consultation group.<br>Overall attrition: 0% | Moderate |
| Marcantonio et al. (2010) | Design: RCT<br>Setting: Nursing homes<br>Country: U.S.<br>Funding: Government | Randomized N: 457<br>Analyzed N: 370<br>Intervention (N=282): Delirium Abatement Program (DAP); 1) assessment for delirium within 5 days of post-acute care admission, 2) assessment and correction of common reversible causes of delirium, 3) prevention of complications of delirium, and 4) restoration of function<br>Control (N=175): Usual care<br>Intervention duration: At admission; if negative, again when warranted<br>Control duration: At admission<br>Follow-up (days): 14, 28 | Inclusion: ≥65 years, admitted directly from an acute medical or surgical hospitalization<br>Exclusion: End-stage dementia and those who had complete functional dependence before hospitalization | Mean age: 84<br>Female %: 64<br>Race %:<br>Caucasian: 92<br>Black/African American: NR<br>Asian: NR<br>Other: NR<br>Delirium %: 100<br>Mean delirium severity at baseline (scale 0 to 30): 12.4<br>Mean Charlson comorbidity score (mean, scale 0 to 37): 2.6<br>Clinical Dementia %: 40<br>Postop %: NR<br>Cancer %: NR | Main outcomes: Nurses at DAP sites detected delirium in 41% of intervention participants vs. 12% in usual care sites (p<0.001). The DAP intervention had no effect on delirium persistence based on 2 measurements at 2 weeks (68% vs. 66%) and 1 month (60% vs. 51%) (adjusted p=0.20). Adjusting for baseline differences between DAP and usual care participants and restricting analysis to DAP participants in whom delirium was detected did not alter the results.<br>Attrition at 4 weeks: 25% vs. 21% | High |
| Pitkälä et al. (2006; 2008) | Design: RCT<br>Setting: Inpatient | Randomized N: 174<br>Analyzed N: 174<br>Intervention (N=87): Multi-component intervention consisting | Inclusion: >69 years admitted to the general medicine services at 1 hospital | Mean age: 83<br>Female %: 73.6<br>Race %: NR<br>Delirium %: 100 | Main outcomes: Delirium was alleviated more rapidly during hospitalization, and cognition | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Country: Finland<br>Funding: University | of geriatric assessment and recognition of delirium, avoidance of conventional neuroleptics and administering atypical antipsychotics as necessary, general orientation (calendars, clocks, photos), physiotherapy, general geriatric interventions (nutritional supplements, calcium, hip protectors, etc.), cholinesterase inhibitors if needed, and comprehensive discharge planning (social worker consultation, OT home visit, discharge planning with caregivers)<br>Control (N=87): Usual care<br>Duration: During hospitalization<br>Follow-up (days): 90, 180, 365 | Exclusion: Admission from permanent institutional care to the hospital | Mean (SD) delirium severity, MDAS: 12.5 (5.1)<br>Mean (SD) Barthel Index: 79 (19.7)<br>Mean (SD) Charlson comorbidity index: 2.4 (1.9)<br>Dementia %: 30.4<br>Mean (SD) MMSE: 14.3 (5.2)<br>Cancer %: NR<br>Postop %: NR<br>Mean (SD) number of medications: 7.3 (3.7) | improved significantly at 6 months in the intervention group.<br>Attrition at 3- and 6-month follow-up: 0% vs. 5% | |

*Abbreviations.* CDR=Clinical Dementia Rating; CGBRS=Crichton Geriatric Behavioural Rating Scale; CI=confidence interval; ; DAP=Delirium Abatement Program; GCS=Glasgow Coma Scale; HR=hazard ratio; HR=hazard ratio; ICU=intensive care unit; LOS=length of stay; MDAS Memorial Delirium Assessment Scale; MMSE=Mini-Mental State Examination; N=number; NR=not reported; postop=post-operative; OT=occupational therapy; RCT=randomized controlled trial; RR=relative risk; SD=standard deviation; SPMSQ=Short Portable Mental Status Questionnaire.

## *Single-Component Interventions*

### Computerized Decision Support

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Campbell et al. (2019) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: Government | Randomized N: 200<br>Analyzed N: 200<br>Intervention (N=99): Computerized decision aid consisting of 2 methods: (1) a computerized decision support | Inclusion: ≥18 years, within 24 hours of ICU admission, with delirium on any day of the ICU stay, and patients with contraindication to haloperidol or personal preference to avoid | Mean (SD) age: 61.8 (14.3)<br>Female %: 59<br>Race %:<br>Caucasian: NR<br>Black/African American: 52<br>Asian: NR | Main outcomes: Neither median delirium/coma-free days (p=0.361) nor median change in delirium severity scores (p=0.582 for DRS-R-98; p=0.333 for CAM-ICU-7) were | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | intervention to interrupt orders for strong anticholinergics and (2) human (pharmacist) decision support that included twice-daily surveillance of medication orders and administration records<br>Control (N=101): Usual care<br>Duration: During ICU stay<br>Follow-up (days): 8, 30 | exposure to haloperidol as a delirium treatment<br>Exclusion: Delirium due to alcohol intoxication or aphasic stroke | Other: NR<br>Delirium %: 100<br>Mean (SD) APACHE II: 21.2 (8.3)<br>Mean (SD) Charlson Comorbidity Index: 3.2 (2.5)<br>Mean (SD) IQCODE: 3.3 (0.5)<br>Postop %: 17.6<br>Cancer %: NR<br>Mechanically ventilated %: 71.9 | different between groups. No differences in adverse events or mortality were identified.<br>Attrition: NR | |
| Khan et al. (2019) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: Government | Randomized N: 351<br>Analyzed N: 351<br>Intervention (N=174): Computerized decision support system that generated automated interruptive messages that alerted providers to the risk of anticholinergic in delirium and offered alternative, nonanticholinergic medications; if messages were ignored a study pharmacist called the physician the same day to discuss reducing or discontinuing the anticholinergic medication.<br>Control (N=177): Usual care<br>Intervention duration: Continuous through hospital stay | Inclusion: ≥18 years, admitted to ICU ≥24 hours, and screened positive for delirium<br>Exclusion: Alcohol related delirium | Mean (SD) age: 59.3 (16.9)<br>Female %: 52<br>Race %:<br>Caucasian: NR<br>Black/African American: 42<br>Asian: NR<br>Other: NR<br>Delirium %: 100<br>Mean (SD) Charlson Comorbidity Index: 3.2 (3.0)<br>Dementia %: NR<br>Postop %: 25.4<br>Cancer %: NR<br>Receiving MV %: 72.8 | Main outcomes: There were no differences between the intervention vs. usual care groups in median delirium/coma-free days at day 8 (4 [IQR 2 to 7] days vs. 5 [IQR 1 to 7] days, p=0.888) or at day 30 (26 [IQR 19 to 29] days vs. 26 [IQR, 14 to 29] days, p=0.991). There were no significant differences for decrease in delirium severity at day 8, but at hospital discharge, the intervention group showed a greater reduction in delirium severity (mean decrease in CAM-ICU-7 score: 3.2 [SD 3.3] vs. 2.5 [SD 3.2], p=0.046). | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Control duration: During hospitalization<br>Follow-up (days): 8, 30 | | | Attrition: 3% vs. 1% | |

*Abbreviations.* CAM-ICU=Confusion Assessment Method for the ICU; DRS-R-98=Delirium Rating Scale-Revised-1998; ICU=intensive care unit; IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly; IQR=interquartile range; MV=medical ventilation; N=number; NR=not reported; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

## Acupuncture

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Levy et al. (2022) | Design: RCT<br>Setting: Inpatient<br>Country: Israel<br>Funding: Non-profit | Randomized N: 81<br>Analyzed N: 81<br>Intervention (N=50): Acupuncture plus usual care<br>Control (N=31): Usual care<br>Intervention duration: Once a day, up to 5 days or discharge<br>Control duration: Up to 5 days or discharge<br>Follow-up (days): 5, Discharge | Inclusion: >65 years, hospitalized in a medical inpatient unit, and diagnosed with delirium or subsyndromal delirium within the past 48 hours<br>Exclusion: Contraindication to acupuncture (e.g., platelets ≤20 x 109/L), a history of severe dementia (documented history and/or IQCODE score ≥4), an acute neurological injury (stroke), a history of schizophrenia or a formal thought disorder, an active acute alcohol or drug withdrawal, a history of end stage liver failure (to distinguish between delirium and hepatic encephalopathy), or language barriers preventing delirium assessment | Mean (SD) age: 84.5 (7.4)<br>Female %: 45.7<br>Race %: NR<br>Delirium on admission to hospital %: 51.8<br>Median APACHE II: 9 vs. 11<br>Dementia %: NR, severe dementia excluded<br>Postop %: NR<br>Cancer %: NR | Main outcomes: A multivariate Cox regression analysis showed a shorter time-to first remission of delirium in acupuncture vs. control (HR 0.267, 95% CI 0.098 to 0.726, p=0.010). In the 7 days of evaluation, a significantly higher number of delirium-free days was found in acupuncture vs. control (p<0.001), and CAM-S sum from day 2 to day 7 of evaluation was significantly lower in acupuncture vs. control (p=0.002).<br>Overall attrition: 0% | High |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; CAM-S=Confusion Assessment Method-Severity; CI=confidence interval; HR=hazard ratio; ICU=intensive care unit; IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly; N=number; NR=not reported; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

### Family Member Delivered Intervention

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Mailhot et al. (2017) | Design: RCT<br>Setting: Postop cardiac<br>Country: Canada<br>Funding: Government | Randomized N: 30<br>Analyzed N: 30<br>Intervention (N=16): Nurse mentor provided information on delirium and guidance to the family caregiver who was there to intervene in delirium management<br>Control (N=14): Usual care<br>Intervention duration: Twice a day during hospitalization<br>Control duration: During hospitalization<br>Follow-up (days): Until discharge | Inclusion: POD, undergoing CABG or heart valve surgery, and a family caregiver who could visit with 24 hours of delirium onset and visit twice a day during the study<br>Exclusion: Preop diagnosis of cognitive impairment or irreversible postop cognitive damage | Mean age: 75<br>Female %: NR<br>Race %: NR<br>Delirium %: 100<br>Past episode of Delirium %: 16.7<br>Functioning: NR<br>Dementia %: NR, cognitive impairment excluded<br>Postop %: 100<br>Cancer %: NR<br>Drank daily %: 10<br>Depression %: 33.3 | Main outcomes: Mean delirium severity scores showed similar trajectories on days 1, 2 and 3 in both groups.<br>Attrition: 2% vs. 0% | Moderate |

*Abbreviations.* CABG=coronary artery bypass graf; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; RCT=randomized controlled trial.

### Massage

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Makinian et al. (2015) | Design: RCT<br>Setting: Inpatient<br>Country: Iran<br>Funding: University | Randomized N: 88<br>Analyzed N: 88<br>Intervention (N=NR): Face, head, and neck massage therapy plus single dose of haloperidol<br>Control (N=NR): Single dose of haloperidol | Inclusion: ≥60-year-old women hospitalized in coronary care units, received a diagnosis of delirium, and not on MV<br>Exclusion: Those with skin lesions or tender area in the face and the head and those needing another dose of haloperidol | Mean age: 74.1<br>Female %: 100<br>Race %: NR<br>Delirium %: 100<br>Functioning: NR<br>Dementia %: NR, excluded those with cognitive disorders | Main outcomes: After the study intervention, the mean total delirium score in the intervention group was significantly higher than that of the control group (17.6 vs. 16.7, p=0.03).<br>Attrition: NR | High |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | Intervention duration: Twice a day for 2 days; haloperidol at admission<br>Control duration: At admission<br>Follow-up (days): Until discharge | | Postop %: NR<br>Cancer %: NR | | |

*Abbreviations.* MV=medical ventilation; N=number; NR=not reported; postop=post-operative; RCT=randomized controlled trial.

## Bright Light Therapy

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Yang et al. (2012) | Design: RCT<br>Setting: Inpatient, psychiatry<br>Country: South Korea<br>Funding: None | Randomized N: 36<br>Analyzed N: 36<br>Intervention 1 (N=20): Adjuvant bright light therapy with risperidone starting at 0.5 mg/day; increased daily until a score <12 on the DRS or a 50% reduction of the baseline DRS score was achieved during the study period<br>Intervention 2 (N=16): Risperidone alone, starting at 0.5 mg/day; increased daily until a score <12 on the DRS or a 50% reduction of the baseline DRS score was achieved during the study period<br>Duration: During hospitalization; 5 days<br>Follow-up (days): 0, 1, 2, 3, 4, 5 | Inclusion: DRS score >12 (moderate to severe)<br>Exclusion: Other axis I disorders on the DSM-IV, prolonged QTc interval on electrocardiography, history of hypersensitivity or intolerance to risperidone, and injected with antipsychotics or benzodiazepines before screening | Mean (SD) age: 69.58 (15.13)<br>Female %: 36<br>Race %: NR<br>Delirium %: 100 (DRS score >12)<br>Baseline scale of function (physical or cognitive)<br>CGI-S: 5.31±0.95 vs. 5.05±0.76<br>Dementia %: 0, excluded if had other axis I disorders on the DSM-IV<br>Postop %: 55<br>Cancer %: NR<br>Hepatic or renal impairment: NR<br>Alcohol use: NR<br>Drug use: NR<br>Mean (SD) number of medications taken at baseline: NR | Main outcomes: Risperidone with light therapy group showed a significantly greater decrease in the DRS score than the risperidone-only group (F=2.87, p=0.025), but the MDAS score was not significantly different between the 2 groups.<br>Attrition: NR | Moderate |

*Abbreviations.* CGI-S=Clinical global impression-severity; DRS=Delirium Rating Scale; DSM-IV= Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; MDAS Memorial Delirium Assessment Scale; MV=medical ventilation; N=number; NR=not reported; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

# Pharmacological Interventions for Prevention of Delirium

## *Dexmedetomidine*

### Dexmedetomidine vs. Usual Care/Normal Saline

#### In Surgical Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| Chen et al. (2021) | Design: RCT<br>Setting: Intra-operative, cranial surgery<br>Country: Taiwan<br>Funding: Unclear | Randomized N: 160<br>Analyzed N: 160<br>Intervention (N=80): Dexmedetomidine 0.5 µg/kg/hour IV<br>Control (N=80): Normal saline<br>Duration: Intra-operative<br>Follow-up (days): Until discharge | Inclusion: Age ≥20 years, elective cranial surgery for brain tumor resection, aneurysm clipping, intracranial bypass, and microvascular decompression<br>Exclusion: Age >80 years, metastatic brain tumor, revision surgery, history of arrhythmia or heart failure, liver cirrhosis, or renal insufficiency | Mean age: 57.5<br>Female %: 60.6<br>Race %: NR<br>Delirium %: NR<br>ASA I-III %: 100<br>Dementia %: NR<br>Postop %: 100<br>Tumor excision %: 69.4<br>Aneurysm clipping %: 13.1<br>Intracranial bypass %: 10.6<br>Microvascular decompression %: 6.9 | Main outcomes: The dexmedetomidine group had a more favorable ICDSC score, with more patients receiving an ICDSC score of 0 than the control group (84.6% vs. 64.2%, p=0.012).<br>Overall attrition: 0% | Low |
| He et al. (2018) | Design: RCT<br>Setting: Intra-operative, orthopedic<br>Country:<br>Funding: China Government | Randomized N: 90<br>Analyzed N: 90<br>Intervention 1 (N=30): Dexmedetomidine 0.5 µg/kg initial bolus, then maintained at 0.4 µg/kg/hour<br>Intervention 2 (N=30): Midazolam IV of 0.03 mg/kg<br>Intervention 3 (N=30): Normal saline<br>Intervention 1 duration: 10 minutes before anesthesia induction, then during surgery | Inclusion: Age 75-90 years with thoracic or lumbar vertebral fractures and receiving selective operation at grade I to III in the ASA classification<br>Exclusion: CNS disease, mental illness, or ≤23 on MMSE | Mean (SD) age: 82.5 (5.6)<br>Female %: 42<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR | Main outcomes: The incidence rate of POD in the dexmedetomidine group was apparently lower than those in the other 2 groups ($p<0.05$); the incidence rate of POD at 1-2 days after operation in midazolam group was higher than that in the normal saline group ($p<0.05$). There was no significant difference in the incidence rate of POD at 3-5 days after operation between the midazolam and normal saline groups ($p>0.05$).<br>Attrition: NR | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | Intervention 2, Intervention 3<br>duration: Before anesthesia<br>Follow-up (days): 5 | | | | |
| Hu et al. (2020) | Design: RCT<br>Setting: Intra-operative, esophagectomy<br>Country: China<br>Funding: Government | Randomized N: 177<br>Analyzed N: 177<br>Intervention (N=90): Dexmedetomidine IV loading dose of 0.4 ml/kg over 15 minutes, then 0.1 ml/kg/hour<br>Control (N=87): Usual care<br>Intervention duration: Loading dose immediately prior to induction of anesthesia, then until 1 hour until anticipated end of surgery<br>Control duration: During surgery<br>Follow-up (days): 4 | Inclusion: Age 60-80 years with ASA I-III and scheduled for an open transthoracic esophagectomy under general endotracheal anesthesia<br>Exclusion: BMI >30, severe pulmonary, cardiac, renal, hepatic, cerebrovascular, comorbidities, chronic pain, or substance abuse disorders, or dementia or being treated with antipsychotic agents | Mean (SD) age: 69.3 (4.8)<br>Female %: 17.6<br>Race %: NR<br>Delirium %: NR<br>ASA II %: 72.3<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Delirium occurred in 15 (16.7%) of 90 cases given dexmedetomidine and in 32 (36.8%) of 87 cases given saline (p=0.0036).<br>Attrition: 14% vs. 14% | Low |
| Huyan et al. (2019) | Design: RCT<br>Setting: Intra-operative, cardiothoracic<br>Country: China<br>Funding: Mixed | Randomized N: 360<br>Analyzed N: 346<br>Intervention (N=180): Dexmedetomidine continuous IV infusion of 0.5μg/kg bolus preop followed by 0.1 μg/kg/hour intra-operatively<br>Control (N=180): Normal saline<br>Intervention duration: Preop to 30 minutes before end of surgery | Inclusion: ≥65 years having radical pulmonary resection<br>Exclusion: Patients with ICDSC score >0 and patients discharged to ICU after surgery | Mean (SD) age: 70.5 (5.52)<br>Female %: 47<br>Race %: NR<br>Delirium %: 0<br>ASA II, III %: 100<br>Dementia %: NR<br>Postop %: 100 pulmonary<br>Cancer %: 100 lung | Main outcomes: During postop days 1-7, delirium occurred in both groups but was lower in the group receiving dexmedetomidine (precise numbers not provided, graph only).<br>Attrition: 4% vs. 4% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | Control duration: Unclear on details<br>Follow-up (days): Through day 7 | | | | |
| Kim J.A. et al. (2019) | Design: RCT<br>Setting: Intra-operative, cardiothoracic<br>Country: South Korea<br>Funding: Industry | Randomized N: 143<br>Analyzed N: 120<br>Intervention 1 (N=73): Dexmedetomidine continuous IV infusion of 0.5 µg/kg/hour<br>Intervention 2 (N=70): Saline (sevoflurane) 0.125 mL/kg/hour<br>Duration: Just prior to induction of anesthesia and discontinued at end of surgery<br>Follow-up (days): Through day 3 | Inclusion: Age 18-75 years undergoing elective video-assisted thoracoscopic lobectomy/segmentectomy for lung cancer<br>Exclusion: Patients with dementia | Median age: 61<br>Female %: 48<br>Race %: NR<br>Delirium %: NR<br>ASA I-III %: 100<br>Dementia %: 0<br>Postop %: 100 pulmonary surgery<br>Cancer %: 100 lung cancer | Main outcomes: The incidence of delirium after discharge from post anesthesia care unit was not different between groups (25% vs. 25%).<br>Attrition: 18% vs. 14% | Low |
| Lee et al. (2018) | Design: RCT<br>Setting: Intra-operative, noncardiac<br>Country: South Korea<br>Funding: University | Randomized N: 354<br>Analyzed N: 318<br>Intervention 1 (N=118): Dexmedetomidine IV 1µg/kg bolus followed by 0.2-0.7 µg/kg/hour<br>Intervention 2 (N=118): Dexmedetomidine IV 1µg/kg bolus<br>Intervention 3 (N=118): Saline<br>Duration: Intra-operative<br>Follow-up (days): Through day 5 | Inclusion: >65 years undergoing laparoscopic major non-cardiac surgery under general anesthesia<br>Exclusion: Patients with cognitive impairment | Mean (SD) age: 73.07 (6.01)<br>Female %: 56<br>Race %: NR<br>Delirium %: NR<br>ASA I, II %: 68.2<br>Cognitive Impairment %: 0<br>Postop %: 100 non-cardiac surgery<br>Cancer %: NR | Main outcomes: The incidence of POD was 9.5% and 18.4% in the 2 groups receiving dexmedetomidine compared with usual care (24.8%, p=0.017).<br>Attrition at follow-up: 19% vs. 3% vs. 8% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| Lee et al. (2019) | Design: RCT<br>Setting: Intra- and post-operative, liver transplant<br>Country: South Korea<br>Funding: Unclear | Randomized N: 217<br>Analyzed N: 201<br>Intervention (N=109): Dexmedetomidine IV 1µg/kg/hour<br>Control (N=108): Normal saline<br>Duration: Intra-operative and postop for 2 days<br>Follow-up (days): Until discharge | Inclusion: ≥18 years undergoing liver transplant (recipient)<br>Exclusion: Pregnancy, preop comatose state, preexisting neurologic deficit, preexisting psychiatric disorders, allergy to dexmedetomidine, no Korean speaker, and hemodynamic instability for >1 hour | Mean (SD) age: 55.5 (range 50-62)<br>Female %: 28<br>Race %: NR<br>Delirium %: NR<br>APACHE II: 23.5<br>Dementia %: NR<br>Postop %: 100 liver transplant<br>Cancer (original diagnosis) %: 63<br>Cancer surgery %: 0 | Main outcomes: There was no significant difference in delirium incidence in the dexmedetomidine group compared to the control group (9% vs. 5.9%, p=0.44).<br>Attrition: 8% vs. 6% | Low |
| Li X. et al. (2017) | Design: RCT<br>Setting: Intra- and post-operative, cardiac<br>Country: China<br>Funding: University | Randomized N: 285<br>Analyzed N: 285<br>Intervention (N=142): Dexmedetomidine IV 0.6 µg/kg for 10 minutes followed by 0.4 µg/kg/hour until end of surgery then 0.1 µg/kg/hour until end of MV<br>Control (N=143): Normal saline<br>Duration: Intra-operatively and during MV<br>Follow-up (days): 1 to 5 | Inclusion: ≥60 years undergoing elective CABG and/or valve replacement surgery<br>Exclusion: Parkinson disease or severe dementia | Mean (SD) age: 66.95 (5.35)<br>Female %: 31<br>Race %: NR<br>Delirium %: 0<br>ASA I, II %: 64.2<br>Severe Dementia %: 0<br>Postop %: 100 cardiac surgery<br>Cancer %: 0 | Main outcomes: Dexmedetomidine did not decrease the incidence of delirium (4.9% vs. 7.7%, p=0.341).<br>Attrition: 5% vs. 8% | Low |
| Li et al. (2020) | Design: RCT<br>Setting: Intra-operative, noncardiac<br>Country: China<br>Funding: Mixed | Randomized N: 620<br>Analyzed N: 619<br>Intervention (N=310): Dexmedetomidine IV 0.6 µg/kg bolus followed by 0.5 µg/kg/hour until 1 hour before end of surgery | Inclusion: ≥60 years undergoing elective major non-cardiac surgery under general anesthesia with an expected duration of 2 hours or more<br>Exclusion: Patients with Parkinson's disease | Mean (SD) age: 69.0 (6.5)<br>Female %: 60<br>Race %: NR<br>Delirium %: 0<br>ASA I, II %: 89.5<br>Dementia %: NR (excluded Parkinson's) | Main outcomes: The incidence of delirium within 5 days of surgery was lower with dexmedetomidine treatment (5.5% vs. 10.3%, p=0.026).<br>Attrition: 0% vs. 0% | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | Control (N=310): Normal saline<br>Duration: Intra-operative<br>Follow-up (days): Up to day 5 or discharge | | Postop %: 100 noncardiac surgery<br>Cancer %: 0 | | |
| Likhvantsev et al. (2021) | Design: RCT<br>Setting: Intra-operative, cardiac surgery<br>Country: Russia<br>Funding: None | Randomized N: 175<br>Analyzed N: 169<br>Intervention (N=87): Dexmedetomidine 100 mg/mL<br>Control (N=88): Placebo; usual care<br>Duration: Started at induction of anesthesia and lasted throughout the procedure<br>Follow-up (days): Until discharge | Inclusion: >45 years undergoing elective CABG or valve surgery or a combination of the 2 with CPB<br>Exclusion: Evidence of preop mental impairment or underwent a second surgery before ICU discharge | Mean (SD) age: 62.5 (9.6)<br>Female %: 27.8<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR, though excluded mental impairment; implied 0%<br>Postop %: 100<br>Cancer %: NR | Main outcomes: A decrease in the rate of delirium for dexmedetomidine vs. placebo was demonstrated (6/84 [7.1%] vs. 16/85 [18.8%], p=0.02, OR 0.33 [95% CI 0.12 to 0.90).<br>Attrition: 3% vs. 3% | Low |
| Liu Y. et al. (2016) | Design: RCT<br>Setting: Intra-operative, orthopedic<br>Country: China<br>Funding: Unclear | Randomized N: 200<br>Analyzed N: 197<br>Intervention (N=100): Dexmedetomidine IV 0.2-0.4 µg/kg/hour until end of surgery<br>Control (N=100): Placebo; normal saline<br>Duration: Intra-operative<br>Follow-up (days): 1, 3, 7 | Inclusion: Age 65-80 years undergoing total hip, knee, or shoulder replacement with general anesthesia<br>Exclusion: Neurological diseases that may affect cognitive function (e.g., subdural hematoma, vascular dementia, frontotemporal dementia, hypothyroidism, alcoholic dementia, vitamin B12 deficiency, encephalitis), hypoxic pulmonary disease, and perioperative serious cardiopulmonary complications | Mean (SD) age: 72.83 (8.39)<br>Female %: 51<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR, though excluded mental impairment; implied 0%<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Dexmedetomidine treatment significantly decreased POD incidence for patients with and without mild cognitive impairment relative to placebo (p<0.05, both comparisons).<br>Attrition: 1% vs. 2% | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| Massoumi et al. (2019) | Design: RCT<br>Setting: Postop, cardiac<br>Country: Iran<br>Funding: University | Randomized N: 93<br>Analyzed N: 88<br>Intervention (N=46): Dexmedetomidine 1 µg/kg over 10 minutes then infusion of 0.2-0.7 µg/kg/hour in 50cc volume by syringe pump until extubation<br>Control (N=47): Placebo; infusion of normal saline with the same volume as drug by the syringe pump<br>Duration: NR<br>Follow-up (days): 3 | Inclusion: Age 40-80 years undergoing CABG surgery<br>Exclusion: History of dementia, "defect in the examined data," need for reoperation due to hemorrhage, "excessive sensitivity" to haloperidol and phenothiazines, glaucoma, or receiving lithium medication | Mean (SD) age: 61.55 (4.80)<br>Female %: 18<br>Race %: NR<br>Delirium %: NR<br>Baseline scale of function: NR<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Administration of dexmedetomidine significantly decreased delirium compared to placebo (9.1% vs 20.5%, p=0.040).<br>Attrition: 4% vs. 6% | Moderate |
| Momeni et al. (2021) | Design: RCT<br>Setting: Postop, cardiac<br>Country: Belgium<br>Funding: Medical associations | Randomized N: 420<br>Analyzed N: 349<br>Intervention 1 (N=210): Dexmedetomidine 0.4 µg/kg/hour plus propofol 1-3 mg/kg/hour<br>Intervention 2 (N=210): Propofol 1-3 mg/kg/hour plus saline 0.9%<br>Intervention 1 duration: Perioperative (Intra-operative and postop)<br>Intervention 2 duration: Postop<br>Follow-up (days): Until discharge | Inclusion: ≥60 years having on-pump cardiac surgery<br>Exclusion: Patients with hepatic dysfunction (liver enzyme 3 x the upper limit of normal + a serum albumin concentration below the normal reference limit), preop delirium, surgery without CPB, minimally invasive or robotic cardiac surgery, emergency surgery, or patients on chronic renal replacement therapy | Mean age: 70.5<br>Female %: 24.2<br>Race %: NR<br>Delirium %: 0 (excluded)<br>Function: NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: There was no difference between treatments in the incidence of POD (p=0.687).<br>Attrition: 16% vs. 18% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| Shi et al. (2019)* | Design: RCT<br>Setting: Intra-operative, cardiac<br>Country: China<br>Funding: Mixed | Randomized N: 168<br>Analyzed N: 164<br>Intervention 1 (N=84): Dexmedetomidine IV 0.4-0.6 µg/kg/hour<br>Intervention 2 (N=84): Usual care; propofol<br>Duration: Intra-operative<br>Follow-up (days): POD 5 | Inclusion: ≥60 years undergoing cardiac surgery<br>Exclusion: Patients with previous history of POD | Mean (SD) age: 74.46 (7.45)<br>Female %: 27<br>Race %: NR<br>Delirium %: 0 with previous POD<br>Function; NR<br>Dementia %: NR<br>Postop %: 100 cardiac surgery<br>Cancer %: NR | Main outcomes: There was no significant difference in the incidence of POD between the dexmedetomidine group and the propofol (usual care) group (39.3% vs. 26.3%, p=0.0758).<br>Attrition: 0% vs. 5% | Low |
| Shi et al. (2020) | Design: RCT<br>Setting: Intra-operative, thoracic<br>Country: China<br>Funding: Government | Randomized N: 106<br>Analyzed N: 106<br>Intervention (N=53): Dexmedetomidine IV 0.5 µg/kg/hour<br>Control (N=53): Normal saline<br>Duration: Started at induction of anesthesia and continued until chest closure<br>Follow-up (days): 1, 3, 7 | Inclusion: ≥65 years males, scheduled for thoracoscopic lobectomy with one-lung ventilation, and received general anesthesia<br>Exclusion: Neurologically impaired (MMSE ≤23); systolic BP ≥180 or <90 mmHg or diastolic BP ≥110 or <60 mmHg; serious heart, liver, kidney, lung, endocrine, or nervous system diseases; severe infection; abnormal results on MMSE, MoCA, or CAM; epidural puncture failure; sleep disorders | Mean (SD) age: 68.7 (4.06)<br>Female %: 0<br>Race %: NR<br>Delirium %: NR<br>ASA II %: 88.7<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: The incidence of postop cognitive dysfunction and POD in the dexmedetomidine group was 13.2 and 7.5%, respectively, while that in the saline group was 35.8 and 11.3%, respectively.<br>Overall attrition: 0% | Low |
| Shu et al. (2017) | Design: RCT<br>Setting: Intra-operative, cardiac<br>Country: China | Randomized N: 60<br>Analyzed N: 60<br>Intervention (N=30): Dexmedetomidine IV 1.0 µg/kg bolus preop, followed | Inclusion: Age 45-75 years undergoing elective cardiac valve replacement<br>Exclusion: NR | Mean (SD) age: 47.25 (8.08)<br>Female %: 43<br>Race %: NR<br>Delirium %: NR<br>ASA II, III %: 100 | Main outcomes: The POD score of the dexmedetomidine group was significantly decreased (15.8±4.2) compared with the control group (18.6±6.2) (p<0.05). There was no difference in the incidence of | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | Funding: Unclear | by 0.5 µg/kg/hour<br>Control (N=30): Normal saline<br>Duration: Preop, Intra-operative<br>Follow-up (days): Discharge | | Dementia %: NR<br>Postop %: 100 cardiac surgery<br>Cancer %: 0 | delirium in the dexmedetomidine group compared with the control group (23.3% vs. 13.3%, p>0.05).<br>Attrition: NR | |
| Soh et al. (2020) | Design: RCT<br>Setting: Intra- and post-operative, cardiac<br>Country: South Korea<br>Funding: None | Randomized N: 108<br>Analyzed N: 108<br>Intervention (N=54): Dexmedetomidine 200 µg mixed with 0.9% saline to achieve a concentration of 4 µg/kg/hour<br>Control (N=54): Normal saline<br>Duration: Started immediately after anesthetic induction and continued for 24 hours<br>Follow-up (days): 7 | Inclusion: ≥20 years scheduled for aortic surgery under CPB using either moderate hypothermic circulatory arrest with antegrade cerebral perfusion via the right axillar artery or aortic cross clamp interrupting renal blood flow<br>Exclusion: Congestive heart failure with a left ventricular ejection fraction <30%, uncontrolled arrhythmia combined with unstable hemodynamics, acute coronary syndrome, estimated glomerular filtration rate <15 ml/minute/1.73 $m^2$, or use of ventricular assist devices | Mean age: 65<br>Female %: 38.9<br>Race %: NR<br>Delirium %: NR<br>Katz grade I and II %: 10.2<br>Katz grade III %: 38.0<br>Katz grade IV %: 27.8<br>Katz grade V %: 8.3<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Secondary outcomes, including stroke, mortality, and delirium, were similar between subjects randomized to dexmedetomidine and control groups (16/54 [30%] vs. 22 [41%], OR 0.61, 95% CI 0.28 to 2.36). POD in the 7 days after surgery was also similar between the groups (2/54 [4%] vs. 7/54 [13%], OR 0/26, 95% CI 0.05 to 1.31).<br>Attrition: 6% vs. 2% | Low |
| Su et al. (2016) Zhang et al. (2019) | Design: RCT<br>Setting: Postop, noncardiac<br>Country: China<br>Funding: Mixed | Randomized N: 700<br>Analyzed N: 700<br>Intervention (N=350): Dexmedetomidine IV 0.1 µg/kg/hour<br>Control (N=350): Placebo; normal saline | Inclusion: ≥65 years who underwent elective noncardiac surgery under general anesthesia<br>Exclusion: Patients with parkinsonism or profound dementia | Mean (SD) age: NR<br>Female %: NR<br>Race %: NR<br>Delirium %: NR<br>APACHE II: 10.4<br>Severe Dementia %: 0<br>Postop %: 100 noncardiac surgery<br>Cancer %: NR | Main outcomes: The incidence of POD was significantly lower in the dexmedetomidine group compared with placebo (9% vs. 23%, p<0.001).<br>Attrition: 33% vs. 22% | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | Duration: Postop<br>Follow-up (days): Through POD 7 | | | | |
| Sun et al. (2019)* | Design: RCT<br>Setting: Postop, noncardiac<br>Country: China<br>Funding: None | Randomized N: 618<br>Analyzed N: 557<br>Intervention (N=309): Dexmedetomidine IV 0.1 µg/kg/hour<br>Control (N=309): Placebo; saline<br>Duration: Postop<br>Follow-up (days): Through POD 5 | Inclusion: ≥65 years undergoing major elective noncardiac surgery without a planned ICU stay<br>Exclusion: Parkinson's or frank dementia | Median age: 68.5<br>Female %: 43<br>Race %: NR<br>Delirium %: NR<br>ASA I-II: 79.5<br>MMSE: 24.5<br>Postop %: 100 noncardiac surgery<br>Cancer %: 50 | Main outcomes: The incidence of POD was not different between dexmedetomidine and placebo (11.7% vs. 13.8%, p=0.47).<br>Attrition: 9% vs. 11% | Low |
| Tang et al. (2018) | Design: RCT<br>Setting: Intra-operative, brain<br>Country: China<br>Funding: Unclear | Randomized N: 112<br>Analyzed N: 106<br>Intervention (N=56): Dexmedetomidine IV 1.0 µg/kg bolus followed by 0.3 µg/kg/hour<br>Control (N=56): Normal saline (sevoflurane)<br>Duration: Intra-operative<br>Follow-up (days): 1 | Inclusion: Age 18-70 years undergoing brain aneurysm embolism surgery with Glasgow coma scale >11<br>Exclusion: Coagulation dysfunction, history of drug allergy to dexmedetomidine or sevoflurane, severe hypertension or cardiovascular disease, liver or kidney dysfunction, use of sedatives within 2 days prior to surgery, sinus bradycardia, known history of second- or third-degree heart block, and ischemic heart disease | Mean (SD) age: 61.56 (7.91)<br>Female %: 53<br>Race %: NR<br>Delirium %: NR<br>ASA I-IV %: 100<br>Dementia %: NR<br>Postop %: 100 brain vascular surgery<br>Cancer %: NR | Main outcomes: There was less severe POD in the group that received dexmedetomidine than normal saline (p=0.038).<br>Attrition: 4% vs. 7% | Moderate |
| Tang C. et al. (2020) | Design: RCT<br>Setting: Postop, esophageal | Randomized N: 60<br>Analyzed N: 53<br>Intervention 1 (N=30): | Inclusion: Age 18-80 years with ASA status I-III and undergoing thoracoscopic-laparoscopic | Mean (SD) age: 61.5 (7.7)<br>Female %: 47.2<br>Race %: NR | Main outcomes: The simultaneous administration of dexmedetomidine and sufentanil significantly reduced | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | cancer<br>Country: China<br>Funding: Government | Dexmedetomidine 2.5 µg/mL plus sufentanil 1 µg/mL PCA<br>Intervention 2 (N=30): Sufentanil 1 µg/mL PCA<br>Duration: During post anesthesia care unit stay<br>Follow-up (days): 1, 2 | esophagectomy<br>Exclusion: Obstructive or restrictive lung disease with FEV1/FVC% < 70% and 50% predict FEV1 < 80% predict, asthma and sleep apnea syndrome, liver or urinary bladder disorders, regular use of pain perception-modifying drugs and opioids or sedative medications in the week prior to surgery, known history of second- or third-degree heart block and ischemic heart diseases, difficulties with the use of PCA, known cognitive dysfunction/dementia, and BMI >35 kg/$m^2$ | Delirium %: NR<br>ASA I %: 32.1<br>ASA II %: 62.3<br>ASA III %: 5.7<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: 100 | plasma interleukin-6 and tumor necrosis factor-α concentrations and increased interleukin-10 level (p<0.0001, p=0.0003, and p=0.0345, respectively), accompanied by better POD categories and health statuses of patients (p=0.024 and p<0.05, respectively). There was no hypotension, bradycardia, respiratory depression, or over sedation in the dexmedetomidine group.<br>Attrition: 10% vs. 13% | |
| Turan et al. (2020); DECADE | Design: RCT<br>Setting: Intra- and post-operative, cardiac<br>Country: U.S.<br>Funding: Industry | Randomized N: 798<br>Analyzed N: 794<br>Intervention (N=400): Dexmedetomidine IV bolus (0.1 µg/kg/hour), then 0.2 µg/kg/hour during surgery and 0.4 µg/kg/hour postop surgery<br>Control (N=398): Placebo; normal saline<br>Duration: Bolus given before induction of anesthesia, then during surgery, and postop | Inclusion: Age 18-85 years who were scheduled for cardiac surgery with CPB and who had heart rates ≥50 beats per minute<br>Exclusion: Sick-sinus or Wolff-Parkinson-White syndromes, atrioventricular block, atrial fibrillation within 30 days, permanent pacemaker, amiodarone or dexmedetomidine use within 30 days, an ejection fraction <30% or severe heart failure, MI | Mean (SD) age: 62.5 (11.5)<br>Female %: 29.8<br>Race %:<br>Caucasian: 91.7<br>Black/African American: NR<br>Asian: NR<br>Other: NR<br>Delirium %: NR<br>ASA III %: 25.3<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: The incidence of delirium was 67 patients (17%) in the dexmedetomidine group and 46 patients (12%) in the placebo group (RR 1.48, 97.8% CI 0.99 to 2.23, p=0.026 [p≤0.022 required for significance]).<br>Attrition: 1% vs. 1% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | Follow-up (days): 5 or until discharge | within 7 days, BMI ≥40, or clonidine use within 48 hours | | | |
| van Norden et al. (2021) | Design: RCT<br>Setting: Intra-operative, cardiac and abdominal<br>Country: Germany<br>Funding: Industry | Randomized N: 63<br>Analyzed N: 60<br>Intervention (N=30): Dexmedetomidine 0.7 µg/kg IV then 0.4 µg/kg/hour IV<br>Control (N=33): Placebo; normal saline<br>Duration: During surgery and in ICU<br>Follow-up (days): 14 or until discharge | Inclusion: ≥60 years, undergoing either major elective cardiac or major open abdominal surgery<br>Exclusion: Valvular surgery, off-pump cardiac surgery, previously diagnosed or suspected to suffer from major neurocognitive disorder (MMSE <24), severe audiovisual impairment, TBI, intracranial bleeding <1 year before study, psychiatric illness, hemodynamic dysfunction, second- or third-degree atrioventricular heart block, spinal injury with autonomic dysfunction, preop cerebrovascular accident with residual neurological deficit, Child C liver cirrhosis, intra-operative use of remifentanil or clonidine, additional administration of dexmedetomidine within 3 months after inclusion, and planned postop deep sedation below a RASS of 4 | Mean (SD) age: 70.5 (6.7)<br>Female %: 30<br>Race %: NR<br>Delirium %: NR<br>Charlson comorbidity index score: 3.3 (2.18)<br>Dementia %: 0 (excluded MMSE <24)<br>Postop %: 100<br>-Cardiac: 23<br>-Pancreatic: 48<br>-Other intra-abdominal: 28<br>Cancer %: 67 | Main outcomes: Dexmedetomidine was associated with a reduced incidence of POD within the first 5 postop days (17.9% vs. 43.8%, p=0.038). There was no difference in the severity of POD between groups and no difference in mean (SD) duration of delirium between the dexmedetomidine and placebo group (2.00 [1.41] vs. 0.89 [0.94] days respectively, p=0.149). No patients in the dexmedetomidine group died while 5 (15.6%) patients in the placebo group died (p=0.029).<br>Attrition: 7% vs. 3% | Moderate |
| Wu et al. (2016) | Design: RCT<br>Setting: Postop, noncardiac | Randomized N: 76<br>Analyzed N: 61<br>Intervention (N=38): | Inclusion: ≥65 years who underwent noncardiac surgery during general anesthesia and | Mean (SD) age: 75 (5.5)<br>Female %: 42.1<br>Race %: NR | Main outcomes: The incidences of delirium and other complications | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | Country: China<br>Funding: Government | Dexmedetomidine 0.1 µg/kg/hour<br>Control (N=38): Normal saline 50 mL<br>Duration: 15 hours from 5:00pm on the day of surgery until 8:00am on the first day after surgery<br>Follow-up (days): 7, discharge, 30 | were admitted to the surgical ICU<br>Exclusion: History of schizophrenia, epilepsy, or parkinsonism; history of sleep disorders (requirement of hypnotics/sedatives during the last month); history of obstructive sleep apnea syndrome; preop sick sinus syndrome, severe sinus bradycardia (heart rate less than 50 beats/minute), or atrioventricular block of second degree or above without pacemaker; preop coma; brain injury or neurosurgery; serious hepatic dysfunction (Child-Pugh class C); serious renal dysfunction (undergoing dialysis before surgery); or requirement of MV | Delirium %: NR<br>ASA II %: 51.3<br>ASA III %: 48.7<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | after surgery were not statistically different between the 2 groups.<br>Attrition: 21% vs. 18% | |
| Xin et al. (2021) | Design: RCT<br>Setting: Intra-operative, cholecystectomy<br>Country: China<br>Funding: Government | Randomized N: 60<br>Analyzed N: 60<br>Intervention (N=30): Dexmedetomidine 0.5 µg/kg IV bolus then 0.4 µg/kg/hour IV<br>Control (N=30): Normal saline<br>Duration: During surgery<br>Follow-up (days): 7 | Inclusion: >65 years, undergoing laparoscopic cholecystectomy, with mild cognitive impairment (MoCA 15-24; MMSE <27; CDR of 0.5 points; and ADL score <26)<br>Exclusion: Preop delirium, preop neurological diseases affecting cognitive function (such as vascular dementia), severe liver | Mean age: 68.5<br>Female %: 63<br>Race %: NR<br>Delirium %: 0 (excluded)<br>ASA II %: 90<br>Dementia %: NR (excluded vascular dementia)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: POD occurred in 10/30 patients (33.3%) in the control group, and in 3/30 patients (10%) given dexmedetomidine (OR 0.222, 95% CI 0.054 to 0.914, p=0.028).<br>Overall attrition: 0% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | | and renal insufficiency, autoimmune diseases, recent use of sedatives, antidepressants or immunosuppressive drugs, TBI, or history of alcoholism | | | |
| Xuan et al. (2018) | Design: RCT<br>Setting: Postop, ortho<br>Country: China<br>Funding: Government | Randomized N: 453<br>Analyzed N: 453<br>Intervention (N=227): Dexmedetomidine 0.1 µg/kg/hour<br>Control (N=226): Placebo; normal saline<br>Duration: Daily for 3 days<br>Follow-up (days): 3, 7, 30 | Inclusion: >60 years with joint replacement surgery and admitted to the ICU<br>Exclusion: High cholesterol combined with diabetes; brain injury or neurosurgery; severe sinus bradycardia; sick sinus syndrome; neurological disease; abnormal liver enzymes, patients with rhabdomyolysis, and myopathy; history of mental illness and epilepsy; severe lung disease and multiple organ dysfunction. | Mean (SD) age: 66.7 (6.4)<br>Female %: 56.5<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR, history of mental illness excluded<br>Postop %: 100<br>-Total hip: 56.7<br>-Total knee: 43.3<br>Cancer %: NR | Main outcomes: Incidence of POD was significantly lower in the dexmedetomidine group (30/227 [13.2%]) than the placebo group (64/226 [28.3%]) (OR 0.385, 95% CI 0.238 to 0.624, p<0.0001).<br>Regarding safety, incidence of hypertension was higher with placebo (32/226 [14.2%]) than with dexmedetomidine (18/227 [7.9%]) (OR 0.522, 95% CI 0.284 to 0.961, p=0.034).<br>Attrition: 8% vs. 4% | Low |
| Yang et al. (2015) | Design: RCT<br>Setting: Intra- and post-operative, free flap surgery<br>Country: China<br>Funding: Unclear | Randomized N: 80<br>Analyzed N: 79<br>Intervention (N=40): Dexmedetomidine IV 0.5 µg/kg for 1 hour before surgery followed by 0.2-0.7µg/kg/hour postop<br>Control (N=40): Placebo; normal saline<br>Duration: Intra-operative, postop | Inclusion: Age 18-80 years undergoing maxillofacial free flap surgery<br>Exclusion: Severe dementia | Mean (SD) age: 50.45 (13.7)<br>Female %: 47<br>Race %: NR<br>Delirium %: NR<br>ASA I,II %: 100<br>Severe Dementia %: 0<br>Postop %: 100 maxillofacial free flap surgery<br>Cancer %: NR | Main outcomes: There was no difference in the incidence of delirium with dexmedetomidine compared with placebo within 5 days post-operatively (5.1% vs. 12.5%, p=0.432).<br>Attrition: 3% vs. 0% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | Follow-up (days): Through POD 5 | | | | |
| Zhang et al. (2020) | Design: RCT<br>Setting: Intra-operative, orthopedic<br>Country: U.S.<br>Funding: Government | Randomized N: 240<br>Analyzed N: 218<br>Intervention (N=120): Dexmedetomidine 0.5 µg/kg/hour IV loading dose, then 0.3 µg/kg/hour<br>Control (N=120): Usual care<br>Intervention duration: Loading dose 30 minutes prior to induction of anesthesia, then until 30 minutes until anticipated end of surgery<br>Control duration: During surgery<br>Follow-up (days): 1, 23 | Inclusion: Age 65-90 years, ASA I-III, and scheduled for hip fracture operation<br>Exclusion: History of psychosis or long-term psychotropic medication use, history of alcohol abuse, patients with preop MMSE ≤23, cerebrovascular accidents such as stroke or TIA within 3 months, or severe infection | Mean (SD) age: 78.5 (6.6)<br>Female %: 68.7<br>Race %: NR<br>Delirium %: NR<br>ASA II %: 64.6<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Dexmedetomidine decreased POD incidence (18.2% vs. 30.6%, p=0.033).<br>Attrition: 8% vs. 19% | Moderate |
| Zhao et al. (2020) | Design: RCT<br>Setting: Intra-operative, noncardiac<br>Country: China<br>Funding: Government | Randomized N: 432<br>Analyzed N: 416<br>Intervention 1 (N=111): Dexmedetomidine 1 µ/kg then dexmedetomidine 100 µg plus sufentanil 150 µg in PCA pump<br>Intervention 2 (N=107): Dexmedetomidine 1 µ/kg then dexmedetomidine 200 µg plus sufentanil 150 µg in PCA pump<br>Intervention 3 (N=108): Dexmedetomidine 1 µ/kg | Inclusion: >65 years scheduled to undergo non-cardiac major surgery with ASA I-III<br>Exclusion: Regular use of opioids, sedatives, antidepressants, or anxiolytic drugs prior to the surgery; drug addiction; preop history of schizophrenia, epilepsy, parkinsonism, or myasthenia gravis; brain injury or a history of neurosurgery; serious hepatic dysfunction (Child-Pugh class C); serious renal dysfunction | Mean (SD) age: 69.5 (4.2)<br>Female %: 44<br>Race %: NR<br>Delirium %: NR<br>ASA II %: 97<br>Median (IQR) MMSE score: 27 (24-30)<br>Postop %: 100<br>-Thoracic: 15.9<br>-Abdominal: 83.9<br>-Orthopedic: 0.2<br>Cancer %: NR | Main outcomes: Incidence rates of POD and early postop cognitive dysfunction 7 days after surgery were lower in the dexmedetomidine 200 mg and 400 mg groups than in the dexmedetomidine 0 mg and 100 mg groups (p<0.05). Compared with dexmedetomidine 200 mg, dexmedetomidine 400 mg reduced early postop cognitive dysfunction in patients who underwent open surgery (p<0.05). There were no intergroup differences in the postop | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | then dexmedetomidine 400 µg plus sufentanil 150 µg in PCA pump<br>Intervention 4 (N=106): Sufentanil 150 µg in PCA pump<br>Intervention 1, Intervention 2, Intervention 3 duration: 10 minutes before anesthesia induction, then post-operatively<br>Intervention 4 duration: Postop<br>Follow-up (days): 1, 2, 3, 7 | (undergoing dialysis before surgery); a preop left ventricular ejection fraction <50%; sick sinus syndrome, severe sinus bradycardia (<50/minute), or a ≥ second-degree atrioventricular block without a pacemaker; and a preop MMSE scores <17 in uneducated patients, <20 for patients with education of ≤6 years, and <24 for patients with education of >6 years | | sedation level, pain intensity, and side effects.<br>Attrition: 3% vs. 1% vs. 6% vs. 4% | |

*This study was identified as part of the systematic review by the Pacific Northwest Evidence-Based Practice Center but was subsequently retracted.
*Abbreviations.* ADL=activities of daily living; APACHE II=Acute Physiology and Chronic Health Evaluation II; ASA=American Society of Anesthesiologists; BMI=body mass index; BP=blood pressure; CABG=coronary artery bypass graf; CAM=Confusion Assessment Method; CDR=Clinical Dementia Rating; CI=confidence interval; CNS=central nervous system; CPB=cardiopulmonary bypass; ICU=intensive care unit; IQR=interquartile range; IV=intravenous; MI=myocardial infarction; MMSE=Mini-Mental State Examination; MoCA=Montreal Cognitive Assessment; MV=medical ventilation; N=number; NR=not reported; OR=odds ratio; PCA=patient-controlled analgesia; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RASS=Richmond Agitation Sedation Scale; RCT=randomized controlled trial; RR=relative risk; SD=standard deviation; TBI=traumatic brain injury; TIA=transient ischemic attack.

## In Intensive Care Unit Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Abdelgalel (2016) | Design: RCT<br>Setting: ICU<br>Country: Egypt<br>Funding: None | Randomized N: 90<br>Analyzed N: 90<br>Intervention 1 (N=30): Dexmedetomidine continuous IV infusion of 0.2-0.7 µg/kg/hour; loading dose of 1.0 µg/kg IV over 10 minutes if needed | Inclusion: Age 26-70 years, ASA status III and IV, and in Zagazig university hospital<br>Exclusion: Patient's or relatives' refusal, allergy to any of the studied drugs, psychiatric disorders or on antipsychotic medications, severe dementia, | Mean (SD) age: 59 (50)<br>Female %: 25<br>Race %: NR<br>Delirium %: NR<br>APACHE II mean score (0 to 71): 17<br>Dementia %: "severe" dementia excluded | Main outcomes: The incidence of delirium was significantly lower in dexmedetomidine group 3/30 (10%) than haloperidol 10/30 (33.3%) and placebo 13/30 (43.3%) groups. The ICU LOS was significantly shorter in | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | Intervention 2 (N=30): Haloperidol continuous IV infusion of 0.5-2 mg/hour; loading dose of 2.5 mg IV over 10 minutes if needed<br>Intervention 3 (N=30): Placebo; normal saline<br>Duration: During MV<br>Follow-up (days): NR | heart rate 650 beats/minute or systolic blood pressure 690 mmhg, prolonged QTc-time (>500 ms), history of clinically relevant ventricular arrhythmia, epilepsy or parkinsonism, and pregnancy | Postop %: 17.8<br>Cancer %: NR | dexmedetomidine group (3.1±0.4 days) than haloperidol and placebo groups (6.5±1.0 and 6.9±1.2 days, respectively).<br>Overall attrition: 0% | |
| Skrobik et al. (2018) | Design: RCT<br>Setting: ICU<br>Country: Canada<br>Funding: Industry | Randomized N: 100<br>Analyzed N: 100<br>Intervention 1 (N=50): Dexmedetomidine IV 0.2 µg/kg/hour<br>Control (N=50): Placebo; dextrose 5% in water<br>Duration: During ICU stay<br>Follow-up (days): Discharge from ICU | Inclusion: ICU patients receiving intermittent or continuous sedatives and expected to need at least 48 hours of ICU care<br>Exclusion: Patients with delirium or evidence of severe dementia | Mean (SD) age: 62.25 (13.66)<br>Female %: 36<br>Race %: NR<br>Delirium %: 0<br>APACHE II (SD): 22.75 (7.85)<br>Severe Dementia %: 0<br>Postop %: 27<br>Cancer %: NR | Main outcomes: Receipt of nocturnal dexmedetomidine in the ICU compared with placebo was associated with less incident delirium (20% vs. 46%, p=0.006).<br>Overall attrition: 0% | Moderate |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; ASA=American Society of Anesthesiologists; ICU=intensive care unit; IV=intravenous; LOS=length of stay; MV=medical ventilation; N=number; NR=not reported; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

## Dexmedetomidine vs. Propofol

### In Surgical Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Chang et al. (2018) | Design: RCT<br>Setting: Postop, major | Randomized N: 60<br>Analyzed N: 60<br>Intervention 1 (N=31): Dexmedetomidine IV 0.1-0.7 | Inclusion: Age 20-99 years undergoing major abdominal surgery<br>Exclusion: Refractory bradycardia less than 60 bpm, high degree | Mean (SD) age: 70.52 (11.08)<br>Female %: 42<br>Race %: NR | Main outcomes: There were no instances of delirium within 24 hours after abdominal surgery. | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | Country: Taiwan<br>Funding: Unclear | µg/kg/h<br>Intervention 2 (N=29): Propofol IV 0.3-1.6 mg/kg/h<br>Duration: Postop<br>Follow-up (days): 0-24 hours postop | atrioventricular block (second or third degree), refractory shock despite resuscitation (MAP <60 mm Hg), new onset of MI, New York Heart Association Class IV heart failure, acute physiology and chronic health evaluation II score >30, severe liver cirrhosis (ChildePugh class B or C), organ transplantation within 1 year, pregnancy, known allergic history to dexmedetomidine or propofol, enrolled in other clinical trial of dexmedetomidine or propofol within 1 month, signed consent of do not resuscitate, other conditions determined by surgeon or primary intensivist, and non-native speaker | Delirium %: NR<br>APACHE II score > 30 %: 0<br>Dementia %: NR<br>Postop %: 100 abdominal surgery<br>Cancer %: NR | Overall attrition: 0% | |
| Djaiani et al. (2016) | Design: RCT<br>Setting: Postop, cardiac<br>Country: Canada<br>Funding: Mixed | Randomized N: 185<br>Analyzed N: 183<br>Intervention 1 (analyzed N=91): Dexmedetomidine continuous IV infusion of 0.4 µg/kg bolus followed by 0.2-0.7 µg/kg/hour; if MV needed beyond 24 hours, patients switched to propofol<br>Intervention 2 (analyzed N=92): Propofol continuous IV infusion 25-50 µg/kg/minute<br>Intervention 1 duration: Postop during MV, maximum 24 hours | Inclusion: ≥60 years undergoing complex cardiac surgery or ≥70 years undergoing coronary revascularization or single-valve repair/replacement with the use of CPB<br>Exclusion: Patients with serious mental illness, delirium, or severe dementia | Mean (SD) age: 72.55 (6.3)<br>Female %: 25<br>Race %: NR<br>Delirium %: 0<br>Function: NR<br>Severe Dementia %: 0<br>Postop %: 100 cardiac surgery<br>Cancer %: 0 | Main outcomes: POD was present in 16 of 91 (17.5%) and 29 of 92 (31.5%) patients in dexmedetomidine and propofol groups, respectively (p=0.028). Duration of POD was 2 days vs. 3 days (p=0.04).<br>Overall attrition: 1% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | Intervention 2 duration: Intra-operative<br>Follow-up (days): Through day 5 | | | | |
| Liu X. et al. (2016) | Design: RCT<br>Setting: Postop, cardiac<br>Country: China<br>Funding: Unclear | Randomized N: 68<br>Analyzed N: 61<br>Intervention 1 (N=34): Dexmedetomidine IV 0.2-1.5 µg/kg/hour<br>Intervention 2 (N=34): Propofol IV 5-50 µg/kg/minute<br>Duration: Postop<br>Follow-up (days): Unclear (delirium listed as an adverse event) | Inclusion: ≥18 years undergoing elective cardiac valve surgery admitted to ICU<br>Exclusion: Patients who received 2 or more sedatives after randomization and had a sedation time <4 hours or ≥24 hours | Median age: 54<br>Female %: 59<br>Race %: NR<br>Delirium %: NR<br>Median APACHE II: 15 or 16<br>Dementia %: NR<br>Postop %: 100 cardiac surgery<br>Cancer %: 0 | Main outcomes: The incidence of delirium was not different in those who received dexmedetomidine vs. propofol (0% vs. 6%, p=0.493).<br>Attrition: 12% vs. 6% | Moderate |
| Maldonado et al. (2009) | Design: RCT<br>Setting: Postop, cardiac<br>Country: U.S.<br>Funding: Unclear | Randomized N: 118<br>Analyzed N: 90<br>Intervention 1 (N=40): Dexmedetomidine IV 0.4 µg/kg bolus followed by 0.2-0.7 µg/kg/hour<br>Intervention 2 (N=38): Propofol IV 25-50 µg/kg/minute<br>Intervention 3 (N=40): Midazolam IV 0.5-2.0 mg/hour<br>Duration: Postop<br>Follow-up (days): Through POD 3 | Inclusion: Age 18-90 years undergoing elective cardiac valve operation<br>Exclusion: Preexisting dementia | Mean (SD) age: 57 (17)<br>Female %: 36<br>Race %: NR<br>Delirium %: NR<br>Mean ASA: 3.4<br>MMSE: 29.4<br>Dementia %: 0<br>Postop %: 100 cardiac surgery<br>Cancer %: 0 | Main outcomes: Postop sedation with dexmedetomidine was associated with significantly lower rates of POD than propofol or midazolam (3% vs. 50% vs. 50%).<br>Attrition: 10% vs. 18% vs. 20% | Moderate |
| Mei et al. (2018) | Design: RCT<br>Setting: Intra-operative, hip<br>Country: China | Randomized N: 336<br>Analyzed N: 296<br>Intervention 1 (N=167): Dexmedetomidine IV 0.8-1.0 | Inclusion: ≥65 years undergoing total hip arthroplasty with nerve block<br>Exclusion: Cognitive impairment and/or preop delirium | Mean (SD) age: 75 (7)<br>Female %: 54<br>Race %: NR<br>Delirium %: 0 | Main outcomes: Patients sedated with dexmedetomidine had a lower incidence of POD than | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | Funding: Government | µg/kg bolus followed by 0.1-0.5 µg/kg/hour until end of surgery<br>Intervention 2 (N=169): Propofol IV 0.8-1.0 µg/mL<br>Duration: Intra-operative<br>Follow-up (days): Through POD 3 | | Mean ASA: 3<br>MMSE: 26<br>Dementia %: 0<br>Postop %: 100 hip arthroplasty<br>Cancer %: 0 | patients sedated with propofol (7% vs. 16%, p=0.030).<br>Attrition: 9% vs. 11% | |
| Mei B. et al. (2020) | Design: RCT<br>Setting: Intra-operative, hip<br>Country: China<br>Funding: Government | Randomized N: 415*<br>*The study noted 207 and 208 patients were assigned to the groups but it is not clear which group had which number of patients.<br>Analyzed N: 366<br>Intervention 1 (N=unclear): Dexmedetomidine IV 0.8-1.0 µg/kg bolus followed by 0.1-0.5 µg/kg/hour until end of surgery<br>Intervention 2 (N=unclear): Propofol IV 0.8 -1.0 µg/mL<br>Duration: Intra-operative<br>Follow-up (days): Through POD 7 | Inclusion: ≥65 years undergoing total hip arthroplasty with nerve block<br>Exclusion: Cognitive impairment and/or preop delirium | Mean (SD) age: 72.5 (10)<br>Female %: 60<br>Race %: NR<br>Delirium %: 0<br>Mean ASA: 2<br>MMSE: 26.9<br>Dementia %: 0<br>Postop %: 100 knee arthroplasty<br>Cancer %: 0 | Main outcomes: Patients sedated with dexmedetomidine had a lower incidence of POD than patients sedated with propofol (14% vs. 23%, p=0.032).<br>Attrition: 5% vs. 8% | Moderate |
| Sheikh et al. (2018) | Design: RCT<br>Setting: Intra-operative, cardiac<br>Country: India<br>Funding: None | Randomized N: 60<br>Analyzed N: 60<br>Intervention 1 (N=30): Dexmedetomidine IV 1.0 µg/kg bolus followed by 0.2-0.6 µg/kg/hour | Inclusion: Age 15-60 years undergoing elective open-heart surgery<br>Exclusion: Patients with neurological/psychological disorders | Mean (SD) age: 34.58 (10.74)<br>Female %: NR<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR | Main outcomes: The risk of delirium was significantly less in the dexmedetomidine group compared with the propofol group (3.3% vs. 23.3%, p=0.02).<br>Attrition: NR | High |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | Intervention 2 (N=30): Propofol IV 0.25-1.0 µg/kg/hour<br>Duration: Intra-operative<br>Follow-up (days): Discharge | | Postop %: 100 cardiac surgery<br>Cancer %: NR | | |
| Susheela et al. (2017); O'Neal et al. (2015) | Design: RCT<br>Setting: Postop, cardiac<br>Country: U.S.<br>Funding: Government | Randomized N: 12<br>Analyzed N: 12<br>Intervention 1 (N=3): Dexmedetomidine IV 0.1-1.0 µg/kg/hour<br>Intervention 2 (N=3): Propofol IV 25-100 µg/kg/minute<br>Intervention 3 (N=3): Dexmedetomidine IV 0.1-1.0 µg/kg/hour plus IV acetaminophen 1 g/6 hours<br>Intervention 4 (N=3): Propofol IV 25-100 µg/kg/minute plus IV acetaminophen 1 g/6 hours<br>Duration: Postop<br>Follow-up (days): Discharge | Inclusion: ≥60 undergoing CABG and/or valve surgery<br>Exclusion: Preexisting cognitive impairment or medications for cognitive decline | Mean (SD) age: NR<br>Female %: NR<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Cognitive Impairment %: 0<br>Postop %: 100<br>Cancer %: 0 | Main outcomes: The incidence of delirium was 2/3 in the dexmedetomidine and the propofol groups, 1/3 in the dexmedetomidine plus acetaminophen group, and 0/3 in the group receiving propofol plus acetaminophen.<br>Overall attrition: 0% | Moderate |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; ASA=American Society of Anesthesiologists; CPB=cardiopulmonary bypass; ICU=intensive care unit; IV=intravenous; MAP=mean arterial pressure; MI=myocardial infarction; MMSE=Mini-Mental State Examination; MV=medical ventilation; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; SD=standard deviation.

## In Intensive Care Unit Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Jakob et al. (2012); PRODEX | Design: RCT<br>Setting: ICU<br>Country: Europe and Russia | Randomized N: 500<br>Analyzed N: 498<br>Intervention 1 (N=251): Dexmedetomidine IV 0.2-1.4 µg/kg/hour | Inclusion: ≥18 years requiring MV with light to moderate sedation for at least 24 hours<br>Exclusion: Acute severe neurological disorder, MAP | Median age: 65<br>Female %: 35<br>Race %: NR<br>Delirium %: NR<br>Simplified Acute Physiology | Main outcomes: There was no difference in the incidence of delirium between the dexmedetomidine group | Low |

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| | Funding: Industry | Intervention 2 (N=249): Propofol IV 0.3-4.0 mg/kg/hour<br>Duration: MV<br>Follow-up (days): Delirium assessed 48 hours after discontinuing sedation | <55 mm Hg, heart rate <50/minute, atrioventricular-conduction grade II or III (unless pacemaker installed), and<br>use of $\alpha_2$ agonists or antagonists within 24 hours prior to randomization | Score II: 46.3<br>Dementia %: NR<br>Postop %: 56.2<br>Cancer %: NR | and the propofol group at 48 hours post sedation (9.6% vs. 13.7%, p=0.231).<br>Attrition: 28% vs. 24% | |
| Li et al. (2019) | Design: RCT<br>Setting: ICU<br>Country: China<br>Funding: Mixed | Randomized N: 126<br>Analyzed N: 126<br>Intervention 1 (N=64): Dexmedetomidine IV 0.8 µg/kg/hour<br>Intervention 2 (N=62): Midazolam IV 0.06 mg/kg/hour or propofol IV 0.5-2 mg/kg/hour<br>Duration: During ICU stay<br>Follow-up (days): Delirium assessed twice daily until discharged from ICU | Inclusion: ≥18 years admitted to general ICU for more than 96 hours under continuous sedation and analgesia for 48 hours or longer<br>Exclusion: GCS <13 at baseline in ED | Mean (SD) age: 43.98 (14.05)<br>Female %: 44<br>Race %: NR<br>Delirium %: NR<br>APACHE II: 20.5<br>Dementia %: NR<br>Postop %: 0 within 24 hours of study<br>Cancer %: 0 | Main outcomes: The rate of delirium was significantly lower in the dexmedetomidine group than in the common sedation (control) group (28% vs. 55%, p=0.0023).<br>Attrition: NR | Moderate |
| Ruokonen et al. (2009) | Design: RCT<br>Setting: ICU<br>Country: Finland<br>Funding: Industry | Randomized N: 85<br>Analyzed N: 85<br>Intervention 1 (N=41): Dexmedetomidine 0.8 µg/kg/hour for 1 hour, then adjusted stepwise at 0.25, 0.5, 0.8, 1.1, and 1.4 µg/kg/hour<br>Intervention 2 (N=44): Standard care: 1) propofol 2.4 mg/kg/hour for 1 hour, then adjusted stepwise at 0.8, 1.6, 2.4, 3.2, and 4.0 mg/kg/hour OR 2) midazolam IV bolus 1-2 mg starting at 3 boluses/hour for 1 hour, thereafter 1-4 boluses/hour; if not sufficient as continuous infusion of 0.2 | Inclusion: ≥18 years, MV, need for sedation for ≥24 hours after randomization, and an expected ICU stay ≥48 hours<br>Exclusion: Acute severe neurological disorder, MAP <55 mmHg despite volume and vasopressors, heart rate <50 beats/minute, atrioventricular conduction block II to III (unless pacemaker installed), hepatic SOFA score >2, bilirubin >101 lmol/L, muscle relaxation, loss of hearing or vision, any other condition interfering with | Median age: 64 vs. 68<br>Female %: 17.6<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR | Main outcomes: Delirium was more common in the dexmedetomidine group than in the standard care group (43.9% vs. 25.0%, p=0.035) when analyzed as the combined endpoint of CAM-ICU and adverse events of delirium and confusion. However, more CAM-ICU assessments were performed in the dexmedetomidine group than in the standard care group (106 vs. 84), and the proportion of positive | Moderate |

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| | | mg/kg/hour for 1 hour followed by adjustment at 0.04, 0.08, 0.12, 0.16, and 0.20 mg/kg/hour<br>Duration: During ICU stay<br>Follow-up (days): 45 | RASS assessment, or use of $\alpha_2$ agonists or antagonists at the time of randomization | | CAM-ICU results was comparable (17.0% vs. 17.9%, p=NS). During the follow-up to ICU discharge, no significant difference was observed in the occurrence rate of positive RASS scores (26% vs. 32%).<br>Attrition: 24% vs. 16% | |
| Winings et al. (2021) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: None | Randomized N: 57<br>Analyzed N: 57<br>Intervention 1 (N=28): Dexmedetomidine mean dose of 0.48 mcg/kg/hour<br>Intervention 2 (N=29): Propofol mean dose of 24.6 mcg/kg/minute<br>Duration: During ICU stay<br>Follow-up (days): 4 | Inclusion: ≥18 years, MV, placed on the institutional sedation protocol, expected to require sedation lasting 24 hours after randomization, and admitted to the Trauma/Surgical ICU and followed by the Trauma/Surgical ICU Service<br>Exclusion: ≥72 hours since sedation protocol initiation, treatment per the institutional TBI protocol, concomitant continuous infusion of a neuromuscular blocking agent, heart rate <50 beats/minute, MAP <55 mmHg despite fluid resuscitation and vasopressors, and/or use of other $\alpha_2$ agonists within 24 hours of randomization | Mean (SD) age: 50.6 (19.2)<br>Female %: 28.9<br>Race %: NR<br>Delirium %: NR<br>Mean (SD) APACHE II: 17.5 (7.4)<br>Dementia %: NR<br>Postop %: 29.8<br>Cancer %: NR | Main outcomes: There was no difference between the groups in ICU mortality, ICU and hospital LOS, or incidence of delirium.<br>Attrition: NR | Moderate |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; CAM-ICU=Confusion Assessment Method for the ICU; ED=emergency department; GCS=Glasgow Coma Scale; ICU=intensive care unit; IV=intravenous; LOS=length of stay; MAP=mean arterial pressure; MV=medical ventilation; N=number; NR=not reported; NS=not significant; postop=post-operative; RASS=Richmond Agitation Sedation Scale; RCT=randomized controlled trial; SD=standard deviation; SOFA=Sequential Organ Failure Assessment; TBI=traumatic brain injury.

## Dexmedetomidine vs. Midazolam

### In Surgical Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Hassan et al. (2021) | Design: RCT<br>Setting: Intra-operative, cardiac<br>Country: Pakistan<br>Funding: NR | Randomized N: 70<br>Analyzed N: 70<br>Intervention 1 (N=35): Dexmedetomidine 0.7 µg/kg/hour IV in operating room then 0.4 µg/kg/hour IV<br>Intervention 2 (N=35): Midazolam 0.05 µg/(kg.h) IV in operating room then 0.02-0.08 µg/(kg.h) IV<br>Duration: Perioperative (intra-operative and postop)<br>Follow-up (days): 1, 2, 3 | Inclusion: Age 55-75 years for elective cardiac surgery<br>Exclusion: History of psychiatric illness or those already diagnosed with cognitive disorder | Mean age: 59.6<br>Female %: 44.3<br>Race %: NR<br>Delirium %: 0 (excluded)<br>ASA: I-II %: 100<br>Dementia %: NR<br>Postop %: 100<br>Cardiac surgery %: 100<br>Cancer NR | Main outcomes: Patients who received dexmedetomidine were less likely to experience POD than patients who received midazolam (8.6% vs. 22.9%, p=0.04).<br>Attrition: NR | Moderate |
| He et al. (2018) | Design: RCT<br>Setting: Intra-operative, orthopedic<br>Country:<br>Funding: China Government | Randomized N: 90<br>Analyzed N: 90<br>Intervention 1 (N=30): Dexmedetomidine 0.5 µg/kg initial bolus, then maintained at 0.4 µg/kg/hour<br>Intervention 2 (N=30): Midazolam IV of 0.03 mg/kg<br>Intervention 3 (N=30): Normal saline<br><br>Intervention 1 duration: 10 minutes before anesthesia induction, then during surgery<br>Intervention 2, Intervention 3 duration: Before anesthesia | Inclusion: Age 75-90 years with thoracic or lumbar vertebral fractures and receiving selective operation at grade I to III in the ASA classification<br>Exclusion: CNS disease, mental illness, or ≤23 on MMSE | Mean (SD) age: 82.5 (5.6)<br>Female %: 42<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR | Main outcomes: The incidence rate of POD in the dexmedetomidine group was apparently lower than those in the other 2 groups (p<0.05); the incidence rate of POD at 1-2 days after operation in midazolam group was higher than that in the normal saline group (p<0.05). There was no significant difference in the incidence rate of POD at 3-5 days after operation between the midazolam | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Follow-up (days): 5 | | | and normal saline groups (p>0.05).<br>Attrition: NR | |
| Maldonado et al. (2009) | Design: RCT<br>Setting: Postop, cardiac<br>Country: U.S.<br>Funding: Unclear | Randomized N: 118<br>Analyzed N: 90<br>Intervention 1 (N=40): Dexmedetomidine IV 0.4 µg/kg bolus followed by 0.2-0.7 µg/kg/hour<br>Intervention 2 (N=38): Propofol IV 25-50 µg/kg/minute<br>Intervention 3 (N=40): Midazolam IV 0.5-2.0 mg/hour<br>Duration: Postop<br>Follow-up (days): Through POD 3 | Inclusion: Age 18-90 years undergoing elective cardiac valve operation<br>Exclusion: Preexisting dementia | Mean (SD) age: 57 (17)<br>Female %: 36<br>Race %: NR<br>Delirium %: NR<br>Mean ASA: 3.4<br>MMSE: 29.4<br>Dementia %: 0<br>Postop %: 100 cardiac surgery<br>Cancer %: 0 | Main outcomes: Postop sedation with dexmedetomidine was associated with significantly lower rates of POD than propofol or midazolam (3% vs. 50% vs. 50%).<br>Attrition: 10% vs. 18% vs. 20% | Moderate |
| Yu et al. (2017) | Design: RCT<br>Setting: Intra-operative, cardiothoracic<br>Country: China<br>Funding: Unclear | Randomized N: 92<br>Analyzed N: 92<br>Intervention 1 (N=46): Dexmedetomidine IV bolus (dose NR) followed by 0.2-0.7 µg/kg/hour<br>Intervention 2 (N=46): Midazolam 0.05 µg/kg bolus followed by 0.02-0.08 µg/kg/hour<br>Duration: Intra-operative<br>Follow-up (days): POD 1-3 | Inclusion: >60 years undergoing elective thoracic surgery<br>Exclusion: Senile dementia | Mean (SD) age: 68.91 (4.57)<br>Female %: 45<br>Race %: NR<br>Delirium %: NR<br>ASA I,II %: 100<br>Senile Dementia %: 0<br>Postop %: 100 thoracic surgery<br>Cancer %: NR | Main outcomes: There was less POD in the dexmedetomidine group compared with the midazolam group (6.52% vs. 21.74%, p<0.05).<br>Attrition: NR | Moderate |

*Abbreviations.* ASA=American Society of Anesthesiologists; CNS=central nervous system; IV=intravenous; MMSE=Mini-Mental State Examination; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

3275 In Intensive Care Unit Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Jakob et al. (2012); MIDEX | Design: RCT<br>Setting: ICU<br>Country: Europe<br>Funding: Industry | Randomized N: 501<br>Analyzed N: 500<br>Intervention 1 (N=249): Dexmedetomidine IV 0.2-1.4 µg/kg/hour<br>Intervention 2 (N=252): Midazolam IV 0.03-0.2 mg/kg/hour<br>Duration: MV<br>Follow-up (days): Delirium assessed 48 hours after discontinuing sedation | Inclusion: ≥18 years requiring MV with light to moderate sedation for at least 24 hours<br>Exclusion: Acute severe neurological disorder, MAP <55 mm Hg, heart rate <50/minute, atrioventricular-conduction grade II or III (unless pacemaker installed), and use of $\alpha_2$ agonists or antagonists within 24 hours prior to randomization | Median age: 65<br>Female %: 34<br>Race %: NR<br>Delirium %: NR<br>Simplified Acute Physiology Score II: 45.5<br>Dementia %: NR<br>Postop %: 70.6<br>Cancer %: NR | Main outcomes: There was no difference in the incidence of delirium between the dexmedetomidine group and the midazolam group at 48 hours post sedation (11.9% vs. 13.9%, p=0.393).<br>Attrition: 13% vs. 20% | Low |
| Li et al. (2019) | Design: RCT<br>Setting: ICU<br>Country: China<br>Funding: Mixed | Randomized N: 126<br>Analyzed N: 126<br>Intervention 1 (N=64): Dexmedetomidine IV 0.8 µg/kg/hour<br>Intervention 2 (N=62): Midazolam IV 0.06 mg/kg/hour or propofol IV 0.5-2 mg/kg/hour<br>Duration: During ICU stay<br>Follow-up (days): Delirium assessed twice daily until discharged from ICU | Inclusion: ≥18 years admitted to general ICU for more than 96 hours under continuous sedation and analgesia for 48 hours or longer<br>Exclusion: GCS <13 at baseline in ED | Mean (SD) age: 43.98 (14.05)<br>Female %: 44<br>Race %: NR<br>Delirium %: NR<br>APACHE II: 20.5<br>Dementia %: NR<br>Postop %: 0 within 24 hours of study<br>Cancer %: 0 | Main outcomes: The rate of delirium was significantly lower in the dexmedetomidine group than in the common sedation (control) group (28% vs. 55%, p=0.0023).<br>Attrition: NR | Moderate |
| MacLaren et al. (2015) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: Industry | Randomized N: 23<br>Analyzed N: 23<br>Intervention 1 (N=11): Dexmedetomidine IV 0.15-1.5 µg/kg/hour<br>Intervention 2 (N=12): Midazolam IV 1-10 mg/hour<br>Duration: MV<br>Follow-up (days): Delirium assessed twice daily | Inclusion: Age 18-85 years, critically ill requiring MV, and receiving a benzodiazepine infusion with an anticipated need of at least 12 additional hours of sedation<br>Exclusion: Baseline dementia | Mean (SD) age: 58.04 (12.53)<br>Female %: 43<br>Race %: NR<br>Delirium %: NR<br>APACHE III: 72.2<br>Dementia %: 0<br>Postop %: 13.0<br>Cancer %: NR | Main outcomes: There was no statistically significant difference between dexmedetomidine and midazolam in new onset delirium (1 vs. 5, p=0.07).<br>Attrition at follow-up: 9% vs. 0% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Ruokonen et al. (2009) | Design: RCT<br>Setting: ICU<br>Country: Finland<br>Funding: Industry | Randomized N: 85<br>Analyzed N: 85<br>Intervention 1 (N=41): Dexmedetomidine 0.8 µg/kg/hour for 1 hour, then adjusted stepwise at 0.25, 0.5, 0.8, 1.1, and 1.4 µg/kg/hour<br>Intervention 2 (N=44): Standard care: 1) propofol 2.4 mg/kg/hour for 1 hour, then adjusted stepwise at 0.8, 1.6, 2.4, 3.2, and 4.0 mg/kg/hour OR 2) midazolam IV bolus 1-2 mg starting at 3 boluses/hour for 1 hour, thereafter 1-4 boluses/hour; if not sufficient as continuous infusion of 0.2 mg/kg/hour for 1 hour followed by adjustment at 0.04, 0.08, 0.12, 0.16, and 0.20 mg/kg/hour<br>Duration: During ICU stay<br>Follow-up (days): 45 | Inclusion: ≥18 years, MV, need for sedation for ≥24 hours after randomization, and an expected ICU stay ≥48 hours<br>Exclusion: Acute severe neurological disorder, MAP <55 mmHg despite volume and vasopressors, heart rate <50 beats/minute, atrioventricular-conduction block II to III (unless pacemaker installed), hepatic SOFA score >2, bilirubin >101 lmol/L, muscle relaxation, loss of hearing or vision, any other condition interfering with RASS assessment, or use of $\alpha_2$ agonists or antagonists at the time of randomization | Median age: 64 vs. 68<br>Female %: 17.6<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR | Main outcomes: Delirium was more common in the dexmedetomidine group than in the standard care group (43.9% vs. 25.0%, p=0.035) when analyzed as the combined endpoint of CAM-ICU and adverse events of delirium and confusion. However, more CAM-ICU assessments were performed in the dexmedetomidine group than in the standard care group (106 vs. 84), and the proportion of positive CAM-ICU results was comparable (17.0% vs. 17.9%, p=NS). During the follow-up to ICU discharge, no significant difference was observed in the occurrence rate of positive RASS scores (26% vs. 32%).<br>Attrition: 24% vs. 16% | Moderate |
| Shu et al. (2019) | Design: RCT<br>Setting: ICU<br>Country: China<br>Funding: Unclear | Randomized N: 80<br>Analyzed N: 80<br>Intervention 1 (N=40): Dexmedetomidine IV 1.0 µg/kg bolus followed by 0.2-0.7 µg/kg/hour<br>Intervention 2 (N=40): Midazolam 0.05 mg/kg bolus followed by 0.05-0.10 mg/kg/hour | Inclusion: >60 years requiring MV for more than 24 hours<br>Exclusion: CNS disease | Mean age: 73.61 (8.28)<br>Female %: 35<br>Race %: NR<br>Delirium %: NR<br>APACHE II score: 22.43 (4.84)<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR | Main outcomes: There was no significant difference between dexmedetomidine and midazolam in the incidence of delirium (0% vs. 10%, p>0.05).<br>Attrition: NR | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Duration: MV<br>Follow-up (days): Day 1 | | | | |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; CAM-ICU=Confusion Assessment Method for the ICU; CNS=central nervous system; ED=emergency department; GCS=Glasgow Coma Scale; ICU=intensive care unit; IV=intravenous; MAP=mean arterial pressure; MV=medical ventilation; N=number; NR=not reported; NS=not significant; postop=post-operative; RASS=Richmond Agitation Sedation Scale; RCT=randomized controlled trial; SD=standard deviation; SOFA=Sequential Organ Failure Assessment.

## Dexmedetomidine vs. Haloperidol

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Abdelgalel (2016) | Design: RCT<br>Setting: ICU<br>Country: Egypt<br>Funding: None | Randomized N: 90<br>Analyzed N: 90<br>Intervention 1 (N=30): Dexmedetomidine continuous IV infusion of 0.2-0.7 µg/kg/hour; loading dose of 1.0 µg/kg IV over 10 minutes if needed<br>Intervention 2 (N=30): Haloperidol continuous IV infusion of 0.5-2 mg/hour; loading dose of 2.5 mg IV over 10 minutes if needed<br>Intervention 3 (N=30): Normal saline<br>Duration: During MV<br>Follow-up (days): NR | Inclusion: Age 26-70 years, ASA status III and IV, and in Zagazig university hospital<br>Exclusion: Patient's or relatives' refusal, allergy to any of the studied drugs, psychiatric disorders or on antipsychotic medications, severe dementia, heart rate 650 beats/minute or systolic blood pressure 690 mmhg, prolonged QTc-time (>500 ms) or history of clinically relevant ventricular arrhythmia, epilepsy or parkinsonism, and pregnancy | Mean (SD) age: 59 (50)<br>Female %: 25<br>Race %: NR<br>Delirium %: NR<br>APACHE II mean score (0 to 71): 17<br>Dementia %: "severe" dementia excluded<br>Postop %: 17.8<br>Cancer %: NR | Main outcomes: The incidence of delirium was significantly lower in dexmedetomidine group 3/30 (10%) than haloperidol 10/30 (33.3%) and placebo 13/30 (43.3%) groups. The ICU LOS was significantly shorter in dexmedetomidine group (3.1±0.4 days) than haloperidol and placebo groups (6.5±1.0 and 6.9±1.2 days, respectively).<br>Overall attrition: 0% | Low |

Abbreviations. APACHE II=Acute Physiology and Chronic Health Evaluation II; ASA=American Society of Anesthesiologists; ICU=intensive care unit; IV=intravenous; LOS=length of stay; MV=medical ventilation; N=number; NR=not reported; postop=post-operative; RCT=randomized controlled trial.

## Dexmedetomidine vs. Melatonin Plus Dexmedetomidine

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Mahrose et al. (2021) | Design: RCT<br>Setting: Preop, cardiac<br>Country: Egypt<br>Funding: NR | Randomized N: 110<br>Analyzed N: 110<br>Intervention 1 (N=55): Melatonin 5 mg plus dexmedetomidine 0.4 µg/kg IV bolus, then 0.2-0.7 µg/kg/hour IV<br>Intervention 2 (N=55): Dexmedetomidine 0.4 µg/kg IV bolus, then 0.2-0.7 µg/kg/hour IV<br>Intervention 1 duration: Melatonin - 10 pm night before surgery and every evening before bed for 3 days; dexmedetomidine - upon arrival to the ICU for 24 hours<br>Intervention 2 duration: Upon arrival to the ICU for 24 hours<br>Follow-up (days): 5 | Inclusion: >60 years having elective CABG surgery<br>Exclusion: Patients undergoing emergency procedures, any preop mental illness, preop renal failure, chronic liver disease (Child classification class B and C), carotid duplex to have carotid disease, or prolonged postop intubation and re-exploration | Mean age: 66.5<br>Female %: 24.5<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR (excluded any mental illness)<br>Postop %: 100<br>CABG surgery %: 100<br>Cancer %: NR | Main outcomes: Fewer patients who received melatonin in addition to dexmedetomidine experienced delirium, and duration of delirium was shorter.<br>Overall attrition: 0% | Moderate |

Abbreviations. CABG=coronary artery bypass graf; ICU=intensive care unit; IV=intravenous; N=number; NR=not reported; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial.

## Dexmedetomidine vs. Opioid

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Park et al. (2014) | Design: RCT<br>Setting: Postop, cardiac | Randomized N: 142<br>Analyzed N: 142<br>Intervention 1 (N=67): Dexmedetomidine loading | Inclusion: Age 18-90 years undergoing cardiac surgery on CPB<br>Exclusion: Re-do and emergency | Mean (SD) age: 52.8 (15)<br>Female %: 44<br>Race %: NR<br>Delirium %: NR | Main outcomes: Delirium incidence was significantly less in dexmedetomidine group (6/67 patients, | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Country: South Korea<br>Funding: None | dose, 0.5 µg/kg; maintenance dose, 0.2-0.8 µg/kg/hour<br>Intervention 2 (N=75): Remifentanil range, 1,000-2,500 µg/hour<br>Duration: Daily<br>Follow-up (days): 3 | surgery, severe pulmonary, or systemic disease, left ventricular ejection fraction <40%, pre-existing renal dysfunction, surgery requiring deep hypothermic circulatory arrest involving thoracic aorta, and documented preop dementia, Parkinson disease, or recent stroke | ASA III-IV %: 17<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR<br>Mean (SD) length of operation, minutes: 344.7 (107) | 8.96%) vs. remifentanil group (17/75 patients, 22.67%) (p<0.05).<br>Attrition: NR | |
| Shehabi et al. (2009) | Design: RCT<br>Setting: Postop, cardiac<br>Country: Australia<br>Funding: Mixed | Randomized N: 306<br>Analyzed N: 299<br>Intervention 1 (N=154): Dexmedetomidine IV 0.1-0.7 µg/kg/hour<br>Intervention 2 (N=152): Morphine IV 10-70 µg/kg/hour<br>Duration: Postop<br>Follow-up (days): Discharge | Inclusion: ≥60 years undergoing pump cardiac surgery (e.g., CABG, valve surgery)<br>Exclusion: Documented preop dementia and Parkinson disease | Median age: 71.3<br>Female %: 25<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: 0<br>Postop %: 100<br>Cancer %: 0 | Main outcomes: Delirium incidence was comparable between dexmedetomidine and morphine (8.6% vs. 15.0%, p=0.088).<br>Attrition: 1% vs. 3% | Low |

*Abbreviations.* ASA=American Society of Anesthesiologists; CABG=coronary artery bypass graf; CPB=cardiopulmonary bypass; IV=intravenous; N=number; NR=not reported; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; SD=standard deviation.

## Dexmedetomidine vs. Clonidine

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Shokri and Ali (2020) | Design: RCT<br>Setting: Intra- and post-operative, cardiac | Randomized N: 294<br>Analyzed N: 286<br>Intervention 1 (N=147): Dexmedetomidine; initial continuous infusion of 0.7-1.2 µg/kg/hour, then adjusted | Inclusion: Age 60-70 years with ASA status II and III, scheduled for elective isolated CABG, and absence of any associated comorbidities or history of MI<br>Exclusion: History of mental | Mean (SD) age: 64.1 (4.1)<br>Female %: 51.4<br>Race %: NR<br>Delirium %: NR, severe delirium excluded<br>ASA II %: 62.6 | Main outcomes: Dexmedetomidine was associated with lower risk and duration of delirium, shorter MV duration and ICU stay, lower mortality | Low |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Country: Egypt<br>Funding: None | based on sedation and analgesia adequacy to a maximum dose of 1-1.4 µg/kg/hour<br>Intervention 2 (N=147): Clonidine IV 0.5 µg/kg slowly over 10-15 minutes, followed by a continuous IV infusion of 1-2 µg/kg/hour<br>Intervention 1 duration: During surgery, then weaned off slowly after surgery<br>Intervention 2 duration: During surgery<br>Follow-up (days): 8 | illness, severe dementia, delirium, or undergoing emergency procedures, or treated with haloperidol impaired renal or hepatic functions | ASA III %: 37.4<br>Dementia %: NR, severe dementia excluded<br>Postop %: 100<br>Cancer %: NR | rate, and lower morphine consumption than the clonidine group. Dexmedetomidine significantly decreased heart rates after ICU admission.<br>Attrition at follow-up: 2% vs. 3% | |

*Abbreviations.* ASA=American Society of Anesthesiologists; CABG=coronary artery bypass graf; ICU=intensive care unit; IV=intravenous; MI=myocardial infarction; MV=medical ventilation; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; SD=standard deviation.

## Dexmedetomidine vs. Dexmedetomidine

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Lee et al. (2018) | Design: RCT<br>Setting: Intra-operative, noncardiac<br>Country: South Korea<br>Funding: University | Randomized N: 354<br>Analyzed N: 318<br>Intervention 1 (N=118): Dexmedetomidine IV 1µg/kg bolus followed by 0.2-0.7 µg/kg/hour<br>Intervention 2 (N=118): Dexmedetomidine IV 1µg/kg bolus<br>Intervention 3 (N=118): Saline<br>Duration: Intra-operative<br>Follow-up (days): Through day 5 | Inclusion: >65 years undergoing laparoscopic major non-cardiac surgery under general anesthesia<br>Exclusion: Patients with cognitive impairment | Mean (SD) age: 73.07 (6.01)<br>Female %: 56<br>Race %: NR<br>Delirium %: NR<br>ASA I, II %: 68.2<br>Cognitive Impairment %: 0<br>Postop %: 100 non-cardiac surgery<br>Cancer %: NR | Main outcomes: The incidence of POD was 9.5% and 18.4% in the 2 groups receiving dexmedetomidine compared with usual care (24.8%, p=0.017).<br>Attrition at follow-up: 19% vs. 3% vs. 8% | Moderate |

*Abbreviations.* ASA=American Society of Anesthesiologists; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

## *Benzodiazepines*

### Midazolam vs. Dexmedetomidine

#### In Surgical Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Hassan et al. (2021) | Design: RCT<br>Setting: Intra-operative, cardiac<br>Country: Pakistan<br>Funding: NR | Randomized N: 70<br>Analyzed N: 70<br>Intervention 1 (N=35): Dexmedetomidine 0.7 µg/kg/hour IV in OR then 0.4 µg/kg/hour IV<br>Intervention 2 (N=35): Midazolam 0.05 µg/(kg.h) IV in OR then 0.02-0.08 µg/(kg.h) IV<br>Duration: Perioperative (intra-operative and postop)<br>Follow-up (days): 1, 2, 3 | Inclusion: Age 55-75 years for elective cardiac surgery<br>Exclusion: History of psychiatric illness or those already diagnosed with cognitive disorder | Mean age: 59.6<br>Female %: 44.3<br>Race %: NR<br>Delirium %: 0 (excluded)<br>ASA: I-II %: 100<br>Dementia %: NR<br>Postop %: 100<br>Cardiac surgery %: 100<br>Cancer NR | Main outcomes: Patients who received dexmedetomidine were less likely to experience POD than patients who received midazolam (8.6% vs. 22.9%, p=0.04).<br>Attrition: NR | Moderate |
| He et al. (2018) | Design: RCT<br>Setting: Intra-operative, orthopedic<br>Country:<br>Funding: China Government | Randomized N: 90<br>Analyzed N: 90<br>Intervention 1 (N=30): Dexmedetomidine 0.5 µg/kg initial bolus, then maintained at 0.4 µg/kg/hour<br>Intervention 2 (N=30): Midazolam IV of 0.03 mg/kg<br>Intervention 3 (N=30): Normal saline | Inclusion: Age 75-90 years with thoracic or lumbar vertebral fractures and receiving selective operation at grade I to III in the ASA classification<br>Exclusion: CNS disease, mental illness, or ≤23 on MMSE | Mean (SD) age: 82.5 (5.6)<br>Female %: 42<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR | Main outcomes: The incidence rate of POD in the dexmedetomidine group was apparently lower than those in the other 2 groups (p<0.05); the incidence rate of POD at 1-2 days after operation in midazolam group was higher than that in the normal saline group (p<0.05). There was no significant difference in the incidence rate of POD at 3-5 days after | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Intervention 1 duration: 10 minutes before anesthesia induction, then during surgery<br>Intervention 2,<br>Intervention 3 duration: Before anesthesia<br>Follow-up (days): 5 | | | operation between the midazolam and normal saline groups (p>0.05).<br>Attrition: NR | |
| Maldonado et al. (2009) | Design: RCT<br>Setting: Postop, cardiac<br>Country: U.S.<br>Funding: Unclear | Randomized N: 118<br>Analyzed N: 90<br>Intervention 1 (N=40): Dexmedetomidine IV 0.4 µg/kg bolus followed by 0.2-0.7 µg/kg/hour<br>Intervention 2 (N=38): Propofol IV 25-50 µg/kg/minute<br>Intervention 3 (N=40): Midazolam IV 0.5-2.0 mg/hour<br>Duration: Postop<br>Follow-up (days): Through POD 3 | Inclusion: Age 18-90 years undergoing elective cardiac valve operation<br>Exclusion: Preexisting dementia | Mean (SD) age: 57 (17)<br>Female %: 36<br>Race %: NR<br>Delirium %: NR<br>Mean ASA: 3.4<br>MMSE: 29.4<br>Dementia %: 0<br>Postop %: 100 cardiac surgery<br>Cancer %: 0 | Main outcomes: Postop sedation with dexmedetomidine was associated with significantly lower rates of POD than propofol or midazolam (3% vs. 50% vs. 50%).<br>Attrition: 10% vs. 18% vs. 20% | Moderate |
| Yu et al. (2017) | Design: RCT<br>Setting: Intra-operative, cardiothoracic<br>Country: China<br>Funding: Unclear | Randomized N: 92<br>Analyzed N: 92<br>Intervention 1 (N=46): Dexmedetomidine IV bolus (dose NR) followed by 0.2-0.7 µg/kg/hour<br>Intervention 2 (N=46): Midazolam 0.05 µg/kg | Inclusion: >60 years undergoing elective thoracic surgery<br>Exclusion: Senile dementia | Mean (SD) age: 68.91 (4.57)<br>Female %: 45<br>Race %: NR<br>Delirium %: NR<br>ASA I,II %: 100<br>Senile Dementia %: 0<br>Postop %: 100 thoracic surgery<br>Cancer %: NR | Main outcomes: There was less POD in the dexmedetomidine group compared with the midazolam group (6.52% vs. 21.74%, p<0.05).<br>Attrition: NR | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | bolus followed by 0.02-0.08 µg/kg/hour<br>Duration: Intra-operative<br>Follow-up (days): POD 1-3 | | | | |

*Abbreviations.* ASA=American Society of Anesthesiologists; CNS=central nervous system; IV=intravenous; MMSE=Mini-Mental State Examination; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

## In Intensive Care Unit Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Jakob et al. (2012); MIDEX | Design: RCT<br>Setting: ICU<br>Country: Europe<br>Funding: Industry | Randomized N: 501<br>Analyzed N: 500<br>Intervention 1 (N=249): Dexmedetomidine IV 0.2-1.4 µg/kg/hour<br>Intervention 2 (N=252): Midazolam IV 0.03-0.2 mg/kg/hour<br>Duration: MV<br>Follow-up (days): Delirium assessed 48 hours after discontinuing sedation | Inclusion: ≥18 years requiring MV with light to moderate sedation for at least 24 hours<br>Exclusion: Acute severe neurological disorder, MAP <55 mm Hg, heart rate <50/minute, atrioventricular-conduction grade II or III (unless pacemaker installed), and use of $\alpha_2$ agonists or antagonists within 24 hours prior to randomization | Median age: 65<br>Female %: 34<br>Race %: NR<br>Delirium %: NR<br>Simplified Acute Physiology Score II: 45.5<br>Dementia %: NR<br>Postop %: 70.6<br>Cancer %: NR | Main outcomes: There was no difference in the incidence of delirium between the dexmedetomidine group and the midazolam group at 48 hours post sedation (11.9% vs. 13.9%, p=0.393).<br>Attrition: 13% vs. 20% | Low |
| Li et al. (2019) | Design: RCT<br>Setting: ICU<br>Country: China<br>Funding: Mixed | Randomized N: 126<br>Analyzed N: 126<br>Intervention 1 (N=64): Dexmedetomidine IV 0.8 µg/kg/hour<br>Intervention 2 (N=62): Midazolam IV 0.06 mg/kg/hour or propofol IV 0.5-2 mg/kg/hour | Inclusion: ≥18 years admitted to general ICU for more than 96 hours under continuous sedation and analgesia for 48 hours or longer<br>Exclusion: GCS <13 at baseline in ED | Mean (SD) age: 43.98 (14.05)<br>Female %: 44<br>Race %: NR<br>Delirium %: NR<br>APACHE II: 20.5<br>Dementia %: NR<br>Postop %: 0 within 24 | Main outcomes: The rate of delirium was significantly lower in the dexmedetomidine group than in the common sedation (control) group (28% vs. 55%, p=0.0023).<br>Attrition: NR | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Duration: During ICU stay<br>Follow-up (days): Delirium assessed twice daily until discharged from ICU | | hours of study<br>Cancer %: 0 | | |
| MacLaren et al. (2015) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: Industry | Randomized N: 23<br>Analyzed N: 23<br>Intervention 1 (N=11): Dexmedetomidine IV 0.15-1.5 µg/kg/hour<br>Intervention 2 (N=12): Midazolam IV 1-10 mg/hour<br>Duration: MV<br>Follow-up (days): Delirium assessed twice daily | Inclusion: Age 18-85 years, critically ill requiring MV, and receiving a benzodiazepine infusion with an anticipated need of at least 12 additional hours of sedation<br>Exclusion: Baseline dementia | Mean (SD) age: 58.04 (12.53)<br>Female %: 43<br>Race %: NR<br>Delirium %: NR<br>APACHE III: 72.2<br>Dementia %: 0<br>Postop %: 13.0<br>Cancer %: NR | Main outcomes: There was no statistically significant difference between dexmedetomidine and midazolam in new onset delirium (1 vs. 5, p=0.07).<br>Attrition at follow-up: 9% vs. 0% | Moderate |
| Ruokonen et al. (2009) | Design: RCT<br>Setting: ICU<br>Country: Finland<br>Funding: Industry | Randomized N: 85<br>Analyzed N: 85<br>Intervention 1 (N=41): Dexmedetomidine 0.8 µg/kg/hour for 1 hour, then adjusted stepwise at 0.25, 0.5, 0.8, 1.1, and 1.4 µg/kg/hour<br>Intervention 2 (N=44): Standard care: 1) propofol 2.4 mg/kg/hour for 1 hour, then adjusted stepwise at 0.8, 1.6, 2.4, 3.2, and 4.0 mg/kg/hour OR 2) midazolam IV bolus 1-2 mg starting at 3 boluses/hour for 1 hour, thereafter 1-4 boluses/hour; if not sufficient as continuous infusion of 0.2 mg/kg/hour for 1 hour | Inclusion: ≥18 years, MV, need for sedation for ≥24 hours after randomization, and an expected ICU stay ≥48 hours<br>Exclusion: Acute severe neurological disorder, MAP <55 mmHg despite volume and vasopressors, heart rate <50 beats/minute, atrioventricular-conduction block II to III (unless pacemaker installed), hepatic SOFA score >2, bilirubin >101 lmol/L, muscle relaxation, loss of hearing or vision, any other condition interfering with RASS assessment, or use of $\alpha_2$ | Median age: 64 vs. 68<br>Female %: 17.6<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR | Main outcomes: Delirium was more common in the dexmedetomidine group than in the standard care group (43.9% vs. 25.0%, p=0.035) when analyzed as the combined endpoint of CAM-ICU and adverse events of delirium and confusion. However, more CAM-ICU assessments were performed in the dexmedetomidine group than in the standard care group (106 vs. 84), and the proportion of positive CAM-ICU results was comparable (17.0% vs. 17.9%, p=NS). During the follow-up to ICU discharge, no significant difference was observed in the | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | followed by adjustment at 0.04, 0.08, 0.12, 0.16, and 0.20 mg/kg/hour<br>Duration: During ICU stay<br>Follow-up (days): 45 | agonists or antagonists at the time of randomization | | occurrence rate of positive RASS scores (26% vs. 32%).<br>Attrition: 24% vs. 16% | |
| Shu et al. (2019) | Design: RCT<br>Setting: ICU<br>Country: China<br>Funding: Unclear | Randomized N: 80<br>Analyzed N: 80<br>Intervention 1 (N=40): Dexmedetomidine IV 1.0 µg/kg bolus followed by 0.2-0.7 µg/kg/hour<br>Intervention 2 (N=40): Midazolam 0.05 mg/kg bolus followed by 0.05-0.10 mg/kg/hour<br>Duration: MV<br>Follow-up (days): Day 1 | Inclusion: >60 years requiring MV for more than 24 hours<br>Exclusion: CNS disease | Mean age: 73.61 (8.28)<br>Female %: 35<br>Race %: NR<br>Delirium %: NR<br>APACHE II score: 22.43 (4.84)<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR | Main outcomes: There was no significant difference between dexmedetomidine and midazolam in the incidence of delirium (0% vs. 10%, p>0.05).<br>Attrition: NR | Moderate |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; CAM-ICU=Confusion Assessment Method for the ICU; CNS=central nervous system; ED=emergency department; GCS=Glasgow Coma Scale; ICU=intensive care unit; IV=intravenous; MAP=mean arterial pressure; MV=medical ventilation; N=number; NS=not significant; NR=not reported; postop=post-operative; RASS=Richmond Agitation Sedation Scale; RCT=randomized controlled trial; SD=standard deviation; SOFA=Sequential Organ Failure Assessment.

## Midazolam vs. Propofol

### In Surgical Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Maldonado et al. (2009) | Design: RCT<br>Setting: Postop, cardiac<br>Country: U.S.<br>Funding: Unclear | Randomized N: 118<br>Analyzed N: 90<br>Intervention 1 (N=40): Dexmedetomidine IV 0.4 µg/kg bolus followed by 0.2-0.7 µg/kg/hour | Inclusion: Age 18-90 years undergoing elective cardiac valve operation<br>Exclusion: Preexisting dementia | Mean (SD) age: 57 (17)<br>Female %: 36<br>Race %: NR<br>Delirium %: NR<br>Mean ASA: 3.4<br>MMSE: 29.4 | Main outcomes: Postop sedation with dexmedetomidine was associated with significantly lower rates of POD than propofol or midazolam (3% vs. 50% vs. 50%).<br>Attrition: 10% vs. 18% vs. 20% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Intervention 2 (N=38): Propofol IV 25-50 µg/kg/minute<br>Intervention 3 (N=40): Midazolam IV 0.5-2.0 mg/hour<br>Duration: Postop<br>Follow-up (days): Through POD 3 | | Dementia %: 0<br>Postop %: 100 cardiac surgery<br>Cancer %: 0 | | |

*Abbreviations.* ICU=intensive care unit; IV=intravenous; MMSE=Mini-Mental State Examination; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

### In Intensive Care Unit Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Chen (2020) | Design: RCT<br>Setting: ICU<br>Country: China<br>Funding: None | Randomized N: 120<br>Analyzed N: 120<br>Intervention 1 (N=60): Midazolam IV 0.05-0.2 mg/kg/hour<br>Intervention 2 (N=60): Propofol IV 0.5-4 mg/kg/hour<br>Duration: During MV<br>Follow-up (days): 28 | Inclusion: Age 18-60 years with expected sedation time of ≤72 hours and required continuous sedation with MV<br>Exclusion: Cerebral surgery; history of CNS and mental illness (including Alzheimer's disease); long-term use of antidepressants or sedatives, and alcoholics; serious liver and kidney dysfunction, internal environment disorder, or hyper-lipidaemia; in a coma; obvious abnormal blood glucose and great fluctuations; sepsis, unstable circulation, severe complicated hypoproteinaemia, anemia, and thrombocytopenia; allergic to midazolam or propofol | Mean age: 41 to 60 years; 51%<br>Female %: 30<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: 0 (excluded)<br>Postop %: NR<br>Cancer %: NR | Main outcomes: The difference in the incidence of delirium, adverse reactions, ICU LOS, and mortality in 28 days between the groups was not statistically significant (p>0.05). However, time to spontaneous eye opening was longer in the midazolam group (p<0.05). The onset effect time of sedatives was slightly longer in the midazolam group, compared with the propofol group (p < 0.05). The difference in the time to reach the optimal level of sedation between these 2 groups was not statistically significant (p>0.05).<br>Attrition: NR | High |

*Abbreviations.* CNS=central nervous system; ICU=intensive care unit; IV=intravenous; LOS=length of stay; MV=medical ventilation; N=number; NR=not reported; RCT=randomized controlled trial.

## Midazolam vs. Melatonin vs. Clonidine vs. No Sedation

### In Surgical Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Sultan (2010) | Design: RCT<br>Setting: Preop, hip<br>Country: Egypt<br>Funding: None | Randomized N: 222<br>Analyzed N: 203<br>Intervention 1 (N=53 analyzed): Melatonin 5 mg, 2 oral doses<br>Intervention 2 (N=50 analyzed): Midazolam 7.5 mg, 2 oral doses<br>Intervention 3 (N=51 analyzed): Clonidine 100 µg, 2 oral doses<br>Intervention 4 (N=49 analyzed): No sedation<br>Duration: One dose the night before surgery and another 90 minutes before surgery<br>Follow-up (days): POD 3 | Inclusion: >65 years, scheduled for hip arthroplasty under spinal anesthesia, and ASA I-III<br>Exclusion: Sensory impairment (blindness, deafness); dementia; severe infections; severe anemia (hematocrit<30%); intracranial events (stroke, bleeding, infection); fluid or electrolyte disturbances; acute cardiac events; acute pulmonary events; and medications including anticonvulsants, antihistamines, and benzodiazepines | Mean (SD) age: 71.01 (36.8)<br>Female %: 51<br>Race %: NR<br>Delirium %: 0 (excluded)<br>ASA I-III: inclusion criterion<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: The melatonin group showed a statistically significant decrease in the percentage of POD (9.43% vs. 32.65% in the other groups).<br>Overall attrition: 9% | High |

*Abbreviations.* ASA=American Society of Anesthesiologists; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; SD=standard deviation.

## Restricted vs. Liberal Benzodiazepine Use

### In Surgical Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Spence et al. (2020) | Design: RCT<br>Setting: Intra-operative, cardiac<br>Country: | Randomized N: 800<br>Analyzed N: 718<br>Intervention 1 (N=411): Restricted benzodiazepine use* | Inclusion: ≥18 years who underwent cardiac surgery at one of the sites during the enrollment period<br>Exclusion: NR | Mean age: 67<br>Female %: 23<br>Race %: NR<br>Delirium %: NR<br>Functioning: NR | Main outcomes: The overall incidence of delirium is 15.9% (17.5% during the restricted benzodiazepine periods vs. 14.1% during the liberal benzodiazepine | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Canada<br>Funding: Industry | Intervention 2 (N=389): Liberal benzodiazepine use*<br>*Midazolam used in the majority of cases<br>Duration: Intra-operative<br>Follow-up (days): Until discharge | | Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | periods) (p=0.19, RR increase 24.1% [95% CI -21.1% to 27.1%]). The median (IQR) ICU LOS was 24 (24-72) hours, and the median (IQR) hospital LOS was 7 (5-11) days. The overall incidence of in-hospital mortality was 1.1%.<br>Attrition: 12% vs. 9% | |

*Abbreviations.* CI=confidence interval; ICU=intensive care unit; IQR=interquartile range; LOS=length of stay; N=number; NR=not reported; postop=post-operative; RCT=randomized controlled trial; RR=relative risk; SD=standard deviation.

### *Antipsychotics*

#### In Surgical Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Fukata et al. (2014) | Design: RCT<br>Setting: Postop, abdominal or orthopedic<br>Country: Japan<br>Funding: Government | Randomized N: 121<br>Analyzed N: 120<br>Intervention (N=59): Haloperidol IV 2.5 mg infusion<br>Control (N=62): No treatment<br>Duration: Daily for 3 days<br>Follow-up (days): 3 | Inclusion: >75 years undergoing elective abdominal or orthopedic surgery with general or spinal anesthesia<br>Exclusion: Prior treatment with haloperidol for POD | Mean age: 80<br>Female %: 53<br>Race %: NR<br>Delirium %: 0<br>ADL (Berthel Index): 85<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: 62 | Main outcomes: 42.4% and 33.3% in the intervention and control groups, respectively, had incidences of POD (p=0.309). No adverse events related to haloperidol were reported.<br>Attrition: 0% vs. 3% | Moderate |
| Hollinger et al. (2021) | Design: RCT<br>Setting: Intra-operative, mixed<br>Country: Switzerland | Randomized N: 192<br>Analyzed N: 182<br>Intervention 1 (N=48): Haloperidol 5 µg/kg<br>Intervention 2 (N=49): Ketamine 1 mg/kg | Inclusion: ≥65 years scheduled for visceral, orthopedic, vascular, gynecological, cardiac, or thoracic surgery<br>Exclusion: Delirium at admission or prior to surgery, MMSE <24, DOS | Mean (SD) age: 73.7 (6.1)<br>Female %: 43.4<br>Race %: NR<br>Delirium %: 0 (excluded)<br>Function: NR<br>Dementia %: 0 (excluded) | Main outcomes: None of the 3 study arms – haloperidol, ketamine, or both drugs combined - was significantly superior to placebo for prevention of | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Funding: Non-profit | Intervention 3 (N=49): Haloperidol 5 µg/kg plus ketamine 1 mg/kg<br>Intervention 4 (N=47): Placebo<br>Duration: Once before induction of anesthesia<br>Follow-up (days): 3 | ≥3, dementia, high risk for postop treatment in the ICU, QT interval prolongation, or drugs influencing QT interval, Parkinson's disease, intake of dopaminergic drugs, epilepsy, delay of surgery for >72 hours after set indication for surgery, or weight >100 kg | Postop %: 100<br>Cancer %: NR | postop brain dysfunction and delirium (p=0.39).<br>Attrition: 6% vs. 4% vs. 4% vs. 6% | |
| Kalisvaart et al. (2005) | Design: RCT<br>Setting: Postop, hip<br>Country: The Netherlands<br>Funding: Hospital | Randomized N: 430<br>Analyzed N: 430<br>Intervention 1 (N=212): Haloperidol 1.5 mg oral (0.5 mg three times daily)<br>Intervention 2 (N=218): Placebo<br>Duration: Three times a day 1-6 days (3 days postop, 3-day delay allowed)<br>Follow-up (days): 14 | Inclusion: ≥70 years, acute or elective hip surgery, and at intermediate-high risk for POD (visual impairment, cognitive impairment, severity of illness)<br>Exclusion: Delirium at admission, no risk factors for POD, history of haloperidol allergy, use of cholinesterase inhibitors, parkinsonism, epilepsy, levodopa treatment, inability to participate in interviews, delay of surgery of more than 72 hours after admission, or a prolonged QTc interval of 460 ms or higher for men and 470 ms or higher for women on their electrocardiogram | Mean age: 79<br>Female %: 80<br>Race %: NR<br>Delirium %: 0<br>Barthel Index: 18.78<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: POD in the haloperidol and placebo treatment conditions was 15.1% and 16.5%, respectively (RR 50.91, 95% CI 50.6 to 1.3). No haloperidol-related side effects were noted.<br>Attrition: 9% vs. 13% | Low |
| Khan et al. (2018) | Design: RCT<br>Setting: Postop, cardiothoracic<br>Country: U.S.<br>Funding: Government | Randomized N: 135<br>Analyzed N: 135<br>Intervention 1 (N=68): Haloperidol 1.5 mg oral (0.5 mg three times daily)<br>Intervention 2 (N=67): Placebo | Inclusion: >18 years undergoing thoracic surgery<br>Exclusion: Severe dementia | Mean age: 61<br>Female %: 26<br>Race %: African American: 4<br>Delirium %: NR<br>APACHE II 16.5<br>Dementia %: NR | Main outcomes: No significant differences were observed between those receiving haloperidol and those receiving placebo in incident delirium (15 [22.1%] vs. 19 [28.4%], | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | Duration: Three times a day x 11 doses (3.7 days)<br>Follow-up (days): Unclear (post discharge) | | Postop %: 100<br>Cancer %: NR (history of chemo 54%) | p=0.43), Safety events were comparable between the groups.<br>Overall attrition: 0% | |
| Larsen et al. (2010) | Design: RCT<br>Setting: Postop, orthopedic<br>Country: U.S.<br>Funding: University | Randomized N: 495<br>Analyzed N: 400<br>Intervention 1 (N=243): Olanzapine 5 mg<br>Intervention 2 (N=252): Placebo<br>Duration: 1 dose immediately preop and 1 dose postop (in pre-anesthesia care unit)<br>Follow-up (days): 8 | Inclusion: >65 years or <65 years with a history of POD and scheduled for elective total knee- or total hip-replacement<br>Exclusion: Dementia | Mean age: 74<br>Female %: 54<br>Race %: Caucasian: 98<br>DRS-R: 15 (0-39)<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Administration of 10 mg of oral olanzapine perioperatively vs. placebo was associated with a significantly lower incidence of delirium.<br>Attrition: 19% vs. 15% | Moderate |
| Mokhtari et al. (2020) | Design: RCT<br>Setting: Postop, neurological<br>Country: Iran<br>Funding: NR | Randomized N: 53<br>Analyzed N: 40<br>Intervention 1 (N=28): Aripiprazole 15 mg orally<br>Intervention 2 (N=25): Placebo<br>Duration: Daily 7 days<br>Follow-up (days): 7 | Inclusion: >18 years, stable hemodynamics, breathing spontaneously, and admitted to ICU post neurological surgery<br>Exclusion: Severe dementia or ICU stay anticipated <3 days | Mean age: 47<br>Female %: 28<br>Race %: NR<br>Delirium %: 0<br>APACHE II: 8.5<br>Dementia %: 0<br>Postop %: 100<br>Cancer %: 15 | Main outcomes: Delirium incidence and the mean days to its onset were 20% vs. 55% (p=0.022) and 2.17 (0.41) vs. 2.09 (0.30) (p=0.076) in the aripiprazole and placebo groups, respectively. Serious aripiprazole adverse reactions were not observed.<br>Attrition: 29% vs. 20% | Moderate |
| Prakanrattana and Prapaitrakool (2007) | Design: RCT<br>Setting: Postop, cardiac<br>Country: Thailand | Randomized N: 126<br>Analyzed N: 126<br>Intervention 1 (N=63): Risperidone 1 mg sublingually<br>Intervention 2 (N=63): Placebo | Inclusion: Patients >40 years scheduled for elective cardiac surgery with CPB<br>Exclusion: Admitted to ICU, endotracheal intubation, or preop delirium | Mean age: 61<br>Female %: 49<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR | Main outcomes: A single dose of risperidone administered soon after cardiac surgery with CPB reduced the incidence of POD. | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Funding: Hospital | Duration: Once upon regaining consciousness<br>Follow-up (days): Until ICU discharge | | Postop %: NR<br>Cancer %: NR | Overall attrition: 0% | |
| Wang et al. (2012) | Design: RCT<br>Setting: Postop, noncardiac<br>Country: China<br>Funding: NR | Randomized N: 457<br>Analyzed N: 457<br>Intervention 1 (N=229): Haloperidol 0.5 mg bolus, followed by IV infusion 0.1 mg/hour<br>Intervention 2 (N=228): Placebo<br>Duration: Continuous 7 days<br>Follow-up (days): 7 | Inclusion: >65 years, admitted to ICU after noncardiac surgery<br>Exclusion: Profound dementia | Mean age: 74<br>Female %: 37<br>Race %: NR<br>Delirium %: NR<br>ASA Class III %: 37<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Delirium incidence was 15.3% (35/229) in the haloperidol group and 3.2% (53/228) in the control group (p=0.031). No drug-related side effects were documented.<br>Attrition: 1% vs. 0% | Moderate |

*Abbreviations.* ADL=activities of daily living; APACHE II=Acute Physiology and Chronic Health Evaluation II; ASA=American Society of Anesthesiologists; CI=confidence interval; CPB=cardiopulmonary bypass; DOS=delirium observation scale; DRS-R-98=Delirium Rating Scale-Revised-1998; ICU=intensive care unit; IV=intravenous; MMSE=Mini-Mental State Examination; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; RR=relative risk; SD=standard deviation.

## In Intensive Care Unit Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Abdelgalel (2016) | Design: RCT<br>Setting: ICU<br>Country: Egypt<br>Funding: None | Randomized N: 90<br>Analyzed N: 90<br>Intervention 1 (N=30): Dexmedetomidine continuous IV infusion of 0.2-0.7 µg/kg/hour; loading dose of 1.0 µg/kg IV over 10 minutes if needed<br>Intervention 2 (N=30): Haloperidol continuous IV | Inclusion: Age 26-70 years, ASA status III and IV, and in Zagazig university hospital<br>Exclusion: Patient's or relatives' refusal, allergy to any of the studied drugs, psychiatric disorders or on antipsychotic medications, severe dementia, heart rate 650 beats/minute or systolic blood pressure 690 | Mean (SD) age: 59 (50)<br>Female %: 25<br>Race %: NR<br>Delirium %: NR<br>APACHE II mean score (0 to 71): 17<br>Dementia %: "severe" dementia excluded | Main outcomes: The incidence of delirium was significantly lower in dexmedetomidine group 3/30 (10%) than haloperidol 10/30 (33.3%) and placebo 13/30 (43.3%) groups. The ICU LOS was significantly shorter in dexmedetomidine group (3.1±0.4 days) than haloperidol and placebo groups (6.5±1.0 and 6.9±1.2 days, respectively).<br>Overall attrition: 0% | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | infusion of 0.5-2 mg/hour; loading dose of 2.5 mg IV over 10 minutes if needed<br>Intervention 3 (N=30): Placebo; normal saline<br>Duration: During MV<br>Follow-up (days): NR | mmhg, prolonged QTc-time (>500 ms) or history of clinically relevant ventricular arrhythmia, epilepsy or parkinsonism, and pregnancy | Postop %: 17.8<br>Cancer %: NR | | |
| Abraham et al. (2021) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: None | Randomized N: 82<br>Analyzed N: 71<br>Intervention 1 (N=22): Quetiapine 12.5 mg twice daily, orally or through a nasogastric/enteral tube<br>Control (N=60): No treatment<br>Duration: During ICU stay<br>Follow-up (days): Discharge | Inclusion: ≥18 years and admitted to the surgical trauma ICU<br>Exclusion: Sustained RASS score of -4 or -5 during ICU admission or presence of a condition preventing delirium assessment; anticipated or known ICU LOS <48 hours; use of antipsychotics prior to admission; history of schizophrenia, epilepsy, parkinsonism, or levodopa treatment; admission with a primary neurologic condition or an injury with a GCS score ≤9 during the first 48 hours of their ICU stay; current treatment with a continuous infusion neuromuscular blocking agent; screened positive for delirium upon admission to the ICU; and/or enteral medication route was not available | Median age: 55 vs. 59<br>Female %: 39.4<br>Race %: NR<br>Delirium %: 0 (excluded)<br>Median APACHE II score: 15.0<br>Dementia %: 19.7<br>Postop %: 5.6<br>Cancer %: NR | Main outcomes: The incidence of delirium during admission to the ICU was 45.5% (10/22) in the quetiapine group and 77.6% (38/49) in the no treatment group. The mean time to onset of delirium was 1.4 days for those who did not receive treatment vs. 2.5 days for those who did (p=0.06). The quetiapine group significantly reduced ventilator duration from 8.2 days to 1.5 days (p=0.002).<br>Attrition: 18% vs. 0% | High |
| Al-Qadheeb et al. (2016) | Design: RCT<br>Setting: ICU<br>Country: U.S. | Randomized N: 68<br>Analyzed N: 68<br>Intervention 1 (N=34): | Inclusion: Patients admitted to ICU, expected to stay at least 24 hours but <4 days, and diagnosed | Mean age: 60<br>Female %: 44<br>Race %: NR | Main outcomes: A similar number of patients given haloperidol (12/34 [35%]) and placebo (8/34 [23%]) | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Funding: Government | Haloperidol 1 mg IV<br>Intervention 2 (N=34): Placebo<br>Duration: Every 6 hours<br>Follow-up (days): 10 | with subsyndromal delirium by SAS and ICDSC<br>Exclusion: Age >85 years or severe dementia | Delirium %: 0<br>APACHE II: 20<br>Dementia %: 0 (excluded)<br>Postop %: 6<br>Cancer %: NR | developed delirium (p=0.29). The proportion of patients who developed QTc-interval prolongation (p=0.16), extrapyramidal symptoms (p=0.31), excessive sedation (p=0.31), or new-onset hypotension (p=1.0) that resulted in study drug discontinuation was comparable between the 2 groups.<br>Overall attrition: 0% | |
| Kim Y. et al. (2019) | Design: RCT<br>Setting: ICU<br>Country: South Korea<br>Funding: Government | Randomized N: 37<br>Analyzed N: 35<br>Intervention 1 (N=16): Quetiapine 12.5-25 mg<br>Intervention 2 (N=21): Placebo<br>Duration: Daily<br>Follow-up (days): 10 | Inclusion: 3 of the following were met: age >64 years, APACHE II score >14, suspicion of infection, MV, continuous renal replacement therapy, metabolic acidosis, use of morphine or sedatives, unexpected ICU admission, or non-sustained coma<br>Exclusion: Age <18 years or irreversible neurologic disease | Mean age: 70<br>Female %: 63<br>Race %: NR<br>Delirium %: 0<br>APACHE II: 23.65<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR | Main outcomes: The incidence of delirium during the 10 days after ICU admission was 46.7% (7/15) in the quetiapine group and 55.0% (11/20) in the placebo group (p=0.442). Delirium duration during the study period was significantly shorter with quetiapine (0.28 day vs.1.83 days, p=0.018)<br>Attrition: 6% vs. 5% | Moderate |
| van den Boogaard et al. (2018); Rood et al. (2019) | Design: RCT<br>Setting: ICU<br>Country: The Netherlands<br>Funding: Industry | Randomized N: 1,796<br>Analyzed N: 1,789<br>Intervention 1 (N=353): Haloperidol 1 mg IV<br>Intervention 2 (N=734): Haloperidol 2 mg IV<br>Intervention 3 (N=709): Placebo<br>Duration: Every 8 hours for 4-8 days<br>Follow-up (days): 28 | Inclusion: Adults without delirium anticipated with ICU stay of at least 2 days<br>Exclusion: Dementia | Mean age: 67<br>Female %: 39<br>Race %: NR<br>Delirium %: 0<br>APACHE II: 19.4<br>Dementia %: 0 (Excluded)<br>Postop %: 25<br>Cancer %: NR | Main outcomes: The 1 mg haloperidol group was prematurely stopped because of futility. There was no difference in the median days patients survived in 28 days: 28 days in the 2 mg haloperidol group vs. 28 days in the placebo group, for a difference of 0 days (95% CI 0 to 0, p=0.93) and a HR of 1.003 (95% CI 0.78 to 1.30, p=0.82). All 15 secondary outcomes were not statistically different, including delirium incidence (MD 1.5%, 95% CI −3.6% to | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | | | | 6.7%) and delirium- and coma-free days (MD 0 days, 95% CI 0 to 0 days). The number of reported adverse effects did not differ between groups (2 [0.3%] for the 2 mg haloperidol group vs. 1 [0.1%] for the placebo group).<br>Attrition: 1% vs. 0% vs. 0% | |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; ASA=American Society of Anesthesiologists; CI=confidence interval; GCS=Glasgow Coma Scale; HR=hazard ratio; ICDSC=Intensive Care Delirium Screening Checklist; ICU=intensive care unit; IV=intravenous; LOS=length of stay; MD=mean difference; MV=medical ventilation; N=number; NR=not reported; postop=post-operative; RASS=Richmond Agitation Sedation Scale; RCT=randomized controlled trial; SAS=Sedation Agitation Scale; SD=standard deviation.

## In General Inpatient Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Schrijver et al. (2018) | Design: RCT<br>Setting: Non-ICU Inpt<br>Country: The Netherlands<br>Funding: None | Randomized N: 245<br>Analyzed N: 242<br>Intervention 1 (N=119): Haloperidol 1 mg orally<br>Intervention 2 (N=126): Placebo<br>Duration: Twice daily for 7 days<br>Follow-up (days): 7 | Inclusion: >70 years, acutely hospitalized through ED or to medical or surgical wards, at risk for delirium by Dutch Safety Management Program scale (1 point of 3), and enrolled within 24 hours of admission<br>Exclusion: Vascular or Lewy body Dementia | Mean age: 83<br>Female %: 55<br>Race %: NR<br>Delirium %: 0<br>Katz ADLs: 3<br>Dementia %: 0<br>Postop %: 23<br>Cancer %: NR | Main outcomes: In the haloperidol and placebo group, delirium incidence was 19.5% vs. 14.5% (OR 1.43, 95% CI 0.72 to 2.78); median (IQR) delirium duration 4 (2-5) vs. 3 (1-6) days (p=0.366); maximum DRS-R-98 score 16 (9.8-19.5) vs. 10 (5.5-22.5) (p=0.549; 53.7% missing data); hospital LOS 7 (4-10.3) vs. 7 (5-11.8) days (p=0.343); 3-month mortality 9.9% vs. 12.5% (OR 0.77, 95% CI 0.34 to 1.75), respectively. No treatment-limiting side effects were noted.<br>Attrition: 6% vs. 7% | Moderate |
| Thanaplueti wong et al. (2021) | Design: RCT<br>Setting: Non-ICU Inpatient | Randomized N: 122<br>Analyzed N: 114<br>Intervention 1 (N=61): | Inclusion: >65 years acutely hospitalized in a medical specialty | Mean (SD) age: 75.3 (7.1)<br>Female %: 45.6 | Main outcomes: The incidence of delirium in the quetiapine group was | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | Country: Thailand<br>Funding: Hospital | Quetiapine 12.5 mg/day<br>Intervention 2 (N=61): Placebo<br>Duration: Daily 7 days<br>Follow-up (days): 7 | Exclusion: Dementia and severe Parkinson's epilepsy | Race %: NR<br>Delirium %: 0 (excluded)<br>ASA II: NR (65% independent)<br>Dementia %: 0 (excluded)<br>Postop %: NR<br>Cancer %: NR | 14% vs. 8.8% in the placebo group (OR 1.698, 95% CI 0.520 to 5.545, p=0.381).<br>Attrition: 7% vs. 7% | |

*Abbreviations.* ASA=American Society of Anesthesiologists; CI=confidence interval; DRS-R-98=Delirium Rating Scale-Revised-1998; ED=emergency department; ICU=intensive care unit; IQR=interquartile range; LOS=length of stay; N=number; NR=not reported; OR=odds ratio; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

## *Melatonin*

### Melatonin vs. Placebo

#### In Surgical Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| de Jonghe et al. (2014); MAPLE (de Jonghe et al. 2011 for study protocol) | Design: RCT<br>Setting: Postop, hip<br>Country: The Netherlands<br>Funding: Government and nonprofit | Randomized N: 452*<br>*8 patients were excluded after randomization due to logistics failure.<br>Analyzed N: 378<br>Intervention 1 (N=219 assigned): Melatonin 3 mg tablet<br>Intervention 2 (N=225 assigned): Placebo tablet<br>Duration: In the evening for 5 consecutive days<br>Follow-up (days): 90 | Inclusion: ≥65 years admitted for emergency surgery for hip fracture, enrolled within 24 hours of admission<br>Exclusion: Delirium at baseline, transferred from another hospital, or anticipation of postop admission to the ICU or coronary care unit | Mean (SD) age: 83.7 (7.8)<br>Female %: 70<br>Race %: NR<br>Delirium %: 0 (excluded)<br>Katz Index of Activities of Daily Living: NR overall<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR<br>Cognitive impairment (based on MMSE, Informant Questionnaire on Cognitive Decline, or | Main outcomes: No effect of melatonin on the incidence of delirium was observed (adjusted OR 1.14, 95% CI 0.71 to 1.83).<br>Attrition from assigned numbers: 16% vs. 15% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | | | dementia on Charlson comorbidity index) %: 55.6 | | |
| Ford et al. (2020) | Design: RCT<br>Setting: Preop and postop, cardiac<br>Country: Australia<br>Funding: Government | Randomized N: 210<br>Analyzed N: 202 at discharge; 166 at 3 months (cognitive only, ITT reported)<br>Intervention 1 (N=105): Melatonin 3 mg<br>Intervention 2 (N=105): Placebo<br>Duration: Once daily, 7 consecutive nights, starting 2 nights before surgery<br>Follow-up (days): 7 (delirium), 90 (cognitive only) | Inclusion: ≥50 years and undergoing elective cardiac surgery<br>Exclusion: Dementia or score ≤19 on TICS-M | Mean (SD) age: 68.3 (8.2)<br>Female %: 22<br>Race %: NR<br>Delirium %: NR<br>Baseline scale of function: NR<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR<br>Cognitive status (TICS-M): 34.8 (3.9) | Main outcomes: Melatonin did not decrease the incidence of delirium compared to placebo (ITT analysis, adjusted OR 0.79, 95% CI 0.36 to 1.76).<br>Attrition: 7% vs. 1% | Low |
| Javaherforoosh Zadeh et al. (2021) | Design: RCT<br>Setting: Preop and postop, cardiac<br>Country: Iran<br>Funding: None | Randomized N: 60<br>Analyzed N: 60<br>Intervention 1 (N=30): Melatonin 3 mg<br>Intervention 2 (N=30): Placebo<br>Duration: Evening before surgery, morning of surgery, and daily until 2nd postop day<br>Follow-up (days): POD 2, until discharge | Inclusion: ≥30 years, candidate for elective on-pump CABG, ASA II-III, minimum ejection fraction of 30%, and admitted to the hospital<br>Exclusion: Melatonin contraindications, chronic or recent use of melatonin or hypnotic drugs, receiving barbiturates or antipsychotics, history of liver or kidney disease or chronic pulmonary disease, history of neurological or psychological diseases, alcohol consumption, inability to communicate verbally, and the occurrence of serious and life-threatening events during or after | Mean (SD) age: 61.58 (8.82)<br>Female %: 30<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR<br>Postop %: 100 cardiac surgery<br>Cancer %: NR | Main outcomes: On the 1st postop day, 4 (13.3%) patients in the melatonin group vs. 11 (36.6%) patients in the placebo group developed delirium (p=0.037). On 2nd postop day, 3 (10%) patients in the melatonin group vs. 14 (46.6%) patients in the control group developed delirium (p=0.029). The severity of delirium between the groups was significant on the 1st and 2nd postop days (p=0.003).<br>Overall attrition: 0% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Sharaf et al. (2018) | Design: RCT<br>Setting: Preop and postop, cardiac<br>Country: Egypt<br>Funding: NR | Randomized N: 50<br>Analyzed N: 50<br>Intervention 1 (N=25): Melatonin 3 mg<br>Intervention 2 (N=25): Placebo<br>Duration: Night before surgery, 30 minutes before surgery, and night after surgery<br>Follow-up (days): 3 | Inclusion: ≥60 years, ASA status III to IV, and undergoing elective CABG with 2 or 3 vessel grafts<br>Exclusion: Emergent CABG, ASA status ≥V, ejection fraction <40%, MMSE ≤24, history of neuropsychiatric disorders, history of liver cirrhosis or renal failure, history of chronic pulmonary diseases, uncontrolled systemic disease, prolonged postop ventilation >8 hours, or history of chronic sedative hypnotics use ≥3 times/week | Mean (SD) age: 62.7 (4.5)<br>Female %: 48<br>Race %: NR<br>Delirium %: NR<br>ASA III %: 54<br>ASA IV %: 46<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: The incidence of delirium was 8% in the melatonin group vs. 28% in the control group (p=0.046).<br>Attrition: NR | Low |

*Abbreviations.* ASA=American Society of Anesthesiologists; CABG=coronary artery bypass graf; CI=confidence interval; ICU=intensive care unit; ITT=intention-to-treat; MMSE=Mini-Mental State Examination; N=number; NR=not reported; OR=odds ratio; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; SD=standard deviation; TICS-M=Modified Telephone Interview for Cognitive Status.

### In Intensive Care Unit Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Abbasi et al. (2018) | Design: RCT<br>Setting: ICU<br>Country: Iran<br>Funding: University | Randomized N: 172<br>Analyzed N: 137<br>Intervention 1 (N=87): Melatonin 3 mg tablet<br>Intervention 2 (N=85): Placebo tablet<br>Duration: Once daily, at 9:00 pm for 5 continuous days<br>Follow-up (days): NR | Inclusion: >18 years, ICU admission within last 24 hours, RASS >-4, GCS >8, and no delirium before ICU admission<br>Exclusion: <5 days of ICU stay and severe heart failure | Mean (SD) age: 51.2 (18.7)<br>Female %: 43<br>Race %: NR<br>Delirium %: NR<br>APACHE II: mean 7.7 (4.5)<br>Dementia %: NR<br>Postop %: 58 surgical admission<br>Cancer %: NR | Main outcomes: No significant effect of melatonin was found on incidence of delirium, adjusted for baseline characteristics (OR 0.71, 95% CI 0.06 to 9.15, p=0.80).<br>Attrition: 23% vs. 18% | Moderate |
| Bellapart et al. (2020) | Design: RCT | Randomized N: 63<br>Analyzed N: 33 | Inclusion: Patients expected to have a minimal length of 5 days | Median age: 55<br>Female %: NR | Main outcomes: Baseline delirium scores showed no | High |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Setting: ICU<br>Country: Australia<br>Funding: None | Intervention 1 (N=30): Melatonin 6 mg enteral, via NG tube, each night<br>Intervention 2 (N=33): Placebo<br>Duration: Nightly during ICU stay<br>Follow-up (days): 1, 3 | of respiratory weaning, with a preserved enteral absorption or the absence of ileus, and without known history of sleep disorders<br>Exclusion: Taking beta-blockers, vasopressors, corticosteroids, non-steroidal drugs, naloxone, or pre-intensive care prescription of antipsychotics; advanced liver disease; burns prior to debridement and grafts; ongoing sepsis; neurocritical patients | Race %: NR<br>Delirium %: NR<br>Median APACHE II: 22<br>Median APACHE III: 74<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR | difference between the groups when compared to post-intervention scores. RASS scores were 1 in both groups at baseline vs. 0 (intervention group) and 0.5 (placebo group) post treatment. CAM scores were 0 (intervention group) and 1 (placebo group) at baseline vs. 0 (in both groups) postintervention.<br>Attrition: 37% vs. 63% | |
| Gandolfi et al. (2020) | Design: RCT<br>Setting: ICU<br>Country: Brazil<br>Funding: None | Randomized N: 206<br>Analyzed N: 203<br>Intervention 1 (N=103): Melatonin 10 mg tablet at 8pm (2 hours after dinner)<br>Intervention 2 (N=103): Placebo<br>Duration: 7 days<br>Follow-up (days): 7, Until discharge | Inclusion: ≥18 years with ≥1 night in the ICU<br>Exclusion: History of seizures, neurologic or psychiatric illness, sleep apnea, renal or hepatic impairment, intestinal obstruction or other condition that affected intestinal absorption, autoimmune diseases, deaf or mute, pregnant, and lactating | Mean (SD) age: 58.5 (15.1)<br>Female %: 40<br>Race %: NR<br>Delirium %: NR<br>Mean (SD) Simplified Acute Physiology Score III: 42 (12.6)<br>Dementia %: NR<br>Postop %: 46.3<br>Cancer %: 11.9<br>Median days on MV: 2 vs. 3.5 (1-7) | Main outcomes: No significant difference between groups was found in the occurrence of delirium, pain, and anxiety.<br>Attrition: 1% vs. 1% | Moderate |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; CAM=Confusion Assessment Method; CI=confidence interval; GCS=Glasgow Coma Scale; ICU=intensive care unit; MV=medical ventilation; N=number; NG=nasogastric; NR=not reported; OR=odds ratio; postop=post-operative; RASS=Richmond Agitation Sedation Scale; RCT=randomized controlled trial; SD=standard deviation.

## In General Inpatient/Palliative Care Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Jaiswal et al. (2018) | Design: RCT<br>Setting: Non-ICU inpatient<br>Country: U.S.<br>Funding: Government and nonprofit | Randomized N: 87<br>Analyzed N: 87<br>Intervention 1 (N=43): Melatonin 3 mg nightly<br>Intervention 2 (N=44): Placebo<br>Duration: Maximum of 14 consecutive nights<br>Follow-up (days): NR | Inclusion: ≥65 years, admitted to internal medicine wards (non-ICU), and expected stay ≥48 hours<br>Exclusion: Those admitted with stroke or with conditions associated with encephalopathy (e.g., cirrhosis, hypernatremia, hypercalcemia, alcohol withdrawal) | Mean (SD) age: 80.6 (7.8)<br>Female %: 62<br>Race %: Caucasian: 92<br>Delirium %: 0 (excluded)<br>Baseline scale of function: NR<br>Dementia %: NR (advanced dementia excluded)<br>Postop %: 23<br>Cancer %: 3 (primary admission diagnosis) | Main outcomes: Delirium occurred in 22.2% (8/36) of subjects who received melatonin vs. in 9.1% (3/33) who received placebo (p=0.19). Melatonin did not prevent delirium in non-ICU hospitalized patients (RR 2.3, 95% CI 0.8 to 6.9).<br>Attrition: 16% vs. 25% | Moderate |
| Lawlor et al. (2020) | Design: RCT<br>Setting: Palliative care<br>Country: Canada<br>Funding: University | Randomized N: 60<br>Analyzed N: 60<br>Intervention 1 (N=30): Melatonin 3 mg<br>Intervention 2 (N=30): Placebo<br>Duration: Daily for 28 days or until discharge or death<br>Follow-up (days): 28 | Inclusion: ≥18 years, documented diagnosis of advanced cancer, admitted to the inpatient PCU, rating ≥30% on the PPS, and cognitive capacity to give informed consent<br>Exclusion: Delirium present on admission, known psychotic disorder other than dementia, use of melatonin within the 2 weeks preceding admission, on warfarin or other oral anticoagulants, or on immunosuppressant medication | Median age: 67 (range 60-75)<br>Female %: 45<br>Race %: NR<br>Delirium %: 0% (excluded)<br>Median (IQR) Charlson Comorbidity Index: 10 (9-12)<br>Dementia %: 6.7<br>Cancer %: 100<br>Postop %: NR | Main outcomes: Melatonin vs. placebo outcomes were as follows: incident delirium in 11/30 (36.7%, 95% CI 19.9 to 56.1) vs. 10/30 (33%, 95% CI 17.3 to 52.8); early discharge (6 vs. 5); withdrawal (6 vs. 3); death (0 vs. 1); 7 (23%) vs. 11 (37%) reached the 28-day end point.<br>Attrition: 40% vs. 27% | Low |

*Abbreviations.* CI=confidence interval; ICU=intensive care unit; IQR=interquartile range; N=number; NR=not reported; PCU=palliative care unit; postop=post-operative; PPS=Palliative Performance Scale; RCT=randomized controlled trial; RR=relative risk; SD=standard deviation.

## Melatonin Plus Dexmedetomidine vs. Dexmedetomidine

### In Surgical Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Mahrose et al. (2021) | Design: RCT<br>Setting: Preop, cardiac<br>Country: Egypt<br>Funding: NR | Randomized N: 110<br>Analyzed N: 110<br>Intervention 1 (N=55): Melatonin 5 mg plus dexmedetomidine 0.4 µg/kg IV bolus, then 0.2-0.7 µg/kg/hour IV<br>Intervention 2 (N=55): Dexmedetomidine 0.4 µg/kg IV bolus, then 0.2-0.7 µg/kg/hour IV<br>Intervention 1 duration: Melatonin - 10 pm night before surgery and every evening before bed for 3 days; dexmedetomidine - upon arrival to the ICU for 24 hours<br>Intervention 2 duration: Upon arrival to the ICU for 24 hours<br>Follow-up (days): 5 | Inclusion: >60 years having elective CABG surgery<br>Exclusion: Patients undergoing emergency procedures, any preop mental illness, preop renal failure, chronic liver disease (Child classification class B and C), carotid duplex to have carotid disease, or prolonged postop intubation and re-exploration | Mean age: 66.5<br>Female %: 24.5<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR (excluded any mental illness)<br>Postop %: 100<br>CABG surgery %: 100<br>Cancer %: NR | Main outcomes: Fewer patients who received melatonin in addition to dexmedetomidine experienced delirium, and duration of delirium was shorter.<br>Overall attrition: 0% | Moderate |

*Abbreviations.* CABG=coronary artery bypass graf; ICU=intensive care unit; IV=intravenous; N=number; NR=not reported; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial.

## Melatonin vs. Midazolam vs. Clonidine vs. No Sedation

### In Surgical Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Sultan (2010) | Design: RCT<br>Setting: Preop, hip<br>Country: Egypt<br>Funding: None | Randomized N: 222<br>Analyzed N: 203<br>Intervention 1 (N=53 analyzed): Melatonin 5 mg, 2 oral doses<br>Intervention 2 (N=50 analyzed): Midazolam 7.5 mg, 2 oral doses | Inclusion: >65 years, scheduled for hip arthroplasty under spinal anesthesia, and ASA I-III<br>Exclusion: Sensory impairment (blindness, deafness); dementia; severe infections; severe anemia (hematocrit <30%); | Mean (SD) age: 71.01 (36.8)<br>Female %: 51<br>Race %: NR<br>Delirium %: 0 (excluded)<br>ASA I-III: inclusion criterion<br>Dementia %: 0 (excluded) | Main outcomes: The melatonin group showed a statistically significant decrease in the percentage of POD (9.43% vs. 32.65% in the other groups). | High |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Intervention 3 (N=51 analyzed): Clonidine 100 µg, 2 oral doses<br>Intervention 4 (N=49 analyzed): No sedation<br>Duration: One dose the night before surgery and another 90 minutes before surgery<br>Follow-up (days): POD 3 | intracranial events (stroke, bleeding, infection); fluid or electrolyte disturbances; acute cardiac events; acute pulmonary events; and medications including anticonvulsants, antihistamines, and benzodiazepines | Postop %: 100<br>Cancer %: NR | Overall attrition: 9% | |

*Abbreviations.* ASA=American Society of Anesthesiologists; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; SD=standard deviation.

## *Ramelteon*

### Ramelteon vs. placebo

#### In Surgical Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Gupta et al. (2019) | Design: RCT<br>Setting: Preop, mixed<br>Country: India<br>Funding: NR | Randomized N: 100<br>Analyzed N: 100<br>Intervention 1 (N=50): Ramelteon 8 mg tablets, 2 doses<br>Intervention 2 (N=50): Placebo<br>Duration: 1 tablet 12 hours before surgery and 1 tablet 1 hour before surgery<br>Follow-up (days): POD 3 | Inclusion: >65 years, admitted for surgery requiring neuraxial anesthesia with duration longer than 1 hour, and ASA physical status 1 and 2<br>Exclusion: History of dementia, severe infections, intracranial bleed, or acute cardiac event | Mean (SD) age: 69.97 (3.91)<br>Female %: 32<br>Race %: NR<br>Delirium %: NR (0% on POD 1)<br>ASA physical status ≥3 %: 0<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Incidence of delirium was lower with ramelteon compared with placebo (4% vs. 12%), but the difference was not statistically significant.<br>Overall attrition: 0% | Moderate |
| Jaiswal et al. (2019) | Design: RCT<br>Setting: Preop and postop, | Randomized N: 120<br>Analyzed N: 117<br>Intervention 1 (N=59): Ramelteon 8 mg | Inclusion: ≥18 years undergoing elective pulmonary thromboendarterectomy | Mean (SD) age: 57.1 (15.0)<br>Female %: 50<br>Race %: NR<br>Delirium %: NR | Main outcomes: Ramelteon 8 mg did not prevent POD in patients admitted for elective | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | cardiothoracic<br>Country: U.S.<br>Funding: Government | Intervention 2 (N=61): Placebo<br>Duration: Nightly from the night before surgery for a maximum of 7 nights, or until ICU discharge if sooner<br>Follow-up (days): ≤9 | Exclusion: Cirrhosis or use of fluvoxamine | Baseline scale of function: NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | cardiac surgery (RR 0.9, 95% CI 0.5 to 1.4).<br>Attrition: 0% vs. 5% | |
| Oh E.S. et al. (2021) | Design: RCT<br>Setting: Preop and postop, orthopedic<br>Country: U.S.<br>Funding: Non-profit | Randomized N: 80<br>Analyzed N: 80<br>Intervention 1 (N=41): Ramelteon 8 mg<br>Intervention 2 (N=39): Placebo<br>Duration: Prior to surgery, the night of surgery, and following postop day 1<br>Follow-up (days): 1, 2 | Inclusion: ≥65 years with planned orthopedic surgery and inpatient stay following surgery and MMSE >15 before surgery<br>Exclusion: Delirium prior to surgery, current moderate to severe liver failure, or evidence of systemic inflammatory response syndrome | Mean (SD) age: 74.8 (5.3)<br>Female %: 54<br>Race %:<br>Caucasian: 73.7<br>Black/African American: 15<br>Asian: NR<br>Other: NR<br>Delirium %: 0 (excluded)<br>Mean (SD) Charlson Comorbidity Index: 1.2 (1.3)<br>Dementia %: NR<br>Mean (SD) MMSE: 28.4 (1.7)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Delirium incidence during the 2 days following surgery was 7% (5/71) with no difference between the ramelteon vs. placebo: 9% (3/33) and 5% (2/38), respectively (adjusted OR 1.28, 95% CI 0.21 to 7.93, z-value 0.27, p=0.79).<br>Attrition: 20% vs. 3% | Low |

*Abbreviations.* ASA=American Society of Anesthesiologists; CI=confidence interval; ICU=intensive care unit; MMSE=Mini-Mental State Examination; N=number; NR=not reported; OR=odds ratio; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; RR=relative risk; SD=standard deviation.

## In Intensive Care Unit/Inpatient Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Nishikimi et al. (2018) | Design: RCT<br>Setting: ICU<br>Country: Japan | Randomized N: 92<br>Analyzed N: 88<br>Intervention 1 (N=47): Ramelteon 8 mg/day | Inclusion: ≥20 years admitted to an emergency and medical ICU who could receive medications orally or through a nasogastric | Median age: 68<br>Female %: 35<br>Race %: NR<br>Delirium %: NR | Main outcomes: A statistically significant decrease in the occurrence rate of delirium (24.4% vs. | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Funding: University | Intervention 2 (N=45): Placebo (lactose powder 1 g/day)<br>Duration: Every night until ICU discharge<br>Follow-up (days): ICU discharge (median 5-6 days) | tube during the first 48 hours of ICU admission<br>Exclusion: Receiving ramelteon or fluvoxamine maleate, known allergy to ramelteon, or refused to provide consent | APACHE II score, mean (SD): 23.97 (7.97)<br>Dementia %: 8<br>Postop %: 0 (surgical ICU patients not included)<br>Cancer %: NR | 46.5%, p=0.044) was observed in the ramelteon group.<br>Attrition: 4% vs. 4% | |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; Intervention 1=group 1; Intervention 2=group 2; ICU=intensive care unit; N=number; NR=not reported; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

### In General Inpatient Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Hatta et al. (2014b) | Design: RCT<br>Setting: Mixed inpatient<br>Country: Japan<br>Funding: Government | Randomized N: 67<br>Analyzed N:67<br>Intervention 1 (N=33): Ramelteon 8 mg/day<br>Intervention 2 (N=34): Placebo<br>Duration: Nightly for 7 days<br>Follow-up (days): 7 | Inclusion: Age 65-89 years, newly admitted to ICUs or "regular acute wards" due to serious medical problems, and able to take medicine orally<br>Exclusion: Expected stay or life expectancy <48 hours, severe liver dysfunction, Lewy body disease, taking fluvoxamine, or delirious at admission | Mean (SD) age: 78.3 (6.7)<br>Female %: 60<br>Race %: NR<br>Delirium %: 0 (excluded)<br>APACHE II: 14.1 (2.9)<br>ECOG performance status: 3.3 (0.8)<br>Dementia %: 19<br>Postop %: NR<br>Cancer %: NR | Main outcomes: After risk factors were controlled for, ramelteon was associated with a lower incidence of delirium compared with placebo (adjusted OR 0.07, 95% CI 0.008 to 0.54).<br>Overall attrition: 0% | Moderate |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; ICU=intensive care unit; N=number; NR=not reported; OR=odds ratio; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

*Suvorexant*

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Azuma et al. (2018) | Design: RCT<br>Setting: ICU<br>Country: Japan<br>Funding: NR | Randomized N: 70<br>Analyzed N: 70<br>Intervention 1 (N=34) *: Suvorexant 20 mg (<65 years) or 15 mg (≥65 years) once daily<br>Control (N=36) *: Usual care<br>*Both groups received ABCDEF multi-component intervention.<br>Duration: At 9:00 pm for 7 days or until patient developed delirium<br>Follow-up (days): NR | Inclusion: ≥20 years admitted within 24 hours to mixed medical ICU<br>Exclusion: Life expectancy <48 hours, baseline dementia or treated delirium, or severe liver dysfunction | Mean (SD) age: 61.7 (20.7)<br>Female %: 23<br>Race %: NR<br>Delirium %: NR<br>APACHE II: 11.1 (7.5)<br>Dementia %: 0 (excluded)<br>Postop %: 0 (medical ICU)<br>Cancer %: NR | Main outcomes: Incidence of delirium was 14.7% in suvorexant group compared to 33.3% in usual care group (p=0.069).<br>Overall attrition: 0% | Moderate |
| Hatta et al. (2017) | Design: RCT<br>Setting: Mixed inpatient<br>Country: Japan<br>Funding: Government | Randomized N: 72<br>Analyzed N: 72<br>Intervention 1 (N=36): Suvorexant 15 mg/day<br>Intervention 2 (N=36): Placebo<br>Duration: Nightly for 3 days<br>Follow-up (days): 7 | Inclusion: Age 65-89 years, newly admitted to ICUs or "regular acute wards" due to emergency, and able to take medicine orally<br>Exclusion: Expected stay or life expectancy <48 hours, taking strong CYP3A inhibitor drugs, narcolepsy, cataplexy, severe liver dysfunction, severe respiratory dysfunction, or delirious at admission | Mean (SD) age: 78.4 (6.4)<br>Female %: 42<br>Race %: Asian: 100<br>Delirium %: 0 (excluded)<br>APACHE II, Acute Physiology Score: 3.1 (2.2)<br>ECOG performance status: 3.2 (0.9)<br>Dementia %:25<br>Postop %: NR<br>Cancer %: NR | Main outcomes: Delirium occurred significantly less often in patients taking suvorexant than those taking placebo (0% vs 17%, p=0.025).<br>Attrition: 6% vs. 8% | Moderate |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; ECOG=Eastern Cooperative Oncology Group; ICU=intensive care unit; N=number; NR=not reported; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

## Pharmacological Interventions for Treatment of Delirium

### *Dexmedetomidine*

#### In Surgical Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Bakri et al. (2015) | Design: RCT<br>Setting: Postop, mixed<br>Country: Saudi Arabia<br>Funding: None | Randomized N: 96<br>Analyzed N: 96<br>Intervention 1 (N=32): Dexmedetomidine continuous IV infusion of 1 µg/kg<br>Intervention 2 (N=32): Ondansetron continuous IV infusion 4 mg<br>Intervention 3 (N=32): Haloperidol continuous IV infusion 5 mg<br>Duration: Twice a day for 3 consecutive days<br>Follow-up (days): POD 3 | Inclusion: Patients who screened positive for delirium within the first 3 days of ICU admission<br>Exclusion: Severely injured, deeply comatose, moribund patients, underlying neurological diseases, significant hearing loss, intracranial injury, or ischemic/hemorrhagic stroke | Mean (SD) age: 31 (5.5)<br>Female %: 9<br>Race %: NR<br>Delirium %: 100 (required)<br>Functioning scale: NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR<br>Mean (SD) duration of surgery, minutes: 211 (34)<br>Mean (SEM) Injury Severity Score: 25.4 (2.9)<br>Patients on MV on ICU admission %: 27 | Main outcomes: At the end of the study, the number of remaining delirious patients was 3, 6, and 2 in dexmedetomidine, ondansetron, and haloperidol groups, respectively, without statistical significance. During the study period, no significant difference was found in the number of patients who needed “rescue haloperidol” between dexmedetomidine and haloperidol groups (5 vs. 3, p=0.7), but the difference was significantly higher in ondansetron and haloperidol groups (11 vs. 3, p=0.03). The mean total “rescue haloperidol” dose was significantly higher in ondansetron group than haloperidol group (p<0.001), but there was no difference between dexmedetomidine and haloperidol groups (p=0.07).<br>Attrition: NR | Moderate |
| Liu et al. (2018) | Design: RCT<br>Setting: Postop, mixed<br>Country: China<br>Funding: Nonprofit | Randomized N: 100<br>Analyzed N: 100<br>Intervention 1 (N=25): Dexmedetomidine IV 0.2 µg/kg bolus followed by 0.6 µg/kg/hour | Inclusion: Age 20-40 years scheduled for general anesthesia<br>Exclusion: Delirium preop | Mean (SD) age: 30.95 (4.87)<br>Female %: 46<br>Race %: NR<br>Delirium %: 100<br>ASA I, II %: 100 | Main outcomes: Dexmedetomidine and sufentanil decreased the duration of POD through 8 hours postop, but more individuals had delirium in the dexmedetomidine group at 8 hours | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Intervention 2 (N=25): Sufentanil IV 0.2 µg/kg bolus followed by 0.2 µg/kg/hour<br>Intervention 3 (N=25): Sufentanil IV 0.2 µg/kg bolus followed by combined dexmedetomidine 0.6 µg/kg/hour and sufentanil 0.2 µg/kg/hour<br>Intervention 4 (N=25): Sufentanil IV 0.2 µg/kg bolus followed by combined dexmedetomidine 0.3 µg/kg/hour and sufentanil 0.1 µg/kg/hour<br>Duration: Postop<br>Follow-up (days): Through 8 hours | | Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | than the other 3 groups (36% vs. 8% to 16%, p<0.05).<br>Overall attrition: 0% | |
| Yapici et al. (2011) | Design: RCT<br>Setting: Postop, cardiac<br>Country: Turkey<br>Funding: Unclear | Randomized N: 72<br>Analyzed N: 72<br>Intervention 1 (N=38): Dexmedetomidine IV 0.3-0.7 µg/kg/hour<br>Intervention 2 (N=34): Midazolam 0.05-0.2 mg/kg/hour<br>Duration: MV<br>Follow-up (days): Delirium assessed daily | Inclusion: Patients undergoing elective CABG, valve replacement, or both who had failed at least 1 extubation attempt<br>Exclusion: Patients who experienced postop coma or death | Mean (SD) age: 59.97 (9.88)<br>Female %: 63<br>Race %: NR<br>Delirium %: 100<br>Dementia %: NR<br>Failed extubation: 100<br>Postop %: 100 cardiac surgery<br>Cancer %: 0 | Main outcomes: At postop hour 60, fewer patients given dexmedetomidine to assist with weaning off of MV had delirium compared with patients given midazolam (2.7% vs. 21%, p<0.05).<br>Attrition: NR | Moderate |

*Abbreviations.* CABG=coronary artery bypass graf; ICU=intensive care unit; IV=intravenous; MV=medical ventilation; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; SD=standard deviation; SEM=standard error of the mean.

3369 In Intensive Care Unit Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Liu et al. (2021) | Design: Retrospective cohort<br>Setting: ICU<br>Country: China<br>Funding: Government | Analyzed N: 263<br>Intervention 1 (N=118): Dexmedetomidine 0.1-0.7 mcg/kg/hour<br>Intervention 2 (N=145): Olanzapine 2.5-10 mg/day<br>Duration: NR<br>Follow-up (days): NR | Inclusion: ≥75 years diagnosed with delirium based on DSM-5 in the ICU and given either dexmedetomidine or olanzapine<br>Exclusion: Patients with endotracheal ventilation, underwent surgery during the hospital stay, advanced-stage tumors, brain tumors or recent brain trauma, underwent blood purification therapy during the use of olanzapine or dexmedetomidine, or with curative effects and adverse effects that could not be evaluated | Mean age: 80.05 vs. 78.99<br>Female %: 18.64 vs. 26.90<br>Race %: NR<br>Delirium %: 100<br>Mean APACHE II score: 18.91 vs. 18.59<br>Dementia %: 10.17 vs. 11.03<br>Postop %: NR<br>Cancer %: 9.32 vs. 8.97 | Main outcomes: RASS scores were significantly higher in the olanzapine group than in the dexmedetomidine group (mean [SD] -0.57 [0.88] vs. 0.88 [0.73], p<0.001).<br>No significant differences were found between the groups in mortality, long-term cognitive function, or recurrence of delirium (mortality 24.5% [29/118] vs. 21.4% [31/145], p=0.336; decrease in long-term cognitive function 23.7% [28/118] vs. 30.3% [44/145]; occurrence of delirium 27.12% [32/118] vs. 36.55% [53/145]). The hospital LOS was longer in the dexmedetomidine group than in the olanzapine group (mean [SD] 9.30 [4.90] vs. 8.83 [3.34], p<0.001).<br>Attrition: NR | Moderate |
| Reade et al. (2016) | Design: RCT<br>Setting: ICU<br>Country: Australia<br>Funding: Mixed | Randomized N: 74<br>Analyzed N: 71<br>Intervention 1 (N=41): Dexmedetomidine IV optional 1.0 µg/kg bolus followed by 0-1.5 µg/kg/hour<br>Intervention 2 (N=33): Standard care; saline<br>Duration: MV<br>Follow-up (days): 7 | Inclusion: ≥18 years with CAM-ICU scores that indicated delirium and who required MV only because their degree of agitation was so severe that lessening sedation and extubation was unsafe<br>Exclusion: Patients with dementia that required professional nursing care | Median age: 57.3<br>Female %: 25<br>Race %: NR<br>Delirium %: 100<br>APACHE II: 14<br>Dementia requiring professional care %: 0<br>Postop %: 59%<br>Cancer %: NR | Main outcomes: Among patients with agitated delirium, the addition of dexmedetomidine to standard care compared with standard care alone resulted in more ventilator-free hours at 7 days (144.8 hours vs. 127.5 hours, p=0.01).<br>Attrition: 5% vs. 3% | Low |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; CAM-ICU=Confusion Assessment Method for the ICU; DSM-5=Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ICU=intensive care unit; IV=intravenous; LOS=length of stay; MV=medical ventilation; N=number; NR=not reported; postop=post-operative; RASS=Richmond Agitation Sedation Scale; RCT=randomized controlled trial; SD=standard deviation.

### *Benzodiazepines*

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Breitbart et al. (1996) | Design: RCT<br>Setting: Inpatient<br>Country: U.S.<br>Funding: Government | Randomized N: 30<br>Analyzed N: 30<br>Intervention 1 (N=11): Haloperidol loading dose oral 0.25-5 mg, followed by maintenance dose of 1.2 the initial dose every 12 hours (IM dosing also allowed)<br>Intervention 2 (N=13): Chlorpromazine loading dose oral 10-200 mg followed by maintenance dose of 1/2 loading dose every 12 hours (IM dosing allowed)<br>Intervention 3 (N=6): Lorazepam loading dose oral 0.5-24 mg followed by maintenance dose of 1/2 loading dose every 12 hours (IM dosing allowed)<br>Duration: Every 12 hours for 6 days<br>Follow-up (days): 6 | Inclusion: Inpatients with AIDS with delirium<br>Exclusion: Patients with dementia or near end of life (within 24 hours) | Mean age: 39<br>Female %: 23<br>Race %:<br>Caucasian: 13<br>Black/African American: 57<br>Asian: 3<br>Delirium %: 100<br>Karnovsky: 52.3<br>Dementia %: 0 (excluded)<br>Postop %: 0<br>Cancer %: NR | Main outcomes: Treatment with either haloperidol or chlorpromazine resulted in significant improvements in symptoms of delirium as measured by DRS. No improvement was seen with lorazepam. Treatment with haloperidol and chlorpromazine resulted in very low prevalence of extrapyramidal side effects.<br>All 6 patients receiving lorazepam developed treatment-limiting adverse effects.<br>Attrition: NR vs. NR vs. 100% | Moderate |
| Hui et al. (2017) | Design: RCT<br>Setting: Palliative care<br>Country: U.S. | Randomized N: 90<br>Analyzed N: 58<br>Intervention 1 (N=47): Lorazepam 3 mg plus haloperidol 2 mg every 4 hours | Inclusion: Adults with advanced cancer in palliative care with diagnosis of delirium | Mean age: 65<br>Female %: 47<br>Race %:<br>Caucasian: 76<br>Black/African American: | Main outcomes: Lorazepam plus haloperidol resulted in a significantly greater reduction of RASS score at 8 hours (−4.1 points) than placebo plus haloperidol (−2.3 points) (MD −1.9 | High |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Funding: Government | IV; additional 2 mg as needed for agitation<br>Intervention 2 (N=43): Placebo plus haloperidol 2 mg every 4 hours IV; additional 2 mg as needed for agitation<br>Duration: Lorazepam or placebo infused intravenously over 1.5 minutes<br>Follow-up: 8 hours | Exclusion: Patients with dementia | 24<br>Asian: NR<br>Delirium %: 100<br>Karnovsky: 10%=21%, 20%=47%, 30%=24%, 40%=9%<br>Dementia %: 0 (Excluded)<br>Postop %: 0<br>Cancer %: 100 | points, 95% CI −2.8 to −0.9, p<0.001). The lorazepam plus haloperidol group required less median rescue neuroleptics (2.0 mg) than the placebo plus haloperidol group (4.0 mg) (MD −1.0 mg, 95% CI −2.0 to 0, p=0.009). No significant between-group differences were found in delirium-related distress and survival. The most common adverse effect was hypokinesia (3 patients in the lorazepam plus haloperidol group [19%] and 4 patients in the placebo plus haloperidol group [27%]).<br>Attrition: 45% vs. 40% | |
| Yapici et al. (2011) | Design: RCT<br>Setting: Postop, cardiac<br>Country: Turkey<br>Funding: Unclear | Randomized N: 72<br>Analyzed N: 72<br>Intervention 1 (N=38): Dexmedetomidine IV 0.3-0.7 µg/kg/hour<br>Intervention 2 (N=34): Midazolam 0.05-0.2 mg/kg/hour<br>Duration: MV<br>Follow-up (days): Delirium assessed daily | Inclusion: Patients undergoing elective CABG valve replacement, or both who had failed at least 1 extubating attempt<br>Exclusion: Patients who experienced postop coma or death | Mean (SD) age: 59.97 (9.88)<br>Female %: 63<br>Race %: NR<br>Delirium %: 100<br>Dementia %: NR<br>Failed extubation: 100<br>Postop %: 100 cardiac surgery<br>Cancer %: 0 | Main outcomes: At postop hour 60, fewer patients given dexmedetomidine to assist with weaning off of MV had delirium compared with patients given midazolam (2.7% vs. 21%, p<0.05).<br>Attrition: NR | Moderate |

*Abbreviations.* CABG=coronary artery bypass graf; DRS=Delirium Rating Scale; IM=intramuscular injection; IV=intravenous; MD=mean difference; MV=medical ventilation; N=number; NR=not reported; postop=post-operative; RASS=Richmond Agitation Sedation Scale; RCT=randomized controlled trial; SD=standard deviation.

3376 *Antipsychotics*

3377 In Surgical Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Atalan et al. (2013) | Design: RCT<br>Setting: Postop, cardiac<br>Country: Turkey<br>Funding: Unclear | Randomized N: 53<br>Analyzed N: 53<br>Intervention 1 (N=27): Morphine; 5mg morphine sulfate intramuscularly*<br>Intervention 2 (N=26): Haloperidol 5mg intramuscularly*<br>*Patients still agitated after administration of 20 mg/day of morphine/haloperidol also received 2.5 mg of lorazepam perorally, twice a day.<br>Duration: Postop, up to 10 days<br>Follow-up: 10, every 12 hours until discharge or 10 days | Inclusion: Cardiac surgery patients with hyperactive-type delirium<br>Exclusion: Patients with dementia, abnormal level of consciousness, Parkinson's disease, recent seizures, or hypoactive-type delirium patients | Mean (SD) age: 65.87 (9.03)<br>Female %: 26<br>Race %: NR<br>Delirium %: 3.0 vs. 2.9 (RASS score)<br>APACHE II score: 6.33 vs. 5.69<br>Dementia %: 0<br>Postop %: 100 cardiac surgeries<br>Cancer %: NR<br>Hepatic or renal impairment: NR<br>Alcohol use %: 19 vs. 4<br>Drug use %: 4 vs. 12<br>Medications taken at baseline %: psychotropic drugs 4 vs. 12 | Main outcomes: Target Richmond Agitation and Sedation Scale scores' percentages of the morphine group were statistically higher than those of the haloperidol group (p=0.042 and p=0.028, respectively). The number of patients requiring additive sedatives was significantly more in the haloperidol group when compared with the morphine group (p=0.011).<br>Attrition: NR | High |
| Bakri et al. (2015) | Design: RCT<br>Setting: Postop, mixed<br>Country: Saudi Arabia<br>Funding: None | Randomized N: 96<br>Analyzed N: 96<br>Intervention 1 (N=32): Dexmedetomidine continuous IV infusion of 1 µg/kg<br>Intervention 2 (N=32): Ondansetron continuous IV infusion 4 mg<br>Intervention 3 (N=32): Haloperidol continuous IV infusion 5 mg | Inclusion: Patients who screened positive for delirium within the first 3 days of ICU admission<br>Exclusion: Severely injured, deeply comatose, moribund patients, underlying neurological diseases, significant hearing loss, intracranial injury, or | Mean (SD) age: 31 (5.5)<br>Female %: 9<br>Race %: NR<br>Delirium %: 100 (required)<br>Functioning scale: NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR<br>Mean (SD) duration of surgery, minutes: 211 (34)<br>Mean (SEM) Injury Severity Score: 25.4 (2.9) | Main outcomes: At the end of the study, the number of remaining delirious patients was 3, 6, and 2 in dexmedetomidine, ondansetron, and haloperidol groups, respectively, without statistical significance. During the study period, no significant difference was found in the number of patients who needed "rescue haloperidol" between dexmedetomidine and haloperidol groups (5 vs. 3, p=0.7), | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | Duration: Twice a day for 3 consecutive days<br>Follow-up (days): POD 3 | ischemic/hemorrhagic stroke | Patients on MV on ICU admission %: 27 | but the difference was significantly higher in ondansetron and haloperidol groups (11 vs. 3, p=0.03). The mean total "rescue haloperidol" dose was significantly higher in ondansetron group than haloperidol group (p<0.001), but there was no difference between dexmedetomidine and haloperidol groups (p=0.07).<br>Attrition: NR | |
| Fukata et al. (2017) | Design: RCT<br>Setting: Postop, orthopedic and abdominal<br>Country: Japan<br>Funding: Government | Randomized N: 201<br>Analyzed N: 199<br>Intervention (N=101): Haloperidol IV 5 mg infusion<br>Control (N=100): No treatment<br>Intervention duration: Once daily for 5 days<br>Control duration: 5 days<br>Follow-up (days): 10 | Inclusion: >75 years undergoing elective abdominal or orthopedic surgery with general or spinal anesthesia; only patients with Neecham score 20 to 24 were treated.<br>Exclusion: Prior treatment with haloperidol for post-op delirium | Mean age: 81<br>Female %: 50<br>Race %: NR<br>Delirium %: 0<br>ADL (Berthel Index): 84<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: 62 | Main outcomes: The incidence of severe POD in the intervention group (18.2%) was significantly lower than that in the control group (32.0%) (p=0.02). No adverse events were noted in the haloperidol group.<br>Attrition: 2% vs. 0% | Moderate |
| Tagarakis et al. (2012) | Design: RCT<br>Setting: Postop, cardiac<br>Country: Greece<br>Funding: NR | Randomized N: 80<br>Analyzed N: 80<br>Intervention 1 (N=40): Ondansetron 8 mg IV<br>Intervention 2 (N=40): Haloperidol 5 mg IV<br>Duration: Once for 10 minutes<br>Follow-up (days): 1 | Inclusion: Developed delirium post on-pump heart surgery, using a 4-point scale (threshold for delirium NR)<br>Exclusion: History of severe psychiatric disease | Mean age: 71<br>Female %: 34<br>Race %: NR<br>Delirium %: NR<br>Baseline scale of function: NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: A statistically significant improvement was shown after the administration of both ondansetron (percentage improvement 61.29%, p<0.01) and haloperidol (percentage improvement 58.06%, p<0.01), but no between group differences were found.<br>Attrition: NR | High |

*Abbreviations.* ADL=activities of daily living; APACHE II=Acute Physiology and Chronic Health Evaluation II; ICU=intensive care unit; MV=medical ventilation; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; RASS=Richmond Agitation Sedation Scale; RCT=randomized controlled trial; SD=standard deviation; SEM=standard error of the mean.

## In Intensive Care Unit Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Boncyk et al. (2021) | Design: Retrospective cohort<br>Setting: ICU<br>Country: U.S.<br>Funding: Non-profit | Analyzed N: 7,879<br>Intervention 1 (N=3,770): Antipsychotics recipients (97.6% of all antipsychotics were haloperidol, olanzapine, and quetiapine)<br>Intervention 2 (N=4,109): Non-recipients<br>Duration: NR<br>Follow-up (days): NR | Inclusion: ≥18 years admitted to medical, surgical, trauma, or cardiovascular ICUs; with delirium based on CAM-ICU<br>Exclusion: Patients with home antipsychotic prescriptions | Median age: 62 vs. 61<br>Female %: 37 vs. 44.4<br>Race %: NR<br>Delirium %: NR<br>Baseline scale of function: NR<br>Dementia %: NR<br>Postop %: 17.9 vs. 19.0<br>Cancer %: NR | Main outcomes: Haloperidol and olanzapine were both independently associated with an increased odds of delirium the following day after adjusting for pre-specified covariates (OR 1.48, 95% CI 1.30 to 1.65, p<0.001 and OR 1.37, 95% CI 1.20 to 1.56, p=0.003, respectively). Haloperidol and olanzapine use were independently associated with an increased hazard of mortality (HR 1.46, 95% CI 1.10 to 1.93, p=0.01 and HR 1.67, 95% CI 1.14 to 2.45, p=0.01, respectively), while quetiapine use was associated with a decreased hazard of mortality (HR 0.58, 95% CI 0.40 to 0.84, p=0.01).<br>Attrition: NR | Moderate |
| Devlin et al. (2010) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: Mixed | Randomized N: 36<br>Analyzed N: 36<br>Intervention 1 (N=18): Quetiapine 50-200 mg, titrated by 50 mg; if needed, haloperidol was received within last 24 hours<br>Intervention 2 (N=18): Placebo | Inclusion: Adult ICU patients with delirium (ICDSC score>4), tolerating enteral nutrition, and without a complicating neurologic condition<br>Exclusion: Prior antipsychotic use within 30 days, not receiving enteral nutrition, primary neurological condition, advanced liver disease, alcohol withdrawal, inability to conduct ICDSC, no delirium, inability to obtain | Mean age: 63<br>Female %: 64<br>Race %: NR<br>Delirium %: 100<br>APACHE II: 16.8<br>Dementia %: NR<br>Postop %: 23<br>Cancer %: NR | Main outcomes: Quetiapine was associated with a shorter time to first resolution of delirium (1.0 days [IQR 0.5 to 3.0] vs.4.5 days [IQR 2.0 to 7.0], p=0.001) and a reduced duration of delirium (36 hours [IQR, 12 to 87] vs. 120 hours [IQR, 60 to 195], p=0.006). Incidence of QTc prolongation and extrapyramidal symptoms was similar between groups. More somnolence was observed with quetiapine (22% vs. 11%, p=0.66). | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | Duration: Every 12 hours, maximum of 10 days<br>Follow-up (days): 10 | informed consent, moribund, irreversible brain disease, current drug therapy w/agents affecting quetiapine concentrations, current drug therapy with Class Ia, Ic or III antiarrhythmics, or baseline QTc interval ≥500 msec | | Attrition: NR | |
| Fox et al. (2020) | Design: Cohort, reported as prospective but unclear from methods<br>Setting: ICU<br>Country: U.S.<br>Funding: None | Analyzed 40: Unclear<br>Intervention 1 (N=20): Quetiapine<br>Intervention 2 (N=20): Lurasidone<br>Duration:<br>Follow-up (days): | Inclusion: CAM-ICU positive<br>Exclusion: <72 hours in the ICU, <72 hours of study medication, received any other SGA during the study period, antipsychotic use prior to admission, alcohol withdrawal, pregnancy, or incarceration | Mean age: 66 vs. 67<br>Female %: 45 vs. 50<br>Race %:<br>White: 70 vs. 60<br>Black: 25 vs. 25<br>Delirium %: 100<br>APACHE II: 32 vs. 23.5<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR | Main outcomes: No statistical difference was found between the groups regarding time to delirium resolution: 3.2 days (2.4) in the quetiapine group vs. 3.4 days (1.1) in the lurasidone group. 65% (13/20) in the quetiapine group vs. 40% (8/20) in the lurasidone group had resolution of delirium (CAM-ICU) (p=0.204). Mean (SD) days of ICU LOS were 14.2 (5.6) in the quetiapine group vs. 12.1 (6.0) in the lurasidone group (p=0.273)<br>Attrition: NR | High |
| Girard et al. (2018) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: Government | Randomized N: 566<br>Analyzed N: 566<br>Intervention 1 (N=190): Ziprasidone IV: 5 mg if <70 years, 2.5 mg if >70 years every 12 hours; titrated to maximum of 40 mg/day<br>Intervention 2 (N=192): Haloperidol IV: 2.5 mg if <70 years, 1.25 mg if >70 years every 12 hours; titrated to maximum of 20 | Inclusion: Adults in a medical or surgical ICU, who were ventilated, on vasopressor drugs, or an intraaortic balloon pump diagnosed with delirium<br>Exclusion: Severe cognitive impairment or severe dementia | Mean age: 61<br>Female %: 43<br>Race %:<br>White: 83<br>Black/African American: 13<br>Asian: NR<br>Delirium %: 100<br>APACHE II: 29<br>Dementia %: 0 (Excluded) | Main outcomes: The median number of days alive without delirium or coma was 8.5 (95% CI 5.6 to 9.9) in the placebo group, 7.9 (95% CI 4.4 to 9.6) in the haloperidol group, and 8.7 (95% CI 5.9 to 10.0) in the ziprasidone group (p=0.26 for overall effect across trial groups). The use of haloperidol or ziprasidone, as compared with placebo, had no significant effect on the primary end point (ORs 0.88 [95% CI 0.64 to 1.21] and 1.04 [95% CI 0.73 to 1.48], | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | mg/day<br>Intervention 3 (N=184): Placebo<br>Duration: Every 12 hours for 14 days<br>Follow-up (days): 14 | | Postop %: 28<br>Cancer %: NR | respectively). There were no significant between-group differences with respect to the secondary end points or the frequency of extrapyramidal symptoms.<br>Attrition: 4% vs. 2% vs. 3% | |
| Liu et al. (2021) | Design: Retrospective cohort<br>Setting: ICU<br>Country: China<br>Funding: Government | Analyzed N: 263<br>Intervention 1 (N=118): Dexmedetomidine 0.1-0.7 mcg/kg/hour<br>Intervention 2 (N=145): Olanzapine 2.5-10 mg/day<br>Duration: NR<br>Follow-up (days): NR | Inclusion: ≥75 years diagnosed with delirium based on DSM-5 in the ICU and given either dexmedetomidine or olanzapine<br>Exclusion: Patients with endotracheal ventilation, underwent surgery during the hospital stay, advanced-stage tumors, brain tumors or recent brain trauma, underwent blood purification therapy during the use of olanzapine or dexmedetomidine, or with curative effects and adverse effects that could not be evaluated | Mean age: 80.05 vs. 78.99<br>Female %: 18.64 vs. 26.90<br>Race %: NR<br>Delirium %: 100<br>Mean APACHE II score: 18.91 vs. 18.59<br>Dementia %: 10.17 vs. 11.03<br>Postop %: NR<br>Cancer %: 9.32 vs. 8.97 | Main outcomes: RASS scores were significantly higher in the olanzapine group than in the dexmedetomidine group (mean [SD] -0.57 [0.88] vs. 0.88 [0.73], p<0.001).<br>No significant differences were found between the groups in mortality, long-term cognitive function, or recurrence of delirium (mortality 24.5% [29/118] vs. 21.4% [31/145], p=0.336; decrease in long-term cognitive function 23.7% [28/118] vs. 30.3% [44/145]; occurrence of delirium 27.12% [32/118] vs. 36.55% [53/145]). The hospital LOS was longer in the dexmedetomidine group than in the olanzapine group (mean [SD] 9.30 [4.90] vs. 8.83 [3.34], p<0.001).<br>Attrition: NR | Moderate |
| Skrobik et al. (2004) | Design: RCT<br>Setting: ICU<br>Country: Canada<br>Funding: Industry | Randomized N: 80<br>Analyzed N: 73<br>Intervention 1 (N=28 analyzed): Olanzapine starting dose 2.5-5 mg daily; mean 4.54 mg (range 2.5-13.5 mg) | Inclusion: Age 18-75 years, admitted to ICU, and diagnosed with delirium by ICU-DSC score ≥4<br>Exclusion: Pregnancy, antipsychotic medication use | Mean age: 65<br>Female %: 27<br>Race %: NR<br>Delirium %: 100<br>APACHE II: 12.7<br>Dementia %: NR | Main outcomes: Delirium Index decreased over time in both groups, as did the administered dose of benzodiazepines. Clinical improvement was similar in both treatment arms. No side effects were noted in the olanzapine group, whereas the use of | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | Intervention 2 (N=45 analyzed): Haloperidol starting dose 0.5-5 mg every 8 hours; mean 6.5 mg (range 1-28 mg) daily<br>Intervention 1 duration: Daily for 5 days<br>Intervention 2 duration: Three times daily for 5 days<br>Follow-up (days): 5 | within 10 days prior to hospital or ICU admission, or contraindications to either haloperidol or olanzapine | Postop %: NR<br>Cancer %: NR | haloperidol was associated with extrapyramidal side effects.<br>Overall attrition: 9% | |
| Smit et al. (2021) | Design: Retrospective cohort<br>Setting: ICU<br>Country: Netherlands<br>Funding: None | Analyzed N: 1,165<br>Intervention 1 (N=NR): Haloperidol only<br>Intervention 2 (N=NR): Clonidine only<br>Intervention 3 (N=NR): Haloperidol plus clonidine<br>Duration: NR<br>Follow-up (days): 24,906 observation days | Inclusion: Admitted to ICU and experienced an episode of delirium<br>Exclusion: ICU admission <24 hours, readmissions, transfers from another ICU, or admission with a primary acute neurological or neurosurgical disorder confounding the delirium diagnosis; or another condition that could hamper the assessment of delirium, such as intellectual disability and anoxic brain injury after cardiopulmonary resuscitation | Median age: 64<br>Female %: 34.5<br>Race %: NR<br>Delirium %: 100<br>Median APACHE IV score: 69<br>Dementia %: NR (excluded primary acute neurological or neurosurgical disorder)<br>Postop %: 58.2<br>Cancer %: NR | Main outcomes: The probability of delirium resolution was lower in delirious patients who received haloperidol (OR 0.47, 95% CI 0.39 to 0.57), clonidine (OR 0.78, 95% CI 0.63 to 0.97), or both (OR 0.45, 95% CI 0.36 to 0.56) compared to untreated delirious patients. Delirious patients who received haloperidol, clonidine, or both had generally longer delirium duration, more delirium and ventilation days, and spent more time in the ICU and in hospital than untreated delirious patients.<br>Attrition: NR | Moderate |
| Thom et al. (2018) | Design: Retrospective cohort<br>Setting: ICU<br>Country: U.S. | Analyzed N: 322<br>Intervention 1 (N=90): Early treatment*; <48 hours after diagnosis<br>Intervention 2 N=57): Late treatment*; >48 hours | Inclusion: At least 1 positive CAM-ICU score during ICU stay<br>Exclusion: Prior antipsychotic use, alcohol or substance withdrawal, missing CAM-ICU data, or developmental delay | Mean age: 63 vs. 58 vs. 62<br>Female %: 43 vs. 39 vs. 52<br>Race %: | Main outcomes: Adjusted HRs for delirium-coma resolution were 1.24 (95% CI 0.77 to 1.99) for the early treatment group and 1.91 (95% CI 0.98 to 3.73) for the late treatment group compared to the no treatment group. | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Funding: Nonprofit | Intervention 3 (N=175): No treatment<br>*Antipsychotics used were haloperidol, risperidone, quetiapine, olanzapine, aripiprazole, or ziprasidone.<br>Duration: NR<br>Follow-up (days): 10 | | White: 81 vs. 79 vs. 63<br>Black: 8 vs. 2 vs. 18<br>Delirium %: 100<br>APACHE II mean score: 24 vs. 25 vs. 24<br>Dementia: NR<br>Postop: NR<br>Cancer %: 10 vs. 11 vs. 7 | Mean (SD) hours alive without coma or delirium were 63.0 (86.7) for the early treatment group vs. 66.3 (91.8) for the late treatment group vs. 89.3 (106.8) for the no treatment group (adjusted p=0.705). Adjusted HR for mortality at 10 days among those with early treatment was 0.68 (95% CI 0.37 to 1.22) and 0.30 (95% CI 0.10 to 0.88) for those with late treatment compared to those with no treatment. Posthoc subgroup analysis excluding comatose patients found no differences in mortality.<br>Attrition: NR | |
| Weaver et al. (2017) | Design: Retrospective cohort<br>Setting: ICU<br>Country: U.S.<br>Funding: None from industry | Analyzed N: 255<br>Intervention 1 (N=69): Treated with antipsychotics*<br>*Antipsychotics used were quetiapine, olanzapine, risperidone, and haloperidol.<br>Intervention 2 (N=186): Not treated with antipsychotics<br>Duration: NR<br>Follow-up (days): NR | Inclusion: Positive delirium screen by ICDSC at least once during ICU stay<br>Exclusion: ICDSC not performed every 24 hours, history of dementia or Parkinson's disease, antipsychotic given for a reason other than delirium, "insufficient medical records," or benzodiazepines for alcohol withdrawal | Mean age: 57 vs. 61<br>Female %: 42 vs. 47<br>Race: NR<br>Delirium %: 100<br>SAPS III: mean 46 vs. 47<br>Dementia: NR<br>Postop: NR<br>Cancer: NR | Main outcomes: Time to resolution of delirium was longer in the antipsychotics group (median 36.0 vs. 13.6, p<0.001) and ICU LOS was also longer (median 5.7 days vs. 3.8 days, p=0.005). There was no difference in mortality (17.4% [12/69] vs. 18.3% [34/185], p=0.870).<br>Attrition: NR | Moderate |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; APACHE IV=Acute Physiology and Chronic Health Evaluation IV; CAM-ICU=Confusion Assessment Method for the ICU; CI=confidence interval; DSM-5=Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; HR=hazard ratio; ICDSC=Intensive Care Delirium Screening Checklist; ICU=intensive care unit; ICU-DSC=ICU Delirium Screening Checklist; IQR=interquartile range; IV=intravenous; LOS=length of stay; N=number; NR=not reported; OR=odds ratio; postop=post-operative; RASS=Richmond Agitation Sedation Scale; RCT=randomized controlled trial; SAPS III=Simplified Acute Physiology Score III; SD=standard deviation.

3385 In General Inpatient Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Breitbart et al. (1996) | Design: RCT<br>Setting: Inpatient<br>Country: U.S.<br>Funding: Government | Randomized N: 30<br>Analyzed N: 30<br>Intervention 1 (N=11): Haloperidol loading dose oral 0.25-5 mg, followed by maintenance dose of 1.2 the initial dose every 12 hours (IM dosing also allowed)<br>Intervention 2 (N=13): Chlorpromazine loading dose oral 10-200 mg followed by maintenance dose of 1/2 loading dose every 12 hours. (IM dosing allowed)<br>Intervention 3 (N=6): Lorazepam loading dose oral 0.5-24 mg followed by maintenance dose of 1/2 loading dose every 12 hours. (IM dosing allowed)<br>Duration: Every 12 hours for 6 days<br>Follow-up (days): 6 | Inclusion: Inpatients with AIDS with delirium<br>Exclusion: Patients with dementia or near end of life (within 24 hours) | Mean age: 39<br>Female %: 23<br>Race %:<br>Caucasian: 13<br>Black/African American: 57<br>Asian: 3<br>Delirium %: 100<br>Karnovsky: 52.3<br>Dementia %: 0 (excluded)<br>Postop %: 0<br>Cancer %: NR | Main outcomes: Treatment with either haloperidol or chlorpromazine resulted in significant improvements in symptoms of delirium as measured by DRS. No improvement was seen with lorazepam. Treatment with haloperidol and chlorpromazine resulted in very low prevalence of extrapyramidal side effects.<br>All 6 patients receiving lorazepam developed treatment-limiting adverse effects.<br>Attrition: NR vs. NR vs. 100% | Moderate |
| Boettger et al. (2011) | Design: Prospective cohort | Analyzed N: 64<br>Intervention 1 (N=32): Haloperidol<br>Intervention 2 (N=32): Risperidone | Inclusion: Patients meeting DSM-IV-TR criteria for delirium | Mean age: 62 vs. 67.5<br>Female %: 37.5 vs. 37.5<br>Race %: NR<br>Delirium %: 100<br>KPS: 22 vs. 24 | Main outcomes: Delirium resolution (MDAS <10) at 4-7 days was 68.8% (22/32) in the haloperidol group vs. 84.4% (27/32) in the risperidone group (p=NS). Delirium severity | High |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Setting: Inpatient<br>Country: U.S.<br>Funding: Not industry sponsored | Duration: NR<br>Follow-up (days): 7 | Exclusion: Severe agitation, critical medical condition, and imminent death | Dementia %: NR<br>Postop %: NR<br>Cancer %: 100 | (MDAS) at 4-7 days was: mean 7.8 (SD 5.6) vs. 7.5 (SD 4.5).<br>Parkinsonism was found in 21.9% (7/32) vs. 3.1% (1/32) and dystonia in 9.4% (3/32) vs. 3.1% (1/32).<br>Attrition: NR | |
| Boettger et al. (2015) | Design: Retrospective cohort<br>Setting: Inpatient<br>Country: U.S.<br>Funding: Government | Analyzed N: 84<br>Intervention 1 (N=21): Haloperidol<br>Intervention 2 (N=21): Risperidone<br>Intervention 3 (N=21): Aripiprazole<br>Intervention 4 (N=21): Olanzapine<br>Duration: NR<br>Follow-up (days): 7 | Inclusion: Patients meeting DSM-IV-TR criteria for delirium<br>Exclusion: Severe agitation | Mean age: 64 vs. 67 vs. 70 vs. 66<br>Female %: 62 vs. 52 vs. 52 vs. 62<br>Race: NR<br>Delirium %: 100<br>Baseline scale of function: NR<br>Dementia %: 24 vs. 24 vs. 29 vs. 29<br>Postop %: NR<br>Cancer %: 100 | Main outcomes: Delirium resolution after 4-7 days (MDAS ≤10) was 76.2% (16/21) vs. 85.7% (18/21) vs. 76.2% (16/21) vs. 61.9% (13/21) (p=0.418).<br>Main outcomes: Mean (SD) delirium severity after 4-7 days (MDAS) was 6.8 (4.8) vs. 7.1 (5.1) vs. 8.3 (8.3) vs. 11.7 (8.8) (p=0.249). Olanzapine most frequently caused side effects, followed by haloperidol, aripiprazole, and risperidone.<br>Dystonia occurred in 9.5% (2/21) in the haloperidol group vs. 0% in the other groups (p=0.1). Parkinsonism occurred in 19% (4/21) vs. 4.8% (1/21) vs. 0% (0/21) vs. 0% (0/21) (p=0.012).<br>Attrition: NR | Moderate |
| Grover et al. (2011) | Design: RCT<br>Setting: Inpatient<br>Country: India<br>Funding: Unclear | Randomized N: 74<br>Analyzed N: 64<br>Intervention 1 (N=26): Olanzapine IV 1.25-20 mg daily<br>Intervention 2 (N=22): Risperidone IV 0.25-4 mg daily | Inclusion: Adult inpatients (medical or surgical) diagnosed with delirium<br>Exclusion: Dementia, alcohol or benzodiazepine withdrawal, terminal illness, or psychotic or mood disorders | Mean age: 45<br>Female %: 30<br>Race %: NR<br>Delirium %: 100<br>Function: NR<br>Dementia %: 0 (excluded)<br>Postop %: NR<br>Cancer %: NR | Main outcomes: All groups had a significant reduction in DRS-R98 severity scores and a significant improvement in MMSE scores over the period of 6 days, with no significant differences between groups. 4 patients in the haloperidol group, 6 subjects in the risperidone | High |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Intervention 3 (N=26): Haloperidol IV 0.25- 10 mg daily<br>Duration: Once a day (> once per day if agitated); duration as per clinical judgement<br>Follow-up (days): 6 | | | group, and 2 subjects in the olanzapine group experienced some side effects.<br>Attrition: 12% vs. 5% vs. 23% | |
| Grover et al. (2016) | Design: RCT<br>Setting: Inpatient<br>Country: India<br>Funding: NR | Randomized N: 70<br>Analyzed N: 63<br>Intervention 1 (N=35): Quetiapine 12.5-75 mg per day<br>Intervention 2 (N=35): Haloperidol 0.25-1.0 mg per day, 2-3 times<br>Duration: Daily for 6 days<br>Follow-up (days): 6 | Inclusion: >18 years, DSM-IV criteria for delirium, and referred to consultation liaison psychiatry service<br>Exclusion: Dementia | Mean age: 46<br>Female %: 78<br>Race %: NR<br>Delirium %: 100<br>Baseline scale of function: NR<br>Dementia %: 0<br>Postop %: NR<br>Cancer %: NR | Main outcomes: At the end of the trial, 68.75% and 67.74% of subjects in the haloperidol and quetiapine group respectively had mean DRS-R-98 scores below 10. By 6$^{th}$ day, 12 (37.5%) patients in haloperidol group and 9 (29.03%) patients in the quetiapine group had a score of "o" with no significant difference between the groups (p=0.47).<br>Attrition: 11% vs. 9% | High |
| Han and Kim (2004) | Design: RCT<br>Setting: Inpatient<br>Country: South Korea<br>Funding: NR | Randomized N: 28<br>Analyzed N: 24<br>Intervention 1 (N=14): Risperidone 0.5-2.0 mg orally<br>Intervention 2 (N=14): Haloperidol 1.0-3.0 mg orally<br>Duration: Daily for 7 days<br>Follow-up (days): 7 | Inclusion: Patients referred to consulting psychiatry division, with score of at least 13 on DRS<br>Exclusion: Dementia | Mean age: 66<br>Female %: 46<br>Race %: NR<br>Delirium %: 100<br>Baseline scale of function: NR<br>Dementia %: 0 (excluded)<br>Postop %: NR<br>Cancer %: 8 | Main outcomes: No significant differences were found between the groups in MDAS score over 7 days. 1 patient in the haloperidol group experienced mild akathisia, but no other patients reported clinically significant side effects.<br>Attrition: 6% vs. 6% | Moderate |
| Hatta et al. (2014a) | Design: Prospective cohort | Analyzed N: 2,453<br>Intervention 1 (N=835): Risperidone | Inclusion: Patients who developed delirium during their admission due to | Mean age, years: 73.5 vs. 74 vs. 67 vs. 70 vs. 72 | Main outcomes: With respect to the duration of delirium, 54% of patients were within 1 week, whereas 25% of | High |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | Setting: Inpatient<br>Country: Japan<br>Funding: Government | Intervention 2 (N=779): Quetiapine<br>Intervention 3 (N=87): Olanzapine<br>Intervention 4 (N=61): Aripiprazole<br>Intervention 5 (N=480): Haloperidol<br>Intervention 6: (N=88): Perospirone<br>Intervention 7: (N=123): Others<br>Duration: NR<br>Follow-up (days): NR | acute medical illness or surgery, and who received antipsychotics for delirium<br>Exclusion: NR | Female %: 35 vs. 39 vs. 39 vs. 52 vs. 33<br>Race %: 100 Asian<br>Delirium %: 100<br>Baseline scale of function: NR<br>Dementia %: 31 vs. 34 vs. 20 vs. 25 vs. 20<br>Postop %: NR<br>Cancer %: NR | patients were more than 2 weeks. The rate of delirium within 1 week was significantly higher in patients with olanzapine than in other patients (67% vs. 54%, p=0.025). 16% of patients died. The rate was significantly higher in patients with haloperidol than in other patients (29% vs. 13%, p<0.0001). A total of 22 serious adverse events (0.9%) were reported, and there was no significant difference between the groups (p=0.40).<br>Attrition: NR | |
| Jain et al. (2017) | Design: RCT<br>Setting: Inpatient<br>Country: India<br>Funding: None | Randomized N: 132<br>Analyzed N: 100<br>Intervention 1 (N=66): Olanzapine 2.5-10 mg daily orally<br>Intervention 2 (N=66): Haloperidol 1-4 mg daily orally<br>Duration: Until resolution<br>Follow-up (days): Until resolution | Inclusion: ≥18 years old admitted to ED with delirium diagnosed per DSM-IV criteria<br>Exclusion: Dementia | Mean age: NR<br>Female %: NR<br>Race %: NR<br>Delirium %: 100<br>Baseline scale of function: NR<br>Dementia %: 0 (excluded)<br>Postop %: NR<br>Cancer %: NR | Main outcomes: Mean duration of treatment in olanzapine group and haloperidol group was 3.57 days and 3.37 days (p=NS). Mean MDAS scores at endpoint were 8.43 and 8.00 with olanzapine and haloperidol (p=0.765). 5 patients experienced drug-related mild side effects.<br>Attrition: 29% vs. 29% | High |
| Kim et al. (2010) | Design: RCT<br>Setting: Inpatient<br>Country: South Korea<br>Funding: NR | Randomized N: 32<br>Analyzed N: 32<br>Intervention 1 (N=15): Olanzapine 21.25-7.5 mg daily orally<br>Intervention 2 (N=17): | Inclusion: Patients with delirium (DSM-IV criteria)<br>Exclusion: Dementia | Mean age: 67<br>Female %: 44<br>Race %: NR<br>Delirium %: 100<br>Baseline scale of function: NR<br>Dementia %: NR | Main outcomes: Risperidone and olanzapine were equally effective in reducing delirium symptoms. Response also did not differ significantly (risperidone group: 64.7% vs. olanzapine group: 73.3%). There was no significant difference in | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | Risperidone 0.25-2 mg daily orally<br>Duration: Daily for 7 days<br>Follow-up (days): 7 | | Postop %: NR<br>Cancer %: 72 | the safety profiles, including extrapyramidal side effects.<br>Attrition: 47% vs. 29% | |
| Lee et al. (2005) | Design: RCT<br>Setting: Inpatient<br>Country: South Korea<br>Funding: Unclear | Randomized N: 40<br>Analyzed N: 31<br>Intervention 1 (N=20): Amisulpride; mean initial dose 96.9 (SD 12.5) mg/day and mean daily dose of 156.4 (SD 97.5) (range 50-800) mg/day<br>Intervention 2 (N=20): Quetiapine; mean initial dose of 63.3 (SD 22.9) mg/day and mean daily dose of 113 (SD 85.5) (range 50-300) mg/day<br>Duration: During hospitalization; treatment was terminated when the CGI had reached 2 or less. Patients were monitored daily by the psychiatrist until the patient went into remission or was discharged.<br>Follow-up (days): Until remission or discharge | Inclusion: Patients with delirium (met DSM-IV criteria for delirium)<br>Exclusion: Patients with psychiatric disorder or taking antipsychotics likely to resolve spontaneously (e.g., those who immediately recovered after a major operation) | Mean (SD) age: 62 (16)<br>Female %: 35<br>Race %: NR<br>Delirium %: 100<br>DRS-R-98: 10.5 (4.1) vs. 10.1 (4.1)<br>CGI-S: Score NR, "no significant group differences"<br>Dementia %: 0 (those with a previous history of psychiatric disorder, who had been taking antipsychotics, and who were likely to resolve spontaneously [e.g. those who immediately recovered after a major operation] were excluded from this study)<br>Postop %: NR<br>Cancer %: NR<br>Hepatic or renal impairment: NR<br>Alcohol use: NR<br>Drug use: NR<br>Mean number of medications taken at baseline: NR | Main outcomes: There was no significant difference in the baseline DRS-R-98 and CGI scores. After treatment, DRS-R-98 scores were significantly decreased from the baseline in both treatment groups ($p<0.001$) without group difference.<br>Attrition: 20% vs. 25% | High |
| Liu et al. (2004) | Design: Retrospective cohort | Analyzed N: 77<br>Intervention 1 (N=41): Risperidone | Inclusion: DSM-IV criteria for diagnosis<br>Exclusion: NR | Mean age: 68 vs. 50<br>Female %: NR<br>Race %: NR | Main outcomes: 95% (39/41) of the risperidone group recovered from delirium vs. 100% of the haloperidol | High |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Setting: Inpatient<br>Country: Northern Taiwan<br>Funding: Industry and government | Intervention 2 (N=36): Haloperidol<br>Intervention 1 duration: 3-18 days (average 7.2 ± 3.7 day)<br>Intervention 2 duration: 2-19 days (average 7.9 ± 4.7 days)<br>Follow-up (days): NR | | Delirium %: 100<br>Baseline scale of function: NR<br>Dementia %: NR<br>Postop %: ≥8 (delirium with Postop etiology)<br>Cancer %: NR | group. Mean delirium severity after treatment (hyperactive) was 0.20 (SD 1.26) in the risperidone group vs. all recovered in the haloperidol group (p=NS). Mean delirium severity after treatment (hypoactive) was 0.40 (SD 0.96) in the risperidone group vs. 0.06 (SD 0.33) in the haloperidol group (p=NS).<br>Attrition: NR | |
| Maneeton et al. (2013) | Design: RCT<br>Setting: Inpatient<br>Country: Thailand<br>Funding: University | Randomized N: 52<br>Analyzed N: 52<br>Intervention 1 (N=24): Quetiapine 25-100 mg<br>Intervention 2 (N=28): Haloperidol 0.5-2.0 mg, evaluated for continued use after 24 hours<br>Duration: Daily<br>Follow-up (days): 7 | Inclusion: Age 18-75 years meeting DSM-IV criteria for delirium (confirmed by CAM) and who had been referred to a consultation–liaison service evaluation<br>Exclusion: Substance-induced delirium, known allergy or intolerance to quetiapine or haloperidol, pregnancy or breast feeding, being on an antipsychotic medication, and renal or hepatic failure | Mean age: 57<br>Female %: 33<br>Race %: NR<br>DRS-R-98: 29.4<br>Function: NR<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: 39 | Main outcomes: Means of the DRS-R-98 severity scores were not significantly different between the quetiapine and haloperidol groups (−22.9 [SD 6.9] vs. −21.7 [SD 6.7], p=0.59).<br>Attrition: 46% vs. 21% | Moderate |
| Tahir et al. (2010) | Design: RCT<br>Setting: Inpatient<br>Country: U.K.<br>Funding: Industry | Randomized N: 42<br>Analyzed N: 29<br>Intervention 1 (N=21): Quetiapine 25-175 mg orally<br>Intervention 2 (N=21): Placebo | Inclusion: Patients with delirium per DSM-IV criteria and DSR-R-98 score of ≥15<br>Exclusion: Major pre-existing cognitive deficits, alcohol withdrawal, pre-existing psychosis, substance dependence, | Mean age: 84<br>Female %: 71<br>Race %: NR<br>Delirium %: 100<br>Baseline scale of function: NR<br>Dementia %: NR<br>Postop %: 45<br>Cancer %: NR | Main outcomes: The quetiapine group recovered 82.7% faster (SE 37.1%, p=0.026) than the placebo group in terms of DRS-R-98 severity score.<br>Attrition: 24% vs. 38% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Duration: Daily for 10 days<br>Follow-up (days): 30 | inability to comply with the constraints of the trial, or use of medication that interacted with quetiapine | | | |
| van der Vorst et al. (2020) | Design: RCT<br>Setting: Inpatient<br>Country: The Netherlands<br>Funding: Government | Randomized N: 100<br>Analyzed N: 98<br>Intervention 1 (N=50): Olanzapine 2.5-20 mg orally or intramuscularly<br>Intervention 2 (N=50): Haloperidol 0.5-20 mg orally or subcutaneously<br>Duration: Daily for 7 days<br>Follow-up (days): 7 | Inclusion: >18 years with advanced cancer and with delirium diagnosed by DOS score 13 or > and confirmed with DRS-R-98 score of 17.75 or ><br>Exclusion: Dementia | Mean age: 69<br>Female %: 31<br>Race %: NR<br>Delirium %: 100<br>Baseline scale of function: NR<br>Dementia %: 0 (excluded)<br>Postop %: NR<br>Cancer %: 100 | Main outcomes: Delirium response rate was 45% (95% CI 31 to 59) for olanzapine and 57% (95% CI 43 to 71) for haloperidol (delirium response change rate −12%, OR 0.61, 95% CI 0.2 to 1.4, p=0.23). Grade ≥3 treatment-related adverse events occurred in 5 patients (10.2%) and 10 patients (20.4%) in the olanzapine and haloperidol arms, respectively.<br>Attrition: 20% vs. 18% | Moderate |
| Yoon et al. (2013) | Design: Prospective cohort<br>Setting: Inpatient<br>Country: South Korea<br>Funding: NR | Analyzed N: 80<br>Intervention 1 (N=23): Haloperidol 0.5-10 mg<br>Intervention 2 (N=21): Risperidone 0.25-4 mg<br>Intervention 3 (N=18): Olanzapine 1-20 mg<br>Intervention 4 (N=18): Quetiapine 25-200 mg<br>Duration: Average 4.9 ± 1.5 days<br>Follow-up (days): 6 | Inclusion: Age >50 years meeting DSM-IV-TR criteria for delirium<br>Exclusion: Dementia or comorbid psychiatric disorder, terminal illness, prolonged QTc, hearing loss, neuroleptic malignant syndrome, or prior use of antipsychotics | Mean age: 74 vs. 70 vs. 69.5 vs. 73<br>Female %: 48 vs. 62 vs. 56 vs. 56<br>Race %: NR<br>Delirium %: 100<br>Baseline scale of function: NR<br>Dementia %: 0 (excluded)<br>Postop %: NR<br>Cancer %: 26 vs. 4.7 vs. 17 vs. 11 | Main outcomes: A significant serial decrease in the mean DRS-K severity score was observed in all groups: on day 6, mean (SD): 7.7 (5.4) vs. 8.3 (7.1) vs. 8.1 (5.5) vs. 6.5 (4.0) (p=0.779). There was no significant difference in the treatment response rate (≥50% decrease in DRS-K severity score) among the 4 groups: 65.2% (15/23) vs. 66.6% (14/21) vs. 66.6% (12/18) vs. 72.2% (13/18) (p=0.969).<br>Attrition: 39% vs. 33% vs. 28% vs. 33% | High |

*Abbreviations.* CAM=Confusion Assessment Method; CGI=Clinical global impression; CGI-S=Clinical global impression-Severity; CI=confidence interval; DOS=Delirium Observation Scale; DRS=Delirium Rating Scale; DRS-K=Delirium Rating Scale-Korean Version; DRS-R-98=Delirium Rating Scale-Revised-1998; DSM-IV= Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV-TR= Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; ED=emergency department; IM=intramuscular injection; IV=intravenous; KPS=Karnofsky Performance Status;

MDAS Memorial Delirium Assessment Scale; MMSE=Mini-Mental State Examination; N=number; NS=not significant; NR=not reported; OR=odds ratio; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation; SE=standard error.

## In Palliative Care Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Agar et al. (2017) | Design: RCT<br>Setting: Palliative care<br>Country: Australia<br>Funding: Government | Randomized N: 249<br>Analyzed N: 247<br>Intervention 1 (N=82): Risperidone oral solution; for ≤65 years, 1 mg loading dose, 0.5 mg every 12 hours, and titrated to max of 4 mg/day; for >65 years, 0.5 mg loading dose, 0.25 mg every 12 hours, and titrated to max 2 mg/day<br>Intervention 2 (N=81): Haloperidol oral solution; for ≤65 years 1 mg loading dose, 0.5 mg every 12 hours, and titrated to max of 4 mg/day; for >65 years, 0.5 mg loading dose, 0.25 mg every 12 hours, and titrated to max 2 mg/day<br>Intervention 3 (N=86): Placebo solution every 12 hours | Inclusion: Adults in hospice or palliative care with advanced, progressive disease, diagnosed with delirium, MDAS of 7 or more, and target symptoms of distress<br>Exclusion: Delirium due to substance withdrawal, history of neuroleptic malignant syndrome, regular use of antipsychotic drugs within 48 hours, previous adverse reaction to antipsychotic drugs, extrapyramidal disorders, prolonged QT interval, clinician-predicted survival of 7 days or fewer, cerebrovascular accident or seizure in the prior 30 days, and pregnancy or breastfeeding | Mean age: 75<br>Female %: 34<br>Race %: NR<br>Delirium %: 100<br>Function: Australian Karnovsky: 43<br>Dementia %: NR<br>Postop %: 0<br>Cancer %: 88 | Main outcomes: At 3 days, both risperidone and haloperidol patients had significantly higher delirium symptom scores than placebo patients (risperidone mean 0.48 units higher, 95% CI 0.09 to 0.86, p=0.02; and haloperidol 0.24, 95% CI 0.06 to 0.42, p=0.009). Both active arms had more extrapyramidal effects (risperidone 0.73, 95% CI 0.09 to 1.37, p=0.03; and haloperidol 0.79, 95% CI 0.17 to 1.41, p=0.01). Participants in the placebo group had better overall survival than those receiving haloperidol (HR 1.73, 95% CI 1.20 to 2.50, p=0.003), but this was not significant for placebo vs. risperidone (HR 1.29, 95% CI 0.91 to 1.84, p=0.14).<br>Attrition: 43% vs. 25% vs. 26% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Duration: Every 12 hours for 72 hours<br>Follow-up (days): 3 | | | | |
| Breitbart et al. (1996) | Design: RCT<br>Setting: Inpatient<br>Country: U.S.<br>Funding: Government | Randomized N: 30<br>Analyzed N: 30<br>Intervention 1 (N=11): Haloperidol loading dose oral 0.25-5 mg, followed by maintenance dose of 1.2 the initial dose every 12 hours (IM dosing also allowed)<br>Intervention 2 (N=13): Chlorpromazine loading dose oral 10-200 mg followed by maintenance dose of 1/2 loading dose every 12 hours. (IM dosing allowed)<br>Intervention 3 (N=6): Lorazepam loading dose oral 0.5-24 mg followed by maintenance dose of 1/2 loading dose every 12 hours. (IM dosing allowed)<br>Duration: Every 12 hours for 6 days<br>Follow-up (days): 6 | Inclusion: Inpatients with AIDS with delirium<br>Exclusion: Patients with dementia or near end of life (within 24 hours) | Mean age: 39<br>Female %: 23<br>Race %:<br>Caucasian: 13<br>Black/African American: 57<br>Asian: 3<br>Delirium %: 100<br>Karnovsky: 52.3<br>Dementia %: 0 (excluded)<br>Postop %: 0<br>Cancer %: NR | Main outcomes: Treatment with either haloperidol or chlorpromazine resulted in significant improvements in symptoms of delirium as measured by DRS. No improvement was seen with lorazepam. Treatment with haloperidol and chlorpromazine resulted in very low prevalence of extrapyramidal side effects. All 6 patients receiving lorazepam developed treatment-limiting adverse effects.<br>Attrition: NR vs. NR vs. 100% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Hui et al. (2017) | Design: RCT<br>Setting: Palliative care<br>Country: U.S.<br>Funding: Government | Randomized N: 90<br>Analyzed N: 58<br>Intervention 1 (N=47): Lorazepam 3 mg plus haloperidol 2 mg every 4 hours IV; additional 2 mg as needed for agitation<br>Intervention 2 (N=43): Placebo plus haloperidol 2 mg every 4 hours IV; additional 2 mg as needed for agitation<br>Duration: Lorazepam or placebo infused intravenously over 1.5 minutes<br>Follow-up (days): 8 hours | Inclusion: Adults with advanced cancer in palliative care with diagnosis of delirium<br>Exclusion: Patients with dementia | Mean age: 65<br>Female %: 47<br>Race %:<br>Caucasian: 76<br>Black/African American: 24<br>Asian: NR<br>Delirium %: 100<br>Karnovsky: 10%=21%, 20%=47%, 30%=24%, 40%=9%<br>Dementia %: 0 (Excluded)<br>Postop %: 0<br>Cancer %: 100 | Main outcomes: Lorazepam plus haloperidol resulted in a significantly greater reduction of RASS score at 8 hours (−4.1 points) than placebo plus haloperidol (−2.3 points) (MD −1.9 points, 95% CI −2.8 to −0.9, p<0.001). The lorazepam plus haloperidol group required less median rescue neuroleptics (2.0 mg) than the placebo plus haloperidol group (4.0 mg) (MD −1.0 mg, 95% CI −2.0 to 0, p=0.009). No significant between-group differences were found in delirium-related distress and survival. The most common adverse effect was hypokinesia (3 patients in the lorazepam plus haloperidol group [19%] and 4 patients in the placebo plus haloperidol group [27%]).<br>Attrition: 45% vs. 40% | High |
| Lin et al. (2008) | Design: RCT<br>Setting: Palliative care<br>Country: Taiwan<br>Funding: NR | Randomized N: 30<br>Analyzed N: 12<br>Intervention 1 (N=16): Olanzapine 5 mg to max 15 mg<br>Intervention 2 (N=14): Haloperidol 5 mg to max 15 mg per day, evaluated | Inclusion: Patients with advanced cancer who were being treating in a hospice and palliative care center and had been referred to a consultation-liaison psychiatry service for evaluation of mental status change and met DSM-IV criteria for delirium | Mean age: 64<br>Female %: 57<br>Race %: NR<br>DRS-C: 17. 07<br>Function: NR<br>Dementia %: NR<br>Postop %: NR | Main outcomes: The results showed that delirium improved in both groups but no statistic difference comparing both groups.<br>Attrition: NR | High |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | for continued use after 24 hours<br>Duration: Daily<br>Follow-up (days): 7 | Exclusion: Past histories of psychiatric disorders, in a coma, unable to swallow oral medication, and treated with neuroleptic agents within 4 weeks prior to the enrollment | Advanced Cancer %: 100 | | |

*Abbreviations.* CI=confidence interval; DRS=Delirium Rating Scale; DRS-C=Delirium Rating Scale-Chinese Version; DSM-IV= Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; HR=hazard ratio; IM=intramuscular injection; IV=intravenous; MD=mean difference; MDAS Memorial Delirium Assessment Scale; N=number; NR=not reported; postop=post-operative; RASS=Richmond Agitation Sedation Scale; RCT=randomized controlled trial.

*Melatonin/Ramelteon*

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Lange et al. (2021) | Design: RCT<br>Setting: Inpatient<br>Country: The Netherlands<br>Funding: Government | Randomized N: 29<br>Analyzed N: 28<br>Intervention 1 (N=14): Melatonin 5 mg orally<br>Intervention 2 (N=15): Placebo<br>Duration: Nightly for 5 nights<br>Follow-up (days): 7 | Inclusion: ≥70 years inpatients with CAM positive hyperactive or mixed delirium<br>Exclusion: Had exclusively hypoactive delirium or expected prognosis or planned further admission to hospital <7 days | Mean (SD) age: 85.6 (5.5)<br>Female %: 53.6<br>Race %: NR<br>Delirium %: 100<br>Mean (SD) Charlson Comorbidity Scale: 6.1 (1.6)<br>History of Dementia %: 50<br>IQCODE ≥3.45 %: 57.1<br>IQCODE ≥3 and/or history %: 75<br>Mean (SD) MMSE: 10.6 (7.4)<br>Postop %: NR<br>Cancer %: NR<br>Use of anticholinergics %: 7.1<br>Use of opioids %: 21.4<br>Use of antipsychotics %: 10.7 | Main outcomes: No adverse effects occurred due to melatonin. In the treatment group, the mean change in MDAS from baseline during treatment period was 2.5±5.0 points vs. 2.1±4.1 points in the placebo group, a non-significant difference. A power calculation accounting for drop-out (31.0%), suggests 120 participants would be required to demonstrate with 90% power that melatonin 5mg reduces the severity of delirium by 3 points or more on MDAS.<br>Attrition at follow-up: 29% vs. 33% | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Thom et al. (2019) | Design: Retrospective cohort<br>Setting: ICU<br>Country: U.S.<br>Funding: | Analyzed N: 322<br>Intervention 1 (N=77): Ramelteon, ≥1 dose<br>Intervention 2 (N=245): Placebo<br>Duration: NR<br>Follow-up (days): 10 | Inclusion: ≥1 positive CAM-ICU score during ICU admission<br>Exclusion: Antipsychotic treatment before admission, CAM-ICU scores not recorded every 8 hours, alcohol or substance withdrawal, or developmental delay | Mean age: 64 vs. 61<br>Female %: 49 vs. 47<br>Race %:<br>White: 81 vs. 68<br>Black, 5 vs. 15<br>Other, 14 vs. 17<br>Delirium %: 100<br>APACHE II, mean: 24.5 vs. 24<br>Dementia: NR<br>Postop: NR<br>Cancer %: 10 vs. 8 | Main outcomes: Adjusted HR delirium-coma resolution for ramelteon was 1.05 (95% CI 0.54 to 2.01). Median hours alive without delirium or coma did not differ between ramelteon and placebo groups: 0 (IQR 0 to 196) vs. 46 (IQR 0 to 168) (adjusted p-value 0.105).<br>Attrition: NR | Moderate |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; CAM=Confusion Assessment Method; CAM-ICU=Confusion Assessment Method for the ICU; CI=confidence interval; HR=hazard ratio; ICU=intensive care unit; IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly; IQR=interquartile range; MDAS Memorial Delirium Assessment Scale; MMSE=Mini-Mental State Examination; N=number; NR=not reported; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

3399 ## Appendix E. Risk of Bias Ratings for Individual Studies Supporting Guideline Statements

| Citation | Randomization/allocation concealment adequate? | Groups similar at baseline? | Patients/provider/outcome assessors masked? | ITT analysis? | Acceptable levels of overall/differential attrition? | Risk of bias |
|---|---|---|---|---|---|---|
| Abbasi et al. 2018 | Yes; Yes | No | Yes; Yes; Unclear | No | No; Yes | Moderate |
| Abbasinia et al. 2021 | Yes; No | Yes | No; No; Unclear | Yes | Yes; Yes | Moderate |
| Abdelgalel 2016 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Abraham et al. 2021 | Unclear; NR | Yes | No; No; No | No | Yes; Yes | High |
| Agar et al. 2017 | Yes; Yes | Unclear | Yes; Yes; Yes | Yes | No; No | Moderate |
| Al Tmimi et al. 2020 | Yes; Unclear | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Al-Qadheeb et al. 2016 | Yes; Yes | Yes | Yes; Yes; Unclear | Yes | Yes; Yes | Low |
| Alvarez et al. 2017 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Arttawejkul et al. 2020 | Yes; NR | Yes | No; No; Yes | Yes | Yes; Yes | Moderate |
| Atalan et al. 2013 | Unclear; Unclear | No | NR; Yes; NR | Unclear | Yes; No | High |
| Avendano-Cespedes et al. 2016 | Yes; Yes | Yes | No; No; Yes | Yes | Yes; Yes | Moderate |
| Avidan et al. 2017 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Azuma et al. 2018 | Yes; Unclear | Unclear | NR; NR; NR | Yes | Yes; Yes | Moderate |
| Bakri et al. 2015 | Yes; Unclear | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Moderate |
| Beaussier et al. 2006 | Yes; Yes | Yes | Yes; Yes; Yes | Unclear | Yes; Yes | Low |
| Bellapart et al. 2020 | Unclear; Unclear | Yes | Yes; Yes; Yes | No | No; No | High |
| Bielza et al. 2020 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Boockvar et al. 2020 | Unclear/no; Unclear | No | No; No; Yes | Yes | Yes; Yes | High |
| Boustani et al. 2012 | Yes; Unclear | No | NR; NR; NR | Yes | Yes; Yes | Moderate |
| Breitbart et al. 1996 | Unclear; Yes | Unclear | Unclear; Unclear; Unclear | Yes | Yes; Yes | Moderate |
| Brown et al. 2019 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Browning et al. 2021 | Unclear; Unclear | No | No; No; No | Yes | Yes; Yes | High |
| Bruera et al. 2013 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |

| Citation | Randomization/allocation concealment adequate? | Groups similar at baseline? | Patients/provider/outcome assessors masked? | ITT analysis? | Acceptable levels of overall/differential attrition? | Risk of bias |
|---|---|---|---|---|---|---|
| Brummel et al. 2014 | Yes; Unclear | Yes | No; No; Yes | Yes | Yes; Yes | Moderate |
| Campbell et al. 2019 | Yes; Yes | Yes | No; No; Yes | Yes | Yes; Yes | Moderate |
| Caplan et al. 2006 | Yes; Yes | Yes | No; No; No | Yes | No; Yes | Moderate |
| Chan et al. 2013 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Chang et al. 2018 | Yes; Yes | Yes | Yes; No; No | Yes | Yes; Yes | Moderate |
| Chen 2020 | Yes; Unclear | Yes | Unclear; Unclear; Unclear | Unclear | Yes; Yes | High |
| Chen et al. 2011 | No; Unclear | No | No; No; Yes | Yes | Yes; Yes | Moderate |
| Chen et al. 2017 | Yes; Yes | Yes | No; No; Yes | Yes | Yes; Yes | Moderate |
| Chen et al. 2021 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Chevillon et al. 2015 | Unclear; NR | Yes | No; No; No | Yes | Yes; Yes | Moderate |
| Clarke et al. 2014 | Yes; Yes | Yes | Yes; Yes; Yes | Unclear | Yes; Yes | Moderate |
| Clarke et al. 2015 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | No; Yes | Moderate |
| Clemmesen et al. 2018 | Yes; Unclear | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Coburn et al. 2018 | Yes; No | Yes | Unclear; Unclear; Yes | Yes | Yes; Yes | Moderate |
| Cole et al. 1994 | Unclear; Unclear | Yes | No; No; Yes | Unclear | Yes; Yes | Moderate |
| Cole et al. 2002 | Yes; Yes | Unclear | No; No; Yes | Yes | Yes; Yes | Moderate |
| Cotae et al. 2021 | Unclear; Unclear | No | Unclear; Unclear; Unclear | No | No; Yes | Moderate |
| Dai et al. 2021 | Unclear; Unclear | Yes | No; No; Unclear | Yes | Yes; Yes | High |
| de Jonghe et al. 2014 | Yes; Yes | Yes | Yes; Yes; Unclear | No | Yes; Yes | Moderate |
| Deng et al. 2020 | Yes; Yes | Yes | No; No; No | Yes | Yes; Yes | Moderate |
| Devlin et al. 2010 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Dieleman et al. 2012 | Yes; Yes | Unclear | Yes; Yes; Unclear | Yes | Yes; Yes | Low |
| Djaiani et al. 2016 | Yes; No | Yes | Yes; No; No | Yes | Yes; Yes | Moderate |
| Dong et al. 2020 | Yes; No | Yes | NR; NR; NR | Yes | Yes; Yes | Moderate |

| Citation | Randomization/allocation concealment adequate? | Groups similar at baseline? | Patients/provider/outcome assessors masked? | ITT analysis? | Acceptable levels of overall/differential attrition? | Risk of bias |
|---|---|---|---|---|---|---|
| Eghbali-Babadi et al. 2017 | Yes; Unclear | Yes | No; No; Yes | Yes | Yes; Yes | Moderate |
| Fahimi et al. 2020 | Yes; Yes | Yes | No; Yes; Yes | Yes | Yes; Yes | Moderate |
| Fazlollah et al. 2021 | Yes; Yes | Yes | No; No; Unclear | Yes | Yes; Yes | Moderate |
| Ford et al. 2020 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Fu et al. 2020 | Unclear; Unclear | Yes | Yes; No; No | No | Yes; Yes | High |
| Fukata et al. 2014 | Yes; Yes | Yes | No; No; No | Yes | Yes; Yes | Moderate |
| Fukata et al. 2017 | Yes; Yes | Yes | No; No; No | Unclear | Yes; Yes | Moderate |
| Gamberini et al. 2009 | Yes; Yes | Unclear | Yes; Yes; Unclear | No | No; Yes | Moderate |
| Gandolfi et al. 2020 | Yes; Yes | Yes | Yes; Yes; No | No | Yes; Yes | Moderate |
| Gao et al. 2018 | Yes; Unclear | Yes | Unclear; NR; Yes | Yes | Yes; Yes | Moderate |
| Girard et al. 2008 | Yes; Yes | Yes | NR; No; No | Yes | Yes; Yes | Moderate |
| Girard et al. 2018 | Yes; Unclear | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Giraud et al. 2016 | No; No | Yes | No; No; No | Yes | Yes; Yes | Moderate |
| Gregersen et al. 2015 | Yes; Yes | Yes | Yes; No; Unclear | Yes | Yes; Yes | Moderate |
| Grover et al. 2011 | Unclear; Unclear | Yes | No; No; Yes | No | Yes; No | High |
| Grover et al. 2016 | Yes; Unclear | Yes | No; No; Yes | No | Yes; Yes | High |
| Gruber-Baldini et al. 2013 | Yes; Yes | No | NR; No; No | Yes | Yes; Yes | Moderate |
| Guo et al. 2016 | Yes; Yes | Yes | No; No; Yes | Unclear | Yes; Yes | Moderate |
| Gupta et al. 2019 | Yes; Unclear | Yes | Yes; Unclear; Yes | Yes | Yes; Yes | Moderate |
| Hamzehpour et al. 2018 | Unclear; Unclear | Unclear | Yes; Yes; Yes | Yes | Yes; Yes | Moderate |
| Han et al. 2004 | Unclear; Unclear | Yes | No; No; Yes | No | Yes; Yes | Moderate |
| Hassan et al. 2021 | Unclear; Unclear | Yes | Yes; Yes; Unclear | Yes | Yes; Yes | Moderate |
| Hatta et al. 2014b | Yes; Unclear | No | No; Unclear; Yes | Yes | No; Yes | Moderate |
| Hatta et al. 2017 | Yes; Unclear | Unclear | Yes; Unclear; Yes | Yes | Yes; Yes | Moderate |

| Citation | Randomization/allocation concealment adequate? | Groups similar at baseline? | Patients/provider/outcome assessors masked? | ITT analysis? | Acceptable levels of overall/differential attrition? | Risk of bias |
|---|---|---|---|---|---|---|
| He et al. 2018 | Yes; Unclear | Yes | Unclear; Unclear; Unclear | Unclear | Unclear; Unclear | Moderate |
| Hempenius et al. 2013 | Yes; Yes | Yes | No; No; Yes | Unclear | Yes; Yes | Moderate |
| Hollinger et al. 2021 | Yes; Yes | Yes | Yes; Yes; NR | No | Yes; Yes | Moderate |
| Hosie et al. 2020 | Yes; Unclear | Yes | No; No; No | Yes | Yes; Yes | Moderate |
| Hov et al. 2019 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Hu et al. 2020 | Yes; Unclear | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Hu et al. 2021 | Yes; Unclear | Yes | Yes; No; Yes | No | Yes; Yes | Moderate |
| Hudetz et al. 2009 | Unclear; No | Yes | Unclear; Unclear; Yes | Unclear | Yes; Yes | Moderate |
| Hui et al. 2017 | Unclear; Yes | No | Yes; Yes; Yes | No | No; Yes | High |
| Humeidan et al. 2021 | Yes; Yes | Yes | No; No; Yes | No (6%) | Yes; Yes | Moderate |
| Huyan et al. 2019 | Unclear; Unclear | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Moderate |
| Ishii et al. 2016 | Unclear; Unclear | Yes | NR; Yes; Unclear | Yes | Yes; Yes | Moderate |
| Jain et al. 2017 | Yes; Unclear | Unclear | No; No; Unclear | No | No; Yes | High |
| Jaiswal et al. 2018 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; No | Moderate |
| Jaiswal et al. 2019 | Yes; Yes | Unclear | Yes; Yes; Unclear | Yes | Yes; Yes | Low |
| Jakob et al. 2012 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Javaherforoosh Zadeh et al. 2021 | Yes; Yes | Yes | Yes; Unclear; Unclear | Yes | Yes; Yes | Moderate |
| Jeffs et al. 2013 | Unclear; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Moderate |
| Jia et al. 2014 | Yes; Yes | Yes | NR; NR; NR | Yes | Yes; Yes | Moderate |
| Jin L. et al. 2020 | Yes; NR | Yes | No; No; NR | Unclear | Yes; Yes | Moderate |
| Johnson et al. 2018 | Unclear; Unclear | Yes | No; No; Unclear | No | Unclear; Yes | High |
| Kalisvaart et al. 2005 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Karadas and Ozdemir 2016 | Yes; Unclear | Unclear | NR; NR; NR | Yes | Yes; Yes | Moderate |

| Citation | Randomization/allocation concealment adequate? | Groups similar at baseline? | Patients/provider/outcome assessors masked? | ITT analysis? | Acceptable levels of overall/differential attrition? | Risk of bias |
|---|---|---|---|---|---|---|
| Kawazoe et al. 2017 | Yes; Yes | Yes | No; No; No | Yes | Yes; Yes | Moderate |
| Khalifezadeh et al. 2011 | Unclear; Unclear | Yes | No; No; Unclear | Unclear | No; Unclear | High |
| Khan et al. 2013 | Yes; Unclear | Yes | NR; NR; NR | Yes | Yes; Yes | Moderate |
| Khan et al. 2018 | Yes; Yes | Unclear | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Khan et al. 2019 | Yes; Unclear | Yes | NR; No; NR | Yes | Yes; Yes | Moderate |
| Khan et al. 2020 | Yes; Unclear | Yes | No; NR; Yes | Yes | Yes; Yes | High |
| Khera et al. 2021 | Yes; Unclear | Mostly | Yes; Yes; Yes | Yes | Yes; Yes | Moderate |
| Kim et al. 1996 | Unclear; Yes | Unclear | NR; NR; Yes | No | Yes; Unclear | Moderate |
| Kim et al. 2010 | Unclear; Unclear | Yes | No; No; Yes | Yes | No; No | Moderate |
| Y. Kim et al. 2019 | Yes; Yes | Unclear | Yes; Yes; Yes | Yes | Yes; Yes | Moderate |
| J.A. Kim et al. 2019 | Yes; Yes | Yes | Yes; Yes; Yes | No | Yes; Yes | Low |
| Kluger et al. 2021 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Kolanowski et al. 2011 | Unclear; Unclear | Yes | No; No; Unclear | Yes | Unclear; Unclear | Moderate |
| Kolanowski et al. 2016 | Yes; Yes | Yes | No; No; Yes | Yes | Yes; Yes | Moderate |
| Kunst et al. 2020 | Yes; Yes | Yes | Yes; Yes; Yes | No | Yes; Yes | Moderate |
| Lange et al. 2021 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Lapane et al. 2011 | Unclear; Unclear | Yes | No; No; Unclear | Unclear | Unclear; Unclear | High |
| Larsen et al. 2010 | Unclear; Yes | Unclear | Yes; Yes; Yes | No | Yes; Yes | Moderate |
| Lawlor et al. 2020 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Unclear; Yes | Low |
| Lee et al. 2005 | Unclear; Unclear | No | NR; NR; NR | No | No; No | High |
| Lee et al. 2018 | Yes; Yes | Yes | Yes; No; Yes | Yes | Yes; No | Moderate |
| Lee et al. 2019 | Yes; Yes | Yes | Yes; Yes; Yes | No | Yes; Yes | Low |
| Lei et al. 2017 | Unclear; Unclear | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Moderate |
| Leong et al. 2021 | Yes; Yes | Yes | No; No; Yes | Yes | Yes; Yes | Moderate |
| Leung et al. 2006 | Yes; Yes | Yes | NR; NR; Yes | Unclear | Unclear; Unclear | Moderate |

| Citation | Randomization/allocation concealment adequate? | Groups similar at baseline? | Patients/provider/outcome assessors masked? | ITT analysis? | Acceptable levels of overall/differential attrition? | Risk of bias |
|---|---|---|---|---|---|---|
| Leung et al. 2017 | Yes; Yes | Yes | Unclear; Unclear; Yes | No | Yes; Yes | Moderate |
| Levy et al. 2022 | No; No | No | No; No; No | Yes | Yes; Yes | High |
| Y.N. Li et al. 2017 | Unclear; Unclear | Yes | NR; NR; NR | Yes | Yes; Yes | Moderate |
| X. Li et al. 2017 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Li et al. 2019 | Yes; Unclear | Yes | NR; NR; NR | Unclear | Yes; Unclear | High |
| Li et al. 2020 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Li et al. 2021 | Yes; Yes | Yes | No; No; Yes | Yes | Yes; Yes | Moderate |
| Likhvantsev et al. 2021 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Lin et al. 2008 | Unclear; Unclear | Yes | No; No; Yes | Unclear | Unclear; Unclear | High |
| Liptzin et al. 2005 | Unclear; Yes | No | Yes; Yes; Yes | No | No; Unclear | Moderate |
| Y. Liu et al. 2016 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| X. Liu et al. 2016 | Yes; Unclear | Yes | Yes; Unclear; Yes | No | Yes; Yes | Moderate |
| Liu et al. 2017 | Unclear; Unclear | Yes | Yes; Unclear; Yes | Yes | Yes; Yes | Moderate |
| Liu et al. 2018 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Lundström et al. 2005 | Unclear; NR | No | No; No; No | Yes | Yes; Yes | Moderate |
| Lundström et al. 2007 | Unclear; Yes | No | No; No; Yes | Yes | Yes; Yes | Moderate |
| Luo et al. 2015 | Yes; Yes | Yes | Unclear; Unclear; Yes | Yes | Yes; Yes | Moderate |
| Lurati Buse et al. 2012 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| MacLaren et al. 2015 | Yes; Unclear | Yes | Yes; Unclear; Yes | Yes | Yes; Yes | Moderate |
| Mahrose et al. 2021 | Unclear; Unclear | Yes | Unclear; Unclear; Unclear | Yes | Yes; Yes | Moderate |
| Mailhot et al. 2017 | Yes; Yes | No | No; No; Unclear | Yes | Yes; Yes | Moderate |
| Makinian et al. 2015 | No; No | Unclear | No; No; NR | Unclear | Unclear; Unclear | High |
| Maldonado et al. 2009 | Unclear; Unclear | Yes | Yes; Unclear; Yes | Yes | Yes; Yes | Moderate |
| Maneeton et al. 2013 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | No; No | Moderate |
| Mann et al. 2000 | Yes; Unclear | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Moderate |

| Citation | Randomization/allocation concealment adequate? | Groups similar at baseline? | Patients/provider/outcome assessors masked? | ITT analysis? | Acceptable levels of overall/differential attrition? | Risk of bias |
|---|---|---|---|---|---|---|
| Marcantonio et al. 2001 | Yes; No | Yes | No; No; Yes | Yes | Yes; Yes | Moderate |
| Marcantonio et al. 2010 | Unclear; Unclear | Yes | No; No; Yes | Unclear | No; Yes | High |
| Mardani and Bigdelian 2012 | Unclear; Unclear | Unclear | NR; NR; NR | No | Yes; Unclear | High |
| Martinez et al. 2012 | Yes; Yes | Yes | No; No; Yes | Yes | Yes; Yes | Moderate |
| Martinez-Velilla et al. 2019 | Yes; Yes | Yes | Unclear; No; Yes | Yes | Yes; Yes | Moderate |
| Massoumi et al. 2019 | Yes; Unclear | Unclear | NR; Yes; Yes | No | Yes; Yes | Moderate |
| Mehta et al. 2012 | Yes; Yes | Yes | No; No; No | Yes | Yes; Yes | Moderate |
| Mei et al. 2018 | Yes; Yes | Yes | Yes; Unclear; Yes | Yes | Yes; Yes | Low |
| B. Mei et al. 2020 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Moderate |
| X. Mei et al. 2020 | Yes; Unclear | Yes | Unclear; Yes; Yes | No | No; Yes | Moderate |
| Mitchell et al. 2017 | Yes; Yes | Yes | Unclear; No; Yes | Yes | Yes; Yes | Moderate |
| Mohammadi et al. 2016 | Unclear; Yes | Unclear | Yes; Yes; Unclear | No | Yes; Yes | Moderate |
| Mokhtari et al. 2020 | Yes; Unclear | Unclear | Yes; Yes; Unclear | No | No; Yes | Moderate |
| Momeni et al. 2021 | Yes; Yes | Yes | Yes; Yes; Yes | Unclear | Yes; Yes | Moderate |
| Moon and Lee 2015 | Unclear; No | Yes | Yes; No; No | Unclear | Yes; Yes | Moderate |
| Morris et al. 2016 | Yes; Unclear | Yes | No; No; Yes | Yes | No; Yes | Moderate |
| Moslemi et al. 2020 | Yes; Unclear | Yes | Yes; Yes; Yes | No | No; Yes | Moderate |
| Mouzopoulos et al. 2009 | Yes; Unclear | Yes | Yes; NR; NR | No | Yes; Yes | Moderate |
| Munro et al. 2017 | Yes; Yes | Yes | NR; NR; NR | Yes | Yes; Yes | Moderate |
| Nadler et al. 2017 | Yes; Yes | Yes | No; No; Yes | Yes | Yes; Yes | Moderate |
| Nakamura et al. 2021 | Yes; Yes | Yesg | Yes; Unclear; Unclear | Yes | Yes; Yes | Moderate |
| Nassar Junior and Park 2014 | Unclear; Unclear | Yes | No; No; No | Yes | Yes; Yes | Moderate |

| Citation | Randomization/allocation concealment adequate? | Groups similar at baseline? | Patients/provider/outcome assessors masked? | ITT analysis? | Acceptable levels of overall/differential attrition? | Risk of bias |
|---|---|---|---|---|---|---|
| Nishikawa et al. 2004 | Unclear; Unclear | Yes | NR; Yes; Yes | Yes | Yes; Yes | Moderate |
| Nishikimi et al. 2018 | Yes; Unclear | No | Yes; Yes; Yes | Yes | Unclear; Unclear | Moderate |
| Nydahl et al. 2020 | Yes; Unclear | Yes | No; No; Yes | Yes | Yes; Yes | Moderate |
| Nydahl et al. 2022 | Yes; Unclear | Yes | No; No; No | Yes | Yes; Yes | Moderate |
| Obanor et al. 2021 | Unclear; Unclear | Unclear | No; No; Unclear | Yes | Yes; Yes | Moderate |
| O'Gara et al. 2020 | Yes; Yes | Yes | No; Yes; Yes | No | Yes; Yes | Moderate |
| E.S. Oh et al. 2021 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Unclear; No | Low |
| C.S. Oh et al. 2021 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Olsen et al. 2020 | Yes; Yes | Yes | NR; NR; NR | Yes | Yes; Yes | Moderate |
| Ono et al. 2011 | Yes; Yes | Yes | NR; NR; NR | Yes | Yes; Yes | Moderate |
| Overshott et al. 2010 | Unclear; Yes | No | Yes; Yes; Yes | Unclear | No; No | Moderate |
| Papadopoulos et al. 2014 | Unclear; Unclear | Yes | Unclear; Unclear; Unclear | Yes | Yes; Yes | Moderate |
| Papaioannou et al. 2005 | Unclear; Unclear | Yes | NR; NR; NR | Yes | Yes; Yes | High |
| Park et al. 2014 | Unclear; Unclear | Yes | NR; NR; NR | Unclear | Unclear; Unclear | Moderate |
| Pitkälä et al. 2006 | Yes; Yes | Yes | NR; NR; NR | Yes | Yes; Yes | Moderate |
| Potharajaroen et al. 2018 | Unclear; Unclear | Yes | No; No; Yes | Yes | Yes; Yes | Moderate |
| Prakanrattana and Prapaitrakool 2007 | Yes; Yes | Yes | Yes; Yes; Yes | Unclear | Unclear; Unclear | Moderate |
| Radtke et al. 2013 | Unclear; Unclear | Yes | Unclear; No; Yes | Yes | Yes; Yes | Moderate |
| Reade et al. 2016 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Rice et al. 2017 | Yes; Yes | Yes | NR; NR; NR | Unclear | Yes; Yes | Moderate |
| Robinson et al. 2014 | Yes; Yes | Yes | Yes; Yes; Unclear | Yes | Yes; Yes | Low |
| Rood et al. 2021 | Unclear; Unclear | Yes | No; No; No | Yes | Yes; Yes | Moderate |
| Rosa et al. 2019 | Yes; Yes | Yes | No; No; Unclear | Yes | Yes; Yes | Moderate |
| Royse et al. 2017 | Yes; Yes | Unclear | Yes; Yes; Yes | No | Yes; Yes | Moderate |

| Citation | Randomization/allocation concealment adequate? | Groups similar at baseline? | Patients/provider/outcome assessors masked? | ITT analysis? | Acceptable levels of overall/differential attrition? | Risk of bias |
|---|---|---|---|---|---|---|
| Rubino et al. 2010 | Unclear; Unclear | Yes | Yes; Yes; Yes | Unclear | Unclear; Unclear | Moderate |
| Ruokonen et al. 2009 | Unclear; Unclear | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Moderate |
| Saager et al. 2015 | Yes; Yes | Yes | Unclear; Unclear; Yes | Yes | Yes; Yes | Moderate |
| Sampson et al. 2007 | Unclear; Yes | No | Yes; Yes; Yes | No | No; Unclear | Moderate |
| Schomer et al. 2020 | Yes; NR | Unclear | Unclear; Yes; Unclear | Yes | Yes; Yes | Moderate |
| Schrijver et al. 2018 | Unclear; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Moderate |
| Schweickert et al. 2009 | Yes; Yes | Yes | No; No; Yes | Yes | Yes; Yes | Moderate |
| Sharaf et al. 2018 | Yes; Unclear | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Shehabi et al. 2009 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Sheikh et al. 2018 | Yes; Yes | Yes | Yes; Unclear; Unclear | Unclear | Unclear; Unclear | High |
| Shi et al. 2019* | Yes; Yes | Yes | Yes; Unclear; Yes | Yes | Yes; Yes | Low |
| Shi et al. 2020 | Yes; Yes | Yes | Yes; NR; Yes | Yes | Yes; Yes | Low |
| Shirvani et al. 2020 | No; No | Yes | Unclear; Unclear; Unclear | Yes | Yes; Yes | High |
| Shokri and Ali 2020 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Shu et al. 2017 | Yes; Unclear | Yes | NR; NR; NR | Yes | Yes; Yes | Moderate |
| Shu et al. 2019 | Unclear; Unclear | No | NR; NR; NR | Yes | Yes; Yes | Moderate |
| Siddiqi et al. 2016 | Yes; Yes | Yes | No; No; Unclear | Unclear | No; Yes | High |
| Sieber et al. 2010 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Sieber et al. 2018 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Siepe et al. 2011 | Yes; Unclear | Yes | NR; NR; Yes | No | Yes; Yes | Moderate |
| Simons et al. 2016 | Yes; No | No | No; No; NR | Yes | Yes; Yes | High |
| Skrobik et al. 2004 | No; No | Unclear | No; No; Yes | No | Yes; Unclear | High |
| Skrobik et al. 2018 | Yes; Yes | No | Yes; Yes; Yes | Yes | Yes; Yes | Moderate |
| Soh et al. 2020 | Yes; Unclear | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Spence et al. 2020 | Yes; NR | Yes | NR; No; No | Yes | Yes; Yes | Moderate |

| Citation | Randomization/allocation concealment adequate? | Groups similar at baseline? | Patients/provider/outcome assessors masked? | ITT analysis? | Acceptable levels of overall/differential attrition? | Risk of bias |
|---|---|---|---|---|---|---|
| Spies et al. 2021 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Stoppe et al. 2013 | Unclear; Unclear | Yes | Unclear; Unclear; Yes | Yes | Yes; Yes | Moderate |
| Strike et al. 2019 | Yes; Yes | Yes | NR; NR; NR | Yes | Yes; Yes | Moderate |
| Strøm et al. 2010 | Unclear; Unclear | No | No; No; No | No | Yes; Yes | Moderate |
| Su et al. 2016 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Sultan 2010 | Unclear; Yes | Unclear | Unclear; Yes; Unclear | No | Yes; Unclear | High |
| Sun et al. 2019* | Yes; Yes | No | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Susheela et al. 2017 | Unclear; Unclear | Yes | Unclear; Unclear; Unclear | Yes | Yes; Yes | Moderate |
| Szwed et al. 2021 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Tagarakis et al. 2012 | No; No | Yes | No; No; No | Unclear | Unclear; Unclear | High |
| Taguchi et al. 2007 | Yes; Unclear | No | NR; NR; NR | No | No; Yes | High |
| Tahir et al. 2010 | Yes; Yes | Yes | Yes; Yes; Unclear | No | No; Yes | Moderate |
| Tanaka et al. 2017 | Yes; Unclear | No | Yes; Yes; Yes | Yes | Yes; Yes | Moderate |
| Tang et al. 2018 | Unclear; Unclear | Yes | Unclear; Unclear; Yes | Yes | Yes; Yes | Moderate |
| C.J. Tang et al. 2020 | Yes; Unclear | Yes | NR; Yes; Yes | No | Yes; Yes | Moderate |
| C. Tang et al. 2020 | Yes; NR | Yes | Unclear; Yes; Unclear | Yes | Yes; Yes | Moderate |
| Tang et al. 2021 | Yes; Yes | Yes | Yes; Unclear; Yes | Unclear | Yes; Yes | Moderate |
| Thanapluetiwong et al. 2021 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Turan et al. 2020. | Yes; Yes | Yes | NR; Yes; Yes | Yes | Yes; Yes | Moderate |
| Unneby et al. 2020 | No; Unclear | Yes | NR; NR; NR | No | No; Yes | High |
| Uysal et al. 2020 | Unclear; Unclear | Yes | Unclear; Unclear; Unclear | No | Yes; Yes | Moderate |
| van den Boogaard et al. 2018 | Unclear; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| van der Vorst et al. 2020 | Unclear; Yes | Yes | No; No; Yes | Yes | Yes; Yes | Moderate |

| Citation | Randomization/allocation concealment adequate? | Groups similar at baseline? | Patients/provider/outcome assessors masked? | ITT analysis? | Acceptable levels of overall/differential attrition? | Risk of bias |
|---|---|---|---|---|---|---|
| van Eijk et al. 2010 | Yes; Yes | No | Yes; Yes; Unclear | Yes | Yes; Yes | Moderate |
| van Norden et al. 2021 | Unclear; Yes | Yes | Yes; Yes; Yes | Yes | No ; Yes | Moderate |
| Van Rompaey et al. 2012 | Yes; Yes | No | No; No; Yes | Unclear | Unclear; Unclear | Moderate |
| Verloo et al. 2015 | Unclear; Yes | Yes | No; No; Yes | Unclear | Yes; Yes | Moderate |
| Vlisides et al. 2019 | Unclear; Unclear | Yes | No; No; Yes | Unclear | Yes; No | High |
| Wang et al. 2012 | Yes; Unclear | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Moderate |
| Wang et al. 2015 | Unclear; Unclear | Yes | NR; NR; Yes | Yes | Yes; Yes | Moderate |
| Wang et al. 2019 | Yes; Unclear | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Moderate |
| J. Wang et al. 2020 | Yes; NR | Yes | Unclear; Yes; Yes | No | Yes; Yes | Moderate |
| Y.Y. Wang et al. 2020 | Yes; Yes | Yes | No; No; Yes | Yes | Yes; Yes | Moderate |
| Watne et al. 2014 | Yes; Yes | Yes | Unclear; No; Yes | Yes | Yes; Yes | Moderate |
| Wildes et al. 2019 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Williams-Russo et al. 1995 | Yes; Unclear | Yes | Unclear; Unclear; Unclear | Yes | Unclear; Unclear | Moderate |
| Winings et al. 2021 | No; No | Yes | NR; NR; NR | Yes | Yes; Yes | Moderate |
| Wu et al. 2016 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Xin et al. 2017 | Yes; Unclear | Yes | Unclear; Unclear; Unclear | Yes | Yes; Yes | Moderate |
| Xin et al. 2021 | Yes; Unclear | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Moderate |
| Xu et al. 2020 | Yes; NR | Yes | NR; No; Yes | No | Yes; Yes | Moderate |
| Xuan et al. 2018 | Yes; Yes | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Low |
| Xue et al. 2020 | Unclear; Unclear | Yes | No; No; NR | Yes | Yes; Yes | Moderate |
| Yang et al. 2012 | Yes; Yes | No | No; No; NR | Yes | Yes; Yes | Moderate |
| Yang et al. 2015 | Yes; Unclear | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Moderate |
| Yapici et al. 2011 | Unclear; Unclear | No | NR; NR; NR | Yes | Yes; Yes | Moderate |
| Youn et al. 2017 | Yes; Yes | No | No; Yes; Yes | No | Unclear; Unclear | Moderate |

| Citation | Randomization/allocation concealment adequate? | Groups similar at baseline? | Patients/provider/outcome assessors masked? | ITT analysis? | Acceptable levels of overall/differential attrition? | Risk of bias |
|---|---|---|---|---|---|---|
| Young et al. 2020 | Yes; Unclear | Yes | No; No; No | Yes | Yes; Yes | Moderate |
| Yu et al. 2017 | Yes; Unclear | Yes | NR; NR; NR | Yes | Yes; Yes | Moderate |
| Zhang et al. 2020 | Yes; NR | Yes | Yes; No; Yes | Yes | Yes; Yes | Moderate |
| K.S. Zhang et al. 2021 | Yes; Unclear | No | No; No; No | No | No; Yes | High |
| Zhao et al. 2020 | Unclear; Unclear | No | Yes; Yes; Yes | Yes | Yes; Yes | Moderate |
| Zhou et al. 2018 | Yes; Unclear | Yes | Yes; Yes; Yes | Yes | Yes; Yes | Moderate |

*This study was identified as part of the systematic review by the Pacific Northwest Evidence-Based Practice Center but was subsequently retracted.
*Abbreviations*. ITT=Intent to treat; NR=Not reported.

# Appendix F. Balancing of Potential Benefits and Harms in Rating the Strength of the Guideline Statements

## Assessment and Treatment Planning

### *Statement 1 – Structured Assessments for Delirium*

APA recommends **(1C)** that patients with delirium or who are at risk for delirium undergo regular structured assessments for the presence or persistence of delirium using valid and reliable measures.

#### Benefits

Use of regular structured and validated assessments in patients with delirium or who are at risk for delirium can help identify the presence or persistence of delirium. Once delirium is identified, possible contributors can be identified and addressed. Thus, the indirect benefits of identifying delirium can potentially include decreases in morbidity due to delirium and its underlying physiological causes. Also, when delirium is identified, education of the patient (where feasible), family, and other care givers can enhance understanding and management of the patient's symptoms.

#### Harms[5]

The harms of regular structured assessments in patients with delirium or who are at risk for delirium include time spent conducting assessments that could be used on other activities of benefit to the patient. In addition, some patients may become frustrated with repeated questions that are part of the assessment. If structured assessment is erroneous in suggesting the presence of delirium, a patient could undergo unnecessary evaluations, including laboratory or other testing. There can also be false negative results of structured assessments, which can provide a false sense of security and lead reversible conditions to be overlooked.

#### Patient Preferences

No specific information is available on patient preferences related to structured assessments for delirium. However, clinical experience suggests that many patients are willing to be assessed. The manifestations of delirium can make it challenging for patients to cooperate with assessment and some patients may choose to avoid repeating questioning.

#### Balancing of Benefits and Harms

The potential benefits of this recommendation were viewed as far outweighing the potential harms.

The level of research evidence is rated as low because evidence on the benefits of structured assessment is indirect and does not come from rigorous clinical studies. However, expert opinion suggests that the harms of structured assessment are negligible compared with the potential benefit of

[5] Harms may include serious adverse events, less serious adverse events that affect tolerability, minor adverse events, negative effects of the intervention on quality of life, barriers and inconveniences associated with treatment and other negative aspects of the treatment that may influence decision making by the patient, the clinician or both. Harms may also include opportunity costs for the clinician who may have to forgo another clinical activity that would be more beneficial for the patient.

such assessments in improving the identification of delirium. For additional discussion of the research evidence, see Appendix C, Statement 1.

### Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

### Review of Available Guidelines from Other Organizations

Most (Aldecoa et al. 2017; American College of Emergency Physicians 2014; BC Centre for Palliative Care 2017a; Cancer Care Ontario 2010; Devlin et al. 2018; Gage and Hogan 2014; Martin et al. 2010; Mohanty et al. 2016; Potter et al. 2006; Scottish Intercollegiate Guidelines Network 2019; Tropea et al. 2008) but not all (Bush et al. 2018) of other clinical practice guidelines suggest use of routine screening with validated scales to identify patients with delirium. Some guidelines specifically mention the need to confirm the diagnosis according to DSM or ICD criteria (BC Centre for Palliative Care 2017a; National Institute for Health and Care Excellence 2023), whereas others note the need for training in the use of the specific rating scales that are chosen for use (Gage and Hogan 2014; Scottish Intercollegiate Guidelines Network 2019; Tropea et al. 2008). Specific scales that are mentioned in other guidelines include the CAM (Gage and Hogan 2014; Potter et al. 2006; Tropea et al. 2008), CAM-ICU (Gage and Hogan 2014; Martin et al. 2010; Mohanty et al. 2016; Scottish Intercollegiate Guidelines Network 2019; Tropea et al. 2008), ICDSC (Mohanty et al. 2016; Scottish Intercollegiate Guidelines Network 2019), Delirium Rating Scale (DRS; Tropea et al. 2008), Delirium Symptom Interview (Gage and Hogan 2014; Tropea et al. 2008), Germany Care Delirium Screening Checklist (Martin et al. 2010), and the 4AT (Scottish Intercollegiate Guidelines Network 2019).

## *Statement 2 – Determination of Baseline Neurocognitive Status*

APA recommends **(1C)** that a patient's baseline neurocognitive status be determined to permit accurate interpretation of delirium assessments.

### Benefits

Determining a patient's baseline neurocognitive status can permit accurate interpretation of delirium assessments and allow delirium to be identified when it is present. Once delirium is identified, possible contributors can be identified and addressed. Knowledge of the patient’s baseline neurocognitive status also facilitates longitudinal monitoring to determine when the patient’s delirium has resolved, including in individuals who had some neurocognitive impairment prior to the onset of delirium. If pre-existing neurocognitive impairments were present, these may also warrant additional evaluation, treatment, or follow-up, each of which could have additional benefits for patients.

### Harms

The harms of determining a patient's baseline neurocognitive status include time spent in obtaining this information (e.g., from collateral history, from electronic records, from clinical assessment), which could be used on other activities of benefit to the patient.

### Patient Preferences

No specific information is available on patient preferences related to determination of neurocognitive status. However, clinical experience suggests that many patients are willing to be assessed and have staff contact family members or others for collateral information. The vast majority of patients would want staff to review prior records for relevant information that would have the potential to improve their care and their outcomes.

### Balancing of Benefits and Harms

The potential benefits of this recommendation were viewed as far outweighing the potential harms.

The level of research evidence is rated as low because evidence on the benefits of obtaining baseline neurocognitive status is indirect and does not come from rigorous clinical studies. However, expert opinion suggests that the harms of delineating the patient's neurocognitive baseline functioning are negligible compared with the potential benefit of such assessments in improving the recognition of and accurate identification of delirium. For additional discussion of the research evidence, see Appendix C, Statement 2.

### Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

### Review of Available Guidelines from Other Organizations

In patients whose characteristics would place them at increased risk for developing delirium, a few other guidelines suggest obtaining cognitive assessment, as part of routine outpatient care (Tropea et al. 2008), pre-operatively (Chow et al. 2012), or upon admission to the hospital (Potter et al. 2006). The potential role of collateral information from a relative or caregiver was also noted (Potter et al. 2006) as was the importance of being aware of pre-existing cognitive impairment in making a diagnosis of delirium (Devlin et al. 2018; Potter et al. 2006).

## *Statement 3 – Review for Predisposing or Contributing Factors*

APA recommends **(1C)** that patients with delirium or who are at risk for delirium undergo a detailed review of possible predisposing or contributing factors.

### Benefits

In patients with delirium or who are at risk for delirium, a detailed review of possible predisposing or contributing factors can help in identifying issues that warrant clinical intervention and ultimately improve patient outcomes. Doing this in a systematic fashion can help to minimize cognitive biases such as anchoring biases.

### Harms

The harms of conducting a detailed review of possible predisposing or contributing factors include time spent on assessment that could be used on other activities of benefit to the patient. If structured assessment is erroneous in identifying predisposing or contributing factors, a patient could undergo

unnecessary evaluations, with associated costs and patient discomfort as well as incidental findings that would not have required additional intervention.

### Patient Preferences

No specific information is available on patient preferences related to review of predisposing or contributing factors of delirium. However, clinical experience suggests that the vast majority of patients would want and would value having a careful and thorough review of possible predisposing or contributing factors, with the potential to improve their care and their outcomes.

### Balancing of Benefits and Harms

The potential benefits of this recommendation were viewed as far outweighing the potential harms.

The level of research evidence is rated as low because evidence on review of possible predisposing or contributing factors is indirect and does not come from rigorous clinical studies. However, expert opinion suggests that the benefits of a review of predisposing or contributing factors of delirium outweigh the harms of such a review, which appear to be minimal. For additional discussion of the research evidence, see Appendix C, Statement 3.

### Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

### Review of Available Guidelines from Other Organizations

Although the specific lists of potential predisposing or contributing factors varies among guidelines, guidelines on delirium are consistent in discussing the importance of reviewing factors that may place individuals at risk for developing delirium or are associated with precipitating, maintaining, or exacerbating delirium (Aldecoa et al. 2017; American College of Emergency Physicians 2014; American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults 2015; BC Centre for Palliative Care 2017a; Chow et al. 2012; Devlin et al. 2018; Gage and Hogan 2014; Martin et al. 2010; Mohanty et al. 2016; National Institute for Health and Care Excellence 2023; Potter et al. 2006; Registered Nurses' Association of Ontario 2016; Scottish Intercollegiate Guidelines Network 2019; Tropea et al. 2008).

## *Statement 4 – Review of Medications*

APA recommends **(1C)** that a detailed medication review be conducted in patients with delirium or who are at risk for delirium, especially those with pre-existing cognitive impairment.

### Benefits

Conducting a detailed medication review in patients with delirium or who are at risk for delirium can help in identifying medications that may be contributing to delirium. Medication review can also identify medications that may be associated with other adverse effects, drug-disease interactions, or drug-drug interactions. Once identified, tapering or discontinuing of non-essential medications can reduce side effects for patients and lower medication costs.

### Harms

The harms of conducting a detailed medication review include time spent on assessment that could be used on other activities of benefit to the patient. If medication review is erroneous in identifying potentially problematic medications, a necessary medication could be inappropriately stopped.

### Patient Preferences

No specific information is available on patient preferences related to review of medications that may be contributing to delirium. However, clinical experience suggests that the vast majority of patients would want and would value having a careful and thorough review of medications, with the potential to improve their care and their outcomes.

### Balancing of Benefits and Harms

The potential benefits of this recommendation were viewed as far outweighing the potential harms.

The level of research evidence is rated as low because there is limited evidence on the benefits of medication reconciliation and deprescribing. The majority of studies that have examined medication-related interventions in patients with delirium have been small multi-component trials or retrospective or observational studies. However, expert opinion suggests that the benefits of a detailed medication review outweigh the harms of such a review, which appear to be minimal. For additional discussion of the research evidence, see Appendix C, Statement 4.

### Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

### Review of Available Guidelines from Other Organizations

The Canadian Coalition for Seniors' Mental Health, National Institute for Health and Care Excellence, and Scottish Intercollegiate Guidelines Network explicitly recommend medication review in patients with delirium or at risk for delirium (Gage and Hogan 2014; National Institute for Health and Care Excellence 2023; Scottish Intercollegiate Guidelines Network 2019). Many other guidelines comment on the importance of specific medications (e.g., psychotropic agents, opioids, anticholinergic agents) or multiple medications as a risk factor for delirium and include assessment of medications as part of reviewing risk factors for delirium (see Statement 3). In addition, this recommendation is generally consistent with that from the American Geriatrics Society Choosing Wisely recommendations, which note the importance of a medication review before prescribing medications (Choosing Wisely 2021).

## *Statement 5 – Use of Restraints*

APA recommends **(1C)** that physical restraints not be used in patients with delirium, except in situations where injury to self or others is imminent and only:

- after review of factors that can contribute to racial/ethnic and other biases in decisions about restraint;
- with frequent monitoring; and

- with repeated reassessment of the continued risks and benefits of restraint use as compared to less restrictive interventions.

### Benefits

The benefits of limiting restraint use in patients with delirium, explicitly considering whether biases are involved in its use, and engaging in appropriate monitoring and reassessment are manifold. These include reduced likelihood of patient injury related to restraint, less emotional distress related to being restrained, and less potential for inequitable use of physical restraint.

### Harms

The harms of limiting restraint use in patients with delirium include possible increases in injury to the patient or others due to agitation or other behaviors that pose an imminent risk.

### Patient Preferences

Studies of patient preferences related to restraint have typically been small qualitative studies and often focus on the experiences of patients in psychiatric settings rather than patients with delirium (Siegrist-Dreier et al. 2023; Tingleff et al. 2017). Clinical experience suggests that few individuals would wish to be physically restrained and that physical restraint is often perceived as a coercive intervention. Thus, it seems likely that patients would be in agreement with a recommendation that limits restraint, insofar as possible, and aims to preserve patient safety and equitable treatment.

### Balancing of Benefits and Harms

The potential benefits of this recommendation were viewed as far outweighing the potential harms.

The level of research evidence is rated as low because there are a limited number of studies that address potential benefits and harms of physical restraint in general and in individuals with delirium in particular. Multiple studies show disparities in the use of physical restraint, but these do not typically include individuals with delirium. Studies that do involve patients with delirium can be difficult to interpret because of concomitant disorders and other confounding factors. For example, individuals with more severe illness may be more likely to have severe hyperactive delirium with agitation but may also be more likely to experience associated morbidity and mortality regardless of restraint use. However, expert opinion and regulatory policy (Code of Federal Regulations 2019) support the appropriateness of limiting restraint use to situations that pose imminent risk and of using ongoing monitoring and frequent reassessment of restraint use as a way to mitigate restraint-related risks. In addition, expert opinion suggests that all interventions, including physical restraint, should be delivered in an equitable fashion without bias based on race, ethnicity, or other factors. For additional discussion of the research evidence, see Appendix C, Statement 5.

### Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

### Review of Available Guidelines from Other Organizations

A number of other guidelines recommend avoiding the use of physical restraints insofar as possible (American College of Emergency Physicians 2014; BC Centre for Palliative Care 2017a; Cancer Care Ontario 2010; Gage and Hogan 2014; National Institute for Health and Care Excellence 2023; Potter et al. 2006; Registered Nurses' Association of Ontario 2016; Tropea et al. 2008). Some of these guidelines also provide specific information on use of de-escalation techniques, less restrictive interventions, and frequent monitoring (e.g., Gage and Hogan 2014, National Institute for Health and Care Excellence 2023). In addition, this recommendation is consistent with that from the American Geriatrics Society Choosing Wisely recommendations on managing behavioral symptoms of hospitalized adults with delirium (Choosing Wisely 2021). Factors related to bias in the use of physical restraints in patients with delirium do not seem to have been noted in other guidelines.

## *Statement 6 – Person-Centered Treatment Planning*

APA recommends **(1C)** that patients with delirium have a documented, comprehensive, and person-centered treatment plan.

### Benefits

Development and documentation of a comprehensive, person-centered treatment plan assures that the clinician has considered available treatment options in the context of individual patient needs, including health-related social needs, with a goal of improving overall outcome. Documentation of a treatment plan also promotes accurate communication among all those caring for the patient.

### Harms

The potential harms from this recommendation relate to the time spent in discussion and documentation of a comprehensive treatment plan that may reduce the opportunity to focus on other aspects of the evaluation.

### Patient Preferences

No specific information is available on patient preferences related to treatment planning in patients with delirium. Clinical experience suggests that families and, insofar as possible, patients are cooperative with and accepting of efforts to establish treatment plans, particularly when they are patient centered.

### Balancing of Benefits and Harms

The potential benefits of this guideline statement were viewed as far outweighing the potential harms.

The level of research evidence is rated as low because no information is available on the harms of a comprehensive, person-centered treatment plan. There is also minimal research on whether developing and documenting a specific treatment plan improves outcomes as compared with assessment and documentation as usual. However, indirect evidence, including expert opinion, supports the benefits of comprehensive treatment planning. For additional discussion of the research evidence, see Appendix C, Statement 6.

### Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

### Review of Available Guidelines from Other Organizations

Although guidelines implicitly describe multiple aspects of the treatment plan that warrant consideration, explicit mention of treatment planning or person-centered care is relatively limited (BC Centre for Palliative Care 2017a, 2017b; Gage and Hogan 2014). Guidelines also vary in the scope of treatment plan elements that are explicitly considered with some focused on geriatric (American College of Emergency Physicians 2014; Potter et al. 2006), post-operative (Aldecoa et al. 2017; American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults 2015; Chow et al. 2012; Martin et al. 2010; Mohanty et al. 2016; Tropea et al. 2008), or oncology/palliative care patients (BC Centre for Palliative Care 2017a, 2017b; Bush et al. 2018; Cancer Care Ontario 2010) with others being broader (Danish Health Authority 2021; Devlin et al. 2018; Gage and Hogan 2014; National Institute for Health and Care Excellence 2023; Scottish Intercollegiate Guidelines Network 2019) in their recommendations related to delirium. In these general guidelines related to delirium, examples of treatment plan elements include aspects of assessment (e.g., physical examination, laboratory tests, imaging studies, electroencephalography, lumbar puncture, evaluation for infection), addressing patient needs (e.g., communication, safety, mobility, pain, bowel and bladder function, sleep, hydration, nutrition, oxygenation, fluid and electrolyte balance, sensory impairment), modifying environmental risk factors, and providing education about delirium to the patient, family, and other care partners.

## Non-Pharmacological Interventions

### *Statement 7 – Multi-component Non-pharmacological Interventions*

APA recommends **(1B)** that patients with delirium or who are at risk for delirium receive multi-component non-pharmacological interventions to manage and prevent delirium.

### Benefits

Use of multi-component non-pharmacological interventions in patients who are at risk for delirium can reduce the incidence and severity of delirium as well as reducing the duration of delirium in individuals who develop it. Other outcomes that are not specific to delirium but are reduced by multi-component non-pharmacological interventions such as the ABCDEF bundle include reductions in hospital death within 7 days, coma, next-day mechanical ventilation, physical restraint use, ICU readmission, and discharge to a facility other than home (Pun et al. 2019).

### Harms

The harms of multi-component non-pharmacological interventions include time spent conducting these interventions that could be used on other activities of benefit to the patient. Because multi-component interventions are delivered predominantly by nursing staff, time spent delivering multi-component interventions may also reduce time available for addressing the care needs of other patients.

### Patient Preferences

No specific information is available on patient preferences related to multi-component interventions. Although some patients may not wish to engage with all of these interventions, clinical experience and expert opinion suggest that patients are generally accepting of the elements of multi-component interventions and that family members and other caregivers are also interested in collaborating with the treatment team in the delivery of multi-component interventions.

### Balancing of Benefits and Harms

The potential benefits of this recommendation were viewed as far outweighing the potential harms of implementing multi-component non-pharmacological interventions for patients with delirium or at risk for delirium.

The level of research evidence is rated as moderate because multiple large studies were available that assessed the effects of multi-component interventions, with almost all of the studies having a moderate rather than a high risk of bias. There was also a dose-response effect for the number of components implemented and the consistency of implementation, which suggests an increased level of confidence in the research evidence findings. For additional discussion of the research evidence, see Appendix C, Statement 7.

### Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

### Review of Available Guidelines from Other Organizations

Many guidelines on delirium specifically recommend multi-component non-pharmacological interventions as a primary intervention (American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults 2015; BC Centre for Palliative Care 2017a; Danish Health Authority 2021; Devlin et al. 2018; Gage and Hogan 2014; Mohanty et al. 2016; National Institute for Health and Care Excellence 2023; Registered Nurses' Association of Ontario 2016; Scottish Intercollegiate Guidelines Network 2019; Tropea et al. 2008). Typically, they do not recommend use of a specific bundle of interventions (e.g., ABCDEF bundle, HELP bundle) but do describe typical interventions that warrant inclusion.

## Pharmacological Interventions

### *Statement 8 – Principles of Medication Use*

APA recommends **(1C)** that antipsychotic agents and other medications to address neuropsychiatric disturbances of delirium be used only when all the following criteria are met:

- verbal and non-verbal de-escalation strategies have been ineffective;
- contributing factors have been assessed and, insofar as possible, addressed; and
- the disturbances cause the patient significant distress and/or present a risk of physical harm to the patient or others.

### Benefits

Limiting use of antipsychotic agents and other medications to address neuropsychiatric disturbances of delirium can reduce the risk of side effects from these medications, which can include increases in weight, diabetes mellitus, metabolic syndrome, parkinsonism, acute dystonic reactions, dysphagia, dyskinetic movements, falls, orthostatic hypotension, and anticholinergic effects, among others (see Statement 8). In individuals with dementia, which is a risk factor for delirium and can co-occur with delirium, use of antipsychotic medication has been associated with increases in mortality and cerebrovascular adverse events. Limiting use of antipsychotic agents can also reduce the risk of drug-drug interactions and decrease the likelihood that unneeded antipsychotic medications will be continued after transitioning to another setting of care.

### Harms

The potential harms of this statement are that a patient who might benefit from an antipsychotic or other medication will not receive it. Additionally, for a patient who is in significant distress or presenting a risk to self or others, harm could occur if a delay in treatment contributed to greater distress or harm.

### Patient Preferences

No specific information is available on patient preferences related to use of antipsychotic agents or other medications to address neuropsychiatric disturbances in individuals with delirium. Clinical experience, including that with other psychiatric disorders in which antipsychotic medications are used, suggests that patients prefer to avoid use of an antipsychotic medication whenever possible.

### Balancing of Benefits and Harms

The potential benefits of this recommendation were viewed as far outweighing the potential harms.

The level of research evidence is rated as low because there was a moderate to high risk of bias in the vast majority of available studies on antipsychotic medications in preventing or treating delirium. Evidence on the use of other medications to address neuropsychiatric disturbances of delirium is even more limited. For antipsychotic medications, studies show minimal to no benefits of treatment in patients with delirium, and the potential harms of antipsychotic side effects (including potential mortality in some patient subgroups) outweigh the benefits of their use. For additional discussion of the research evidence, see Appendix C, Statement 8.

### Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

### Review of Available Guidelines from Other Organizations

Many guidelines recommend that non-pharmacological interventions be used as a primary approach to treatment of neuropsychiatric and behavioral symptoms of delirium with a psychotropic medication considered only in situations in which non-pharmacological interventions are unsuccessful and when patients are significantly distressed or at risk of harming themselves or others (American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults 2015; BC Centre for Palliative Care 2017a; Danish Health Authority 2021; Gage and Hogan 2014; Mohanty et al. 2016; National Institute for

Health and Care Excellence 2023; Scottish Intercollegiate Guidelines Network 2019; Tropea et al. 2008). This recommendation is also consistent with that from the American Geriatrics Society Choosing Wisely recommendations on managing behavioral symptoms of hospitalized adults with delirium (Choosing Wisely 2021).

When a psychotropic medication does appear to be indicated for an individual patient, antipsychotic medications are typically suggested in lieu of benzodiazepines, unless there are specific indications for benzodiazepine use. However, if antipsychotic medications are considered for use, other guidelines offer caveats about using low doses, adjusting doses cautiously, and using second-generation antipsychotic agents rather than haloperidol for patients with Parkinson's disease or dementia with Lewy Bodies (American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults 2015; BC Center for Palliative Care 2017b; Gage and Hogan 2014; Mohanty et al. 2016; National Institute for Health and Care Excellence 2023).

### *Statement 9 – Antipsychotic Agents*

APA recommends **(1C)** that antipsychotic agents not be used to prevent delirium or hasten its resolution.

#### Benefits

Available studies on antipsychotic medications suggest that have minimal benefits in preventing or treating delirium. Limiting use of antipsychotic agents would reduce the risk of side effects from these medications (see Statement 8). In individuals with dementia, which is a risk factor for delirium and can co-occur with delirium, use of antipsychotic medication has been associated with increases in mortality and cerebrovascular adverse events. Limiting use of antipsychotic agents can also reduce the risk of drug-drug interactions and decrease the likelihood that unneeded antipsychotic medications will be continued after transitioning to another setting of care.

#### Harms

The potential harms of this statement are that a patient who might benefit from an antipsychotic medication will not receive it.

#### Patient Preferences

No specific information is available on patient preferences related to the use of antipsychotic agents to address neuropsychiatric disturbances in individuals with delirium. Clinical experience, including that with other psychiatric disorders in which antipsychotic medications are used, suggests that patients prefer to avoid use of an antipsychotic medication whenever possible.

#### Balancing of Benefits and Harms

The potential benefits of this recommendation were viewed as far outweighing the potential harms.

The level of research evidence is rated as low because there was a moderate to high risk of bias in the vast majority of available studies on antipsychotic medications in preventing or treating delirium. Because these studies show minimal to no benefits of antipsychotic treatment in patients with delirium or at risk for delirium, the potential harms of antipsychotic side effects (including potential mortality in

some patient subgroups) were viewed as outweighing the benefits of their use. For additional discussion of the research evidence, see Appendix C, Statement 8.

### Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

### Review of Available Guidelines from Other Organizations

The majority of guidelines on delirium (American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults 2015; BC Centre for Palliative Care 2017a; Danish Health Authority 2021; Devlin et al. 2018; Gage and Hogan 2014; Scottish Intercollegiate Guidelines Network 2019), but not all (Martin et al. 2010), note that there is insufficient evidence to support the use of antipsychotic medication to prevent delirium in at risk patients. In the treatment of delirium, particularly neuropsychiatric symptoms of delirium, a large number of guidelines recommend that non-pharmacological interventions be used as a primary approach to treatment of neuropsychiatric symptoms of delirium with a psychotropic medication considered only in situations in which non-pharmacological interventions are unsuccessful and when patients are significantly distressed or at risk of harming themselves or others (American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults 2015; BC Centre for Palliative Care 2017b; Danish Health Authority 2021; Gage and Hogan 2014; Mohanty et al. 2016; National Institute for Health and Care Excellence 2023; Scottish Intercollegiate Guidelines Network 2019; Tropea et al. 2008). However, several guidelines note that antipsychotic medications may have some role in treatment even when symptoms are less severe (Aldecoa et al. 2017; Cancer Care Ontario 2010; Martin et al. 2010). If an antipsychotic medication does seem appropriate for use in a patient with delirium, several guidelines suggest the need for additional caution in patients with Parkinson's disease or dementia with Lewy Bodies and that a second-generation antipsychotic would be preferred rather than haloperidol (BC Center for Palliative Care 2017 (FPON); Gage and Hogan 2014; National Institute for Health and Care Excellence 2023).

## *Statement 10 – Benzodiazepines*

APA recommends **(1C)** that benzodiazepines not be used in patients with delirium or who are at risk for delirium, including those with pre-existing cognitive impairment, unless there is a specific indication for their use.

### Benefits

Available studies on benzodiazepines suggest that they have minimal benefits in preventing or treating delirium. Limiting use of benzodiazepines would reduce the risk of side effects, drug-drug interactions, or medication misuse and decrease the likelihood that unneeded benzodiazepines will be continued after transitioning to another setting of care.

### Harms

For conditions other than delirium, there are some circumstances in which a benzodiazepine may be an optimal treatment. The potential harms of this statement are that a patient who might benefit from a benzodiazepine will not receive it. However, l

### Patient Preferences

No specific information is available on patient preferences related to the use of benzodiazepines in patients with delirium or who are at risk for delirium. Clinical experience suggests that patients prefer to avoid use of medication whenever possible unless it is clinically indicated.

### Balancing of Benefits and Harms

The potential benefits of this recommendation were viewed as far outweighing the potential harms.

The level of research evidence is rated as low because the number of studies was small, and the available research had a moderate to high risk of bias and inconsistent findings. Because these studies show minimal to no benefits of benzodiazepines in patients with delirium or at risk for delirium, the potential harms of benzodiazepine side effects or medication misuse were viewed as outweighing the benefits of their use, unless another indication for benzodiazepine treatment was present. For additional discussion of the research evidence, see Appendix C, Statement 10.

### Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

### Review of Available Guidelines from Other Organizations

The majority of guidelines note that benzodiazepines should generally not be used in individuals with delirium (American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults 2015; BC Center for Palliative Care 2017b; Cancer Care Ontario 2010; Chow et al. 2012; Gage and Hogan 2014; Martin et al. 2010; Potter et al. 2006). Some guidelines note that a benzodiazepine may be indicated in individuals experiencing alcohol or sedative withdrawal (American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults 2015; Cancer Care Ontario 2010; Gage and Hogan 2014; Martin et al. 2010) and in those already taking a benzodiazepine (Chow et al. 2012). Several guidelines note that benzodiazepines may be appropriate in the context of oncologic and palliative care (BC Centre for Palliative Care 2017a; Bush et al. 2018; Danish Health Authority 2021). If a benzodiazepine is used, one guideline notes that paradoxical agitation may occur (Danish Health Authority 2021).

## *Statement 11 – Dexmedetomidine to Prevent Delirium*

APA suggests **(2B)** that dexmedetomidine be used rather than other sedating agents to prevent delirium in patients who are undergoing major surgery or receiving mechanical ventilation in a critical care setting.

### Benefits

Use of dexmedetomidine in patients who are undergoing major surgery or receiving mechanical ventilation in a critical care setting is associated with variable but consistent benefits in reducing the incidence of delirium relative to placebo or other sedating medications.

### Harms

Potential harms of using dexmedetomidine in patients who are undergoing major surgery or receiving mechanical ventilation in a critical care setting include bradycardia and hypotension.

### Patient Preferences

No information is available on patient preferences related to the use of dexmedetomidine patients at risk for delirium in relation to surgery or critical care settings.

### Balancing of Benefits and Harms

The potential benefits of this recommendation in reducing the incidence of delirium were viewed as likely outweighing the potential harms of bradycardia and hypotension but there may be individual variations in potential risks of dexmedetomidine treatment depending on the patient's clinical status.

The level of research evidence is rated as moderate for reductions in the incidence of delirium because there were a substantial number of studies that had a low to moderate risk of bias and a large number of participants in the trials when taken together. The consistency of the findings in post-operative and ICU patients and in placebo-controlled and head-to-head comparisons increased the confidence in findings. For adverse effects of dexmedetomidine, the strength of research evidence was low, and most studies showed no significant differences in adverse effects between the dexmedetomidine and comparison groups. Nevertheless, the potential balancing of benefits and harms was less clear because of the potential for bradycardia or hypotension in individual patients in the context of a post-operative or critical care setting. For additional discussion of the research evidence, see Appendix C, Statement 11.

### Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

### Review of Available Guidelines from Other Organizations

Few guidelines comment on the use of dexmedetomidine to prevent delirium. The Canadian Coalition for Seniors' Mental Health suggests that dexmedetomidine should be considered as a sedative alternative to benzodiazepines and propofol to reduce delirium risk in mechanically ventilated patients (Gage and Hogan 2014). In contrast, the Society of Critical Care Medicine suggests that dexmedetomidine not be used to prevent delirium in all critically ill adults (Devlin et al. 2018).

### *Statement 12 – Dexmedetomidine in Patients with Delirium*

APA suggests **(2C)** that when patients with delirium are sedated for mechanical ventilation in a critical care setting, dexmedetomidine be used rather than other sedating agents.

### Benefits

Use of dexmedetomidine in patients who are sedated for mechanical ventilation in a critical care setting is associated with variable but greater response of delirium relative to placebo or other sedating medications. It may also reduce time to weaning from mechanical ventilation.

### Harms

Potential harms of using dexmedetomidine in patients who are receiving mechanical ventilation in a critical care setting include bradycardia and hypotension.

### Patient Preferences

No information is available on patient preferences related to the use of dexmedetomidine patients at risk for delirium in relation to surgery or critical care settings.

### Balancing of Benefits and Harms

The potential benefits of this recommendation in the response of delirium symptoms to dexmedetomidine were viewed as likely outweighing the potential harms of bradycardia and hypotension with treatment, but there may be individual variations in potential risks of dexmedetomidine treatment depending upon the patient's clinical status.

The level of research evidence is rated as low for response of delirium symptoms, facilitation of weaning from mechanical ventilation, and adverse effects of dexmedetomidine because the number of studies and the total number of patients was small. The potential balancing of benefits and harms favored use of dexmedetomidine but was less clear because of the potential for bradycardia or hypotension in individual patients in the context of a critical care setting. For additional discussion of the research evidence, see Appendix C, Statement 12.

### Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

### Review of Available Guidelines from Other Organizations

Few guidelines comment on the use of dexmedetomidine in critical care patients with delirium. In this regard, the Society of Critical Care Medicine suggests that dexmedetomidine can be used "in mechanically ventilated adults where agitation is precluding weaning/extubation" (Devlin et al. 2018).

## *Statement 13 – Melatonin and Ramelteon*

APA suggests **(2C)** that melatonin and ramelteon not be used to prevent or treat delirium.

### Benefits

Limiting use of melatonin and ramelteon is beneficial by not giving a medication that does not appear to have benefits for patients in preventing or treating delirium.

### Harms

The potential harms of this statement are that a patient who might benefit from melatonin or ramelteon will not receive it.

### Patient Preferences

No information is available on patient preferences related to the use of melatonin or ramelteon in individuals with delirium or at risk for delirium. Clinical experience suggests that many individuals would benefit from and prefer an enhanced amount and quality of sleep while hospitalized and may be interested in taking a medication to facilitate this even if the benefits are minimal or inconsistent.

### Balancing of Benefits and Harms

The potential benefits of this recommendation were viewed as likely outweighing the potential harms.

Although the benefits of melatonin and ramelteon were minimal in preventing or treating delirium, these medications have been used for treatment of insomnia, particularly in relation to circadian rhythm disturbances, and there are few side effects of these medications. Thus, the potential benefits as well as the potential risks of using melatonin and ramelteon appear to be small, and the balance of benefits and harms is unclear.

The level of research evidence is rated as low because most studies had a moderate risk of bias, many had small samples, and only a few studies were available that assessed effects of these medications in patients with delirium. For additional discussion of the research evidence, see Appendix C, Statement 13.

#### Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

#### Review of Available Guidelines from Other Organizations

Several guidelines note that there is insufficient evidence to support the use of melatonin in patients with delirium or at risk for delirium (BC Centre for Palliative Care 2017a; Danish Health Authority 2021; Gage and Hogan 2014). Other guidelines do not comment on the use of ramelteon in preventing or treating delirium.

## Transitions of Care

### *Statement 14 – Medication Review at Transitions of Care*

APA recommends **(1C)** that, in patients with delirium or who are at risk for delirium, a detailed medication review, medication reconciliation, and reassessment of the indications for medications, including psychotropic medications, be conducted at transitions of care within the hospital.

#### Benefits

In patients with delirium or who are at risk for delirium, a detailed medication review, medication reconciliation, and reassessment of the indications for medications at transitions of care within the hospital can help in identifying medications that may be contributing to delirium. Medication review can also identify medications that may be associated with other adverse effects, drug-disease interactions, or drug-drug interactions. Once identified, tapering or discontinuing of non-essential medications can reduce medication costs and side effects for patients.

#### Harms

The harms of conducting a detailed medication review, medication reconciliation, and reassessment of the indications for medications include time spent on assessment that could be used on other activities of benefit to the patient. If medication review is erroneous in identifying potentially problematic medications, a necessary medication could be inappropriately stopped.

#### Patient Preferences

No specific information is available on patient preferences related to a detailed review of medications that may be contributing to or could predispose someone to developing delirium. However, clinical

experience suggests that the vast majority of patients would want and would value having a careful and thorough review of medications, with the potential to improve their care and their outcomes.

### Balancing of Benefits and Harms

The potential benefits of this recommendation were viewed as far outweighing the potential harms.

The level of research evidence is rated as low because there is limited evidence on the benefits of medication review, medication reconciliation, or reassessment of the indications for medication. The majority of studies that have examined medication-related interventions in patients with delirium have been small multi-component trials or retrospective or observational studies. However, expert opinion suggests that the benefits of a detailed medication review outweigh the harms of such a review, which appear to be minimal. For additional discussion of the research evidence, see Appendix C, Statement 14.

### Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

### Review of Available Guidelines from Other Organizations

Guidelines on delirium do not specifically recommend medication review at transitions of care but they do emphasize the importance of reviewing patients' medications or avoiding use of medications that appear to increase the risk of developing or exacerbating delirium (Aldecoa et al. 2017; American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults 2015; BC Centre for Palliative Care 2017a; Bush et al. 2018; Cancer Care Ontario 2010; Danish Health Authority 2021; Devlin et al. 2018; Gage and Hogan 2014; Mohanty et al. 2016; National Institute for Health and Care Excellence 2023; Potter et al. 2006; Registered Nurses' Association of Ontario 2016; Scottish Intercollegiate Guidelines Network 2019; Tropea et al. 2008). As such, this recommendation is generally consistent with that from the American Geriatrics Society Choosing Wisely recommendations, which note the importance of a medication review before prescribing medications (Choosing Wisely 2021).

### *Statement 15 – Follow-up Planning at Transitions of Care*

APA recommends **(1C)** that, when patients with delirium are transferred to another setting of care, plans for follow-up include:

- continued assessments for persistence of delirium;
- detailed medication review, medication reconciliation, and reassessment of the indications for medications, including psychotropic medications;
- assessment of consequences of delirium (e.g., post-traumatic symptoms, cognitive impairment); and
- psychoeducation about delirium for patients and their care partners.

### Benefits

Attention to follow-up plans when patients with delirium are transferred to another setting of care can help assure that patients are monitored for persistence of delirium and its consequences after transitioning to another setting. Promoting enhanced understanding of delirium in patients and their

care partners may aid in follow-up and help individuals understand emotionally upsetting perceptions or behaviors that may have occurred while a patient was delirious. A detailed medication review, medication reconciliation, and reassessment of the indications for medications at transitions of care can help in identifying medications that may be perpetuating delirium and may identify medications, such as antipsychotic agents or benzodiazepines, that are no longer needed. Once identified, tapering or discontinuing of non-essential medications can reduce medication costs, side effects, and drug-disease or drug-drug interactions.

### Harms

The harms of developing a follow-up plan upon transfer to another setting of care include time spent that could be used on other activities of benefit to the patient. If medication review is erroneous in identifying potentially problematic medications, a necessary medication could be inappropriately stopped.

### Patient Preferences

No specific information is available on patient preferences related to developing a follow-up plan or conducting a detailed review of medications. However, clinical experience suggests that the vast majority of patients would want and would value having a careful and thorough plan for follow-up care as well as a detailed review of medications, with the potential to improve their care and their outcomes.

### Balancing of Benefits and Harms

The potential benefits of this recommendation were viewed as far outweighing the potential harms.

The level of research evidence is rated as low because there is limited evidence on the benefits of developing a follow-up plan or conducting a detailed review of medications. However, these benefits appear to outweigh the harms of a follow-up plan and detailed medication review, which appear to be minimal. For additional discussion of the research evidence, see Appendix C, Statement 15.

### Differences of Opinion Among Writing Group Members

There were no differences of opinion. The writing group voted unanimously in favor of this recommendation.

### Review of Available Guidelines from Other Organizations

Few guidelines discuss aspects of follow-up care for individuals with delirium. Principles of medication review upon transitioning to another setting are consistent with recommendations for medication reconciliation (The Joint Commission 2023) and general guideline recommendations related to medication review (Aldecoa et al. 2017; American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults 2015; BC Centre for Palliative Care 2017a; Bush et al. 2018; Cancer Care Ontario 2010; Choosing Wisely 2021; Danish Health Authority 2021; Devlin et al. 2018; Gage and Hogan 2014; Mohanty et al. 2016; National Institute for Health and Care Excellence 2023; Potter et al. 2006; Registered Nurses' Association of Ontario 2016; Scottish Intercollegiate Guidelines Network 2019; Tropea et al. 2008). Several guidelines also note the importance of follow-up communication and documentation (Gage and Hogan 2014; Scottish Intercollegiate Guidelines Network 2019; Tropea et al. 2008) as well as patient, family, and other caregiver education after discharge (Tropea et al. 2008).

# Appendix G. Description of Additional Studies Reviewed

The Pacific Northwest EPC systematic review included other studies that did not have a sufficient strength of research evidence or evidence of benefits relative to harms to be incorporated into a guideline statement. These are summarized in the sections that follow.

## Additional Non-Pharmacological Interventions for Prevention of Delirium

Non-pharmacological studies identified in the Pacific Northwest EPC systematic review aimed at prevention of delirium included post-operative use of liberal versus restrictive red blood cell transfusion (Gregersen et al. 2015; Gruber-Baldini et al. 2013); use of "fast-track" surgery or enhanced recovery after surgery—an approach to perioperative management designed to prevent post-operative delirium (Jia et al. 2014); variations on mechanical ventilation (e.g., giving patients no sedation, using interrupted sedation, using continuous sedation [Girard et al. 2008; Mehta et al. 2012; Nassar Junior and Park 2014]); and a trial of fluid therapy (Bruera et al. 2013). These interventions largely showed inconsistent or non-significant effects, although "fast-track" colorectal carcinoma surgery was associated with significantly lower delirium incidence versus usual care (3.4% vs. 12.9%, *P*=0.008 [Jia et al. 2014]).

Some of these interventions were explored within subpopulations of ICU patients and showed few significant differences in delirium incidence, mortality, adverse events, or length of stay. In two studies, in a total of 813 ICU patients on mechanical ventilation, a protocol of no sedation was compared with one of sedation that included daily interruption until patients awakened (Olsen et al. 2020; Strøm et al. 2010). In the smaller of the two studies (N=113) comparing no sedation with sedation, the incidence of hyperactive delirium was significantly greater in patients who were not sedated (20% vs. 7%, *P*=0.04 [Strøm et al. 2010]). In this study, patients without sedation had shorter ICU stays (mean 13 days vs. 23 days with interrupted sedation, *P*=0.032 [Strøm et al. 2010]). Hospital stay was a mean of 34 days compared with 58 days (*P*=0.004 [Strøm et al. 2010]). By contrast, the larger of the two studies (N=700) found that patients given no sedation had 1 more day without coma or delirium than those sedated (median 27 days vs. 26 days, 95% CI 0–2 for the difference [Olsen et al. 2020)]. Another two trials (N=758) used sedation with an opioid, benzodiazepine, and/or propofol, and compared daily interruption of sedation with continuous sedation (Girard et al. 2008; Mehta et al. 2012). A fifth trial with high risk of bias also assessed daily interruption of sedation, and compared it with "intermittent" sedation, where interruption was attempted three times daily in 60 participants (Nassar Junior and Park 2014). A sixth study compared Synchronized Intermittent Mandatory Ventilation with Pressure Support (SIMV+PS) to Assist/Control (A/C) ventilation in 40 patients with acute respiratory distress syndrome who were intubated (Luo et al. 2015). The two trials comparing interrupted with continuous sedation found no difference in the incidence of delirium (62% vs. 62%, RR 1.02, 95% CI 0.92–1.14, $I^2$=0% [Girard et al. 2008; Mehta et al. 2012]). Interruption once a day compared with 3 times daily (intermittent sedation) also did not have a significant effect on delirium incidence (40% vs. 30%, *P*=0.47 [Nassar Junior and Park 2014]). There was again no statistically significant difference in delirium incidence between SIMV+PS (0%) and A/C ventilation groups (20%, *P*=0.11 [Luo et al. 2015]).

Eight trials (N=1,254) assessed various mechanical interventions for the prevention of delirium in the surgical setting, including cerebral and cerebral oximetry monitoring (Lei et al. 2017), transcutaneous electrical acupoints stimulation (TEAS; Gao et al. 2018), "fast-track" surgery (Jia et al. 2014), variations in

mean arterial pressure (MAP) intra-operatively (Brown et al. 2019; Xu et al. 2020), variations in mechanical ventilation (Wang et al. 2015; J. Wang et al. 2020), and continuous positive airway pressure (CPAP; Nadler et al. 2017). "Fast-track" surgery was not well described but reportedly included pre-operative oral purgatives, thoracic epidural, and early out of bed mobilization. Comparisons were usual care, sham TEAS (Gao et al. 2018), and varying levels of MAP (Xu et al. 2020). Assessment times ranged from the second post-operative day until discharge. Outcome reporting was uneven, but the most common outcomes were incidence of delirium and length of hospital or ICU stay. Three studies enrolled patients from the United States or Canada (Brown et al. 2019; Lei et al. 2017; Nadler et al. 2017), and five studies enrolled patients in China (Gao et al. 2018; Jia et al. 2014; Wang et al. 2015; J. Wang et al. 2020; Xu et al. 2020). One additional trial (N=55) compared mild hyperthermia (nasopharyngeal temperature of 34°C to 35°C) with usual care (36°C) after acute aortic dissection (Fu et al. 2020). Sample sizes were generally small; most had fewer than 200 subjects. The weighted mean age of patients was 70 years old, and 51% were female. Race was only reported in one trial, which included 13.1% Black patients and 5.5% patients of another race (Brown et al. 2019). Patients with cognitive impairments, such as dementia, were either not reported or excluded, except in one study that included 2% of patients with dementia or severe cognitive impairment (Nadler et al. 2017). The scales used to assess delirium included CAM, CAM-ICU, DSM-IV, DRS-R-98, and RASS.

All nine trials reported incidence of delirium (Table G-1). Two trials found variable lung protective mechanical ventilation during surgery resulted in significantly fewer cases of delirium (Wang et al. 2015; J. Wang et al. 2020). Three other interventions that were associated with a significantly lower incidence of delirium included TEAS during spine surgery (Gao et al. 2018), "fast-track" colorectal carcinoma surgery (Jia et al. 2014), and increased MAP during cardiac bypass surgery (Brown et al. 2019). In the latter study, delirium duration was shorter with the intervention than the control group (elevated MAP median 0 day vs. 1 day, $P$=0.05), but delirium severity did not differ (median 7 vs. 8 respectively, $P$=0.10) (Brown et al. 2019). The remaining studies did not find statistically significant differences in incidence of delirium and used CPAP in orthopedic surgery patients (Nadler et al. 2017), reduced MAP in older orthopedic surgery patients (Xu et al. 2020), and cerebral oximetry monitoring in cardiac surgery patients (Lei et al. 2017).

The effects of these interventions on length of stay were variable. Overall, hospital length of stay was reduced compared to usual care with "fast-track" colorectal carcinoma surgery (9.01 days vs. 13.21 days respectively, $P$<0.001 [Jia et al. 2014]), but not with cerebral oximetry monitoring (median of 8 days in both groups [Lei et al. 2017], variable protective mechanical ventilation (10.3 days vs. 10.7 days respectively, $P$=0.49 [Wang et al. 2015]), or mild hyperthermia (mean of 20.40 days vs. 22.78 days, $P$=0.31 [Fu et al. 2020]). For ICU length of stay, mild hyperthermia was associated with a shorter length of stay (mean of 5.53 days vs. 9.35 days, $P$=0.38 [Fu et al. 2020]), but cerebral oximetry monitoring was not (both median 2.04 days [Lei et al. 2017]). Regarding mortality and adverse events, one trial that compared cerebral oximetry monitoring with usual care during cardiac surgery reported no difference between the intervention and control groups on incidence of mortality (2.4% vs. 3% respectively [Lei et al. 2017]). Adverse events reported were limited to surgical complications.

In palliative care patients, one trial (N=101) explored daily fluid therapy with 1000 mL of normal saline compared with 100 mL saline given as placebo and only found a statistically significant difference between groups for the NuDESC night score, which deteriorated more between baseline and day 4 for placebo than for treated patients (*P*=0.03 [Bruera et al. 2013]).

Table G-1. Delirium incidence in other prevention studies

| **Study**<br>**Risk of Bias**<br>**Sample Size** | **Interventions**<br>**Duration** | **Population** | **Main Findings** |
|---|---|---|---|
| Study: Nadler et al. 2017<br>RoB: Low<br>N: 114 | Interventions: CPAP vs. usual care<br>Duration: During surgery | Age: ≥50 years<br>Surgery type: hip or knee surgery | Difference in delirium incidence not statistically significant (21% vs. 16%, OR 1.36, 95% CI 0.52–3.54, *P*=0.53) |
| Study: Brown et al. 2019<br>RoB: Low<br>N: 199 | Interventions: Elevated MAP during cardiac bypass based above pre-bypass evaluating autoregulation level vs. usual care<br>Duration: During surgery | Age: ≥55 years<br>Surgery type: cardiac surgery | Difference in delirium incidence significantly lower with elevated MAP (POD 3: 38% vs. 53%, OR 0.55, 95% CI 0.31–0.97, P=0.04) |
| Study: Xu et al. 2020<br>RoB: Moderate<br>N: 150 | Interventions: Intra-operative MAP maintained at 10% to 20% below baseline vs. baseline to 10% below vs. 10% above baseline<br>Duration: During surgery | Age: >65 years<br>Surgery type: orthopedic surgery (hip) | Difference between groups not statistically significant (POD 3: 4% vs. 2% vs. 0%, *P*=0.360) |
| Study: Lei et al. 2017<br>RoB: Moderate<br>N: 249 | Interventions: Cerebral oximetry monitoring vs. usual care<br>Duration: Through POD 7 | Age: ≥60 years<br>Surgery type: cardiac surgery | Difference in delirium incidence not statistically significant (24% vs. 25%, OR 0.98, 95% CI 0.55–1.76, *P*=0.97) |
| Study: Gao et al. 2018<br>RoB: Moderate<br>N: 64 | Interventions: TEAS vs. sham<br>Duration: During surgery | Age: ≥55 years<br>Surgery type: spine surgery | Difference in delirium incidence significantly lower with TEAS (6.3% vs. 25.0%, *P*=0.039) |
| Study: Jia et al. 2014<br>RoB: Moderate<br>N: 233 | Interventions: “Fast-track” surgery vs. usual care<br>Duration: Through POD 3 | Age: 70–88 years<br>Surgery type: colorectal carcinoma surgery | Difference in delirium incidence significantly lower with “fast-track” surgery (3.4% vs. 12.9%, *P*=0.008) |
| Study: Wang et al. 2015<br>RoB: Moderate<br>N: 174 | Interventions: Variable lung protection mechanical ventilation vs. usual care<br>Duration: During surgery | Age: ≥60 years<br>Surgery type: gastrointestinal tumor resection | Difference in delirium incidence significantly lower with lung protection (15% vs. 29%, *P*=0.036) |
| Study: Wang J. et al. 2020<br>RoB: Moderate<br>N: 71 | Interventions: Lung protection ventilation vs. usual care<br>Duration: During surgery | Age: ≥65 years<br>Surgery type: mixed surgery | Difference in delirium incidence significantly lower with lung protection (6% vs. 25%, *P*=0.039) |

| Study<br>Risk of Bias<br>Sample Size | Interventions<br>Duration | Population | Main Findings |
|---|---|---|---|
| Study: Fu et al. 2020<br>RoB: High<br>N: 55 | Interventions: Mild hyperthermia vs. usual care<br>Duration: 24 hours | Age: 18–75 years<br>Surgery type: acute aortic dissection | Difference in delirium incidence not statistically significant (37% vs. 465, *P*=0.48) |

*Abbreviations.* CI=confidence interval; CPAP=continuous positive airway pressure; MAP=mean arterial pressure; N=number; OR=odds ratio; POD=post-operative day; RoB=risk of bias; TEAS=transcutaneous electrical acupoint stimulation.

*Source*. Brown et al. 2019; Fu et al. 2020; Gao et al. 2018; Jia et al. 2014; Lei et al. 2017; Nadler et al. 2017; Wang et al. 2015; J. Wang et al. 2020; Xu et al. 2020.

## Additional Pharmacological Interventions for Prevention of Delirium

The Pacific Northwest EPC systematic review included additional pharmacological interventions aimed at prevention of delirium. Bispectral index (BIS)-guided anesthesia demonstrated a lower incidence of delirium, but none of the pooled analyses for other anesthetic comparisons showed significant differences between groups. Steroids resulted in a significant reduction in incident delirium in post-surgical patients. Opioid and GABAergic medications generally had no effect on incidence or related outcomes (e.g., mortality, delirium duration, ICU/hospital length of stay). Cholinesterase inhibitors demonstrated no impact on delirium incidence in post-operative patients, but subgroup analyses showed a significant reduction in orthopedic patients. Finally, among miscellaneous pharmacologic interventions, some did show a significant reduction in delirium incidence in post-operative patients, including hypertonic saline, ondansetron, and methylene blue but the number of studies was small.

### *Electroencephalography-Guided Anesthesia*

The Pacific Northwest EPC identified nine trials (N=4,030) of electroencephalography-guided anesthesia (e.g., BIS) as compared to usual anesthesia care (Chan et al. 2013; Cotae et al. 2021; Kunst et al. 2020; Radtke et al. 2013; Sieber et al. 2010, 2018; C.J. Tang et al. 2020; Wildes et al. 2019; Zhou et al. 2018). The aim of electroencephalography-guided anesthesia was to optimize the depth of anesthesia and avoid deep sedation, although differing anesthetic parameters were used among the studies. Orthopedic surgery was performed in two trials (Sieber et al. 2010, 2018), cardiac surgery in one trial (Kunst et al. 2020), colorectal surgery in one trial (Zhou et al. 2018), trauma surgery in one trial (Cotae et al. 2021), and a variety of surgeries in four trials (Chan et al. 2013; Radtke et al. 2013; C.J. Tang et al. 2020; Wildes et al. 2019). Five trials were rated as having a moderate risk of bias.

BIS-guided anesthesia resulted in a very small but statistically significant difference in incidence of delirium compared with usual anesthesia (8 RCTs, N=3,956; 19.8% vs. 23.8%, RR 0.78, 95% CI 0.61–0.98, $I^2$=64% [Chan et al. 2013; Kunst et al. 2020; Radtke et al. 2013; Sieber et al. 2010, 2018; C.J. Tang et al. 2020; Wildes et al. 2019; Zhou et al. 2018]). The findings did not differ significantly by type of surgery or study risk of bias (interaction *P*-values 0.15). No BIS-guided anesthesia trial reported severity of delirium (Sieber et al. 2010; Wildes et al. 2019), but depth of anesthesia did not alter the duration of delirium significantly (N=331; MD -0.01 days, 95% CI -0.35–0.33, $I^2$=0%). There was also no significant difference in length of hospital stay (6 trials, N=3,665; MD -0.10, 95% CI -0.82–0.61, $I^2$=78%) or length of ICU stay

(N=1,727; MD 0.03 days, 95% CI -0.06–0.12, $I^2$=11%) (Chan et al. 2013; Kunst et al. 2020; Sieber et al. 2010; Wildes et al. 2019) between BIS-guided and usual anesthesia care. Mortality across five trials did not differ significantly between BIS-guided anesthesia and usual anesthesia care (N=2,785; 2.8% vs. 4.1%, RR 0.56, 95% CI 0.24–1.30, $I^2$=50% [Kunst et al. 2020; Radtke et al. 2013; Sieber et al. 2010, 2018; Wildes et al. 2019]). In terms of post-operative complications or adverse effects, findings were mixed. One trial (N=902) reported significantly fewer post-operative complications in the BIS-guided anesthesia group compared with the usual care group (10.7% vs. 20.8%, *P*=0.01 [Chan et al. 2013]), and another trial comparing usual anesthesia care plus anesthesia depth monitoring and nociception reported fewer patients experienced at least 1 episode of hypotension with anesthesia depth monitoring than in the usual care group (18 vs. 36, *P*=0.0001 [Cotae et al. 2021]). In contrast, one trial found no difference in the number of patients with one or more complications (N=114; 46% light sedation vs. 53% deep sedation, *P*=0.57 [Sieber et al. 2010]) and another trial found no difference in the risk of experiencing any adverse event (N=204; 14% intervention vs. 16% standard care, RR 0.88, 95% CI 0.45–1.69 [C.J. Tang et al. 2020]).

### *Additional Anesthetic Comparisons*

26 trials (N=5,819) evaluated other anesthesia comparisons: three of xenon gas versus sevoflurane gas (Al Tmimi et al. 2020; Coburn et al. 2018; Stoppe et al. 2013); four of sevoflurane gas versus propofol (Ishii et al. 2016; Lurati Buse et al. 2012; X. Mei et al. 2020; Nishikawa et al. 2004); one of desflurane versus propofol (Tanaka et al. 2017); three of ketamine versus normal saline (Avidan et al. 2017; Hollinger et al. 2021; Hudetz et al. 2009); nine of a form of regional anesthesia versus placebo, general anesthesia, or opioid therapy (L. Jin et al. 2020; Li et al. 2021; Mann et al. 2000; Mouzopoulos et al. 2009; Papaioannou et al. 2005; Strike et al. 2019; Unneby et al. 2020; Uysal et al. 2020; Williams-Russo et al. 1995); one of a pecto-intercostal fascial plane block versus placebo (Khera et al. 2021), one of a deep versus standard neuromuscular blockade (rocuronium [C.S. Oh et al. 2021]), one of anaortic off-pump coronary bypass with total arterial revascularization versus carbon dioxide field flooding or use of vein grafts (Szwed et al. 2021), one of unilateral spinal anesthesia versus combined lumbar-sacral plexus block plus general anesthesia (Tang et al. 2021); and two of high- versus low-pressure systemic perfusion (Hu et al. 2021; Siepe et al. 2011). Cardiac surgery was performed in six trials (Hudetz et al. 2009; Khera et al. 2021; Siepe et al. 2011; Stoppe et al. 2013; Strike et al. 2019; Szwed et al. 2021), orthopedic surgery in seven trials (Coburn et al. 2018; X. Mei et al. 2020; Mouzopoulos et al. 2009; Tanaka et al. 2017; Unneby et al. 2020; Uysal et al. 2020; Williams-Russo et al. 1995), abdominal surgery in three trials (Ishii et al. 2016; Mann et al. 2000; Nishikawa et al. 2004), one trial of esophageal surgery (L. Jin et al. 2020), and a variety of major surgeries in seven trials (Avidan et al. 2017; Hu et al. 2021; Li et al. 2021; Lurati Buse et al. 2012; C.S. Oh et al. 2021; Papaioannou et al. 2005; Tang et al. 2021). Five trials were rated as having a low risk of bias, one as having a high risk of bias, and the remainder were rated as having moderate risk of bias.

None of the pooled analyses for other anesthetic comparisons showed significant differences between groups. Based on three trials, incidence of delirium was not reduced by the use of ketamine (N=821; RR 0.50, 95% CI 0.21–1.71, $I^2$=58% [Avidan et al. 2017; Hollinger et al. 2021; Hudetz et al. 2009]). A subgroup analysis was not possible with only three studies, but the two studies that enrolled patients

undergoing a variety of types of surgeries clearly showed no effect of ketamine, whereas the single study of patients undergoing cardiac surgery did show a benefit (N=58; 3.4% vs. 31%, RR 0.11, 95% CI 0.02–0.82 [Hudetz et al. 2009]). The incidence of delirium did not differ significantly in comparisons of xenon gas with sevoflurane gas, and sevoflurane or desflurane with propofol, regardless of surgery type (Coburn et al. 2018; Ishii et al. 2016; Lurati Buse et al. 2012; X. Mei et al. 2020; Nishikawa et al. 2004; Stoppe et al. 2013; Tanaka et al. 2017).

Eight trials compared regional/epidural anesthesia with general anesthesia (L. Jin et al. 2020; Papaioannou et al. 2005; Unneby et al. 2020; Williams-Russo et al. 1995), opioids (Mann et al. 2000; Strike et al. 2019) IV acetaminophen (Uysal et al. 2020), or placebo (block given for pain prophylaxis [Mouzopoulos et al. 2009]). A pooled analysis of two trials that compared paravertebral block in cardiac surgery (Strike et al. 2019) or in esophagectomy (L. Jin et al. 2020) found less delirium with the block (N=211; 12.3% vs. 26.7%, RR 0.48, 95% CI 0.26–0.88). One trial enrolled hip fracture patients aged 70 years or older who were deemed to be at intermediate or high risk for delirium and reported prophylactic fascia iliac compartment block was associated with lower delirium incidence than placebo (10.8% vs. 23.8%, RR 0.45, 95% CI 0.24–0.87 [Mouzopoulos et al. 2009]). The difference in absolute incidence of delirium post-operatively was large (14%) in a small study (N=92) of high-pressure systemic perfusion compared with low-pressure perfusion, but the difference was not statistically significant (Siepe et al. 2011). In one cardiac surgery trial, there was no difference between a pecto-intercostal fascial plane block and placebo for midline sternotomy pain on delirium incidence (7.5% vs. 12.5%, RR 0.60, 95% CI 0.15–2.34 [Khera et al. 2021]). In another cardiac surgery trial, however, anaortic off-pump coronary bypass with total arterial revascularization resulted in a lower incidence of delirium than off-pump coronary artery bypass with carbon dioxide surgical field flooding (12.7% vs. 32.8%, RR 0.39, 95% CI 0.19–0.81 [Szwed et al. 2021]). In the same trial, anaortic off-pump coronary bypass with total arterial revascularization also resulted in less delirium than conventional off-pump coronary bypass with vein grafts (12.7% vs. 35.9%, RR 0.35, 95% CI 0.17–0.73), whereas there was no difference in delirium incidence between the two comparisons groups (RR 0.91, 95% CI 0.57–1.48 [Szwed et al. 2021]). In a trial in patients having non-cardiothoracic surgery with general anesthesia, maintaining a high mean arterial pressure versus a low mean arterial pressure resulted in fewer patients with delirium (11.6% vs. 25.2%, RR 0.46, 95% CI 0.28–0.77 [Hu et al. 2021]). There was also a lower incidence of delirium in patients having noncardiac thoracic or abdominal surgery with general anesthesia plus an epidural versus general anesthesia alone (1.8% vs. 5.0%, RR 0.35, 95% CI 0.20–0.63 [Li et al. 2021]). In patients with hip fracture, there was no difference in delirium incidence between unilateral spinal anesthesia compared with combined lumbar-sacral plexus block plus general anesthesia (10.9% vs. 14.3%, RR 0.76, 95% CI 0.28–2.06 [Tang et al. 2021]). In the trial in patients having a hip replacement, patients received a deep neuromuscular blockade with additional rocuronium or a standard neuromuscular blockade and found no difference in delirium incidence base on rocuronium dose (17.1% vs. 34.1%, RR 0.50, 95% CI 0.23–1.11 [C.S. Oh et al. 2021]).

In terms of other delirium outcomes, there was no difference in delirium duration between intra-operative xenon gas and servoflurane gas in a pooled analysis of two trials (N=108; MD -0.08 days, 95% CI, -0.69–0.54 [Al Tmimi et al. 2020; Coburn et al. 2018]). In a comparison of fascial iliac compartment

block and placebo, the duration of delirium was significantly shorter in study participants who experienced it (N=36; MD -5.75 days, 95% CI -9.85 to -1.97 [Mouzopoulos et al. 2009]). All patients received the same epidural anesthesia during surgery in this study. In a trial in patients having non-cardiothoracic surgery with general anesthesia, maintaining a high mean arterial pressure versus a low mean arterial pressure resulted in a shorter duration of delirium (median 2 days vs. 3 days, *P*=0.006 [Hu et al. 2021]). The iliac block group also had significantly lower severity of delirium (moderate size of effect), based on the highest value of the DRS-R-98 (14.34 vs. 18.61 in the placebo group, MD 4.27, 95% CI 1.8–5.64) in one small trial (N=11; Mouzopoulos et al. 2009). Delirium severity was also lower with sevoflurane gas than with propofol in a small trial (N=50) of patients having abdominal surgery (3 to 5 points on post-operative days 2 to 3 [Nishikawa et al. 2004]) but not different between groups in a trial (N=209) of patients having orthopedic surgery (X. Mei et al. 2020). A trial comparing xenon gas with servoflurane gas in cardiac surgery patients also reported no difference in delirium severity post-operatively (Al Tmimi et al. 2020).

Length of ICU stay after cardiac surgery was significantly shorter with paravertebral block compared with patient-controlled opioid analgesia in a single small study (N=44; MD -5.73 days, 95% CI -8.64 to -2.82 [Strike et al. 2019]). Other trials in patients undergoing cardiac surgery found no differences on duration of ICU stay between xenon gas and sevoflurane gas (2 trials, N=220; MD -0.17 days, 95% CI -0.63–0.29 [Al Tmimi et al. 2020; Stoppe et al. 2013]), between ketamine 0.5 mg/kg and normal saline (1 trial, N=58; MD 0.00 days, 95% CI -0.81–0.81 [Hudetz et al. 2009]), or between high-pressure perfusion and low-pressure perfusion (1 trial, N=92; -0.80 days, 95% CI -2.11–0.51 [Siepe et al. 2011]). One trial of pecto-intercostal fascial plane block versus placebo for midline sternotomy pain found no difference between groups in duration of ICU stay (MD -0.30 days, 95% CI -0.98–0.38) or in length of hospital stay (MD 0.83 days, 95% CI, -0.51–2.18 [Khera et al. 2021]). In noncardiac surgery patients, who received epidural plus general anesthesia versus general anesthesia alone, the duration of ICU stay was slightly shorter (HR 1.30, 95% CI 1.05–1.62, *P*=0.017) but the hospital length of stay did not differ (HR 1.01, 95% CI 0.92–1.12, *P*=0.778 [Li et al. 2021]).

One trial found shorter hospital stays with paravertebral block in esophagectomy compared with patient-controlled systemic opioid analgesia (N=167; MD -0.90 days, 95% CI -1.24 to -0.55 [L. Jin et al. 2020]) although there was no difference in hospital stay with paravertebral block versus patient controlled systemic opioids in cardiac surgery (N=44; MD 0.80 days, 95% CI -3.85–5.45 [Strike et al. 2019]) or with femoral nerve block compared with conventional pain management in hip surgery (N=231; MD 1.6 days, 95% CI -2.77–5.97 [Unneby et al. 2020]). Ina pooled analysis of three trials (N=476) of xenon gas versus sevoflurane gas, there was also no difference in length of hospital stay (MD -0.28 days, 95% CI -1.24–0.67 [Al Tmimi et al. 2020; Coburn et al. 2018; Stoppe et al. 2013]). Similarly, one trial each of ketamine versus normal saline (N=58; MD 1.00 days, 95% CI -0.82–2.82 [Hudetz et al. 2009]); high- versus low-pressure systemic perfusion (N=92; MD 0.40 days, 95% CI -2.67–3.47 [Siepe et al. 2011]); and sufentanil plus a bupivacaine epidural followed by sufentanil plus bupivacaine in a patient-controlled anesthesia (PCA) epidural pump versus sufentanil IV followed by a PCA morphine pump (N=64; MD -0.50 days, 95% CI -3.26–2.26 [Mann et al. 2000]) found no differences between comparisons in hospital stay. One trial in noncardiac surgery comparing high mean arterial pressure to low mean

arterial pressure also found no difference in length of hospital stay (MD 0 days, 95% CI -4.24–4.24 [Hu et al. 2021]).

Regarding mortality and adverse events, one trial each reported no deaths with xenon gas or sevoflurane gas (N=30; Stoppe et al. 2013) or with high- or low-pressure systemic perfusion (N=92; Siepe et al. 2011) among cardiac surgery patients. There was no difference in reported deaths in one trial each of: xenon gas versus sevoflurane gas in orthopedic surgery patients (N=256; 0% vs. 4.5%, RR 0.10, 95% CI 0.01–1.73 [Coburn et al. 2018]), sevoflurane gas versus propofol in patients who underwent a variety of surgeries (N=385; 13.6% vs. 11.4%, RR 1.19, 95% CI 0.70–2.02 [Lurati Buse et al. 2012]), and paravertebral block versus patient controlled systemic opioids in cardiac surgery patients (N=44; 4.5% vs. 9.1%, RR 0.50, 95% CI 0.05–5.12 [Strike et al. 2019]). There were no differences between high mean arterial pressure and low mean arterial pressure in in-hospital mortality (0% vs. 0.6% [Hu et al. 2021]) and between general anesthesia plus epidural versus general anesthesia alone in 30-day mortality (0.7% vs. 0.2%) after noncardiac surgery (Li et al. 2021). There was also no difference between off-pump coronary artery bypass methods (1.5% vs. 1.5% vs. 0%) in in-hospital mortality after cardiac surgery (Szwed et al. 2021). An additional study reported that one death occurred but did not report what intervention the patient received (Khera et al. 2021).

There was an increased incidence of systolic hypotension in patients (N=64) undergoing major abdominal surgery with sufentanil plus a bupivacaine epidural followed by sufentanil plus bupivacaine in a PCA epidural pump versus sufentanil IV followed by a PCA morphine pump (16% vs. 0%, $P<0.05$ [Mann et al. 2000]). Significant differences in adverse events (114 vs. 124, $P=0.27$) or severe adverse events (13 vs. 22, $P=0.14$) were not found between study participants who received xenon gas or sevoflurane gas (N=256 [Coburn et al. 2018]). Another trial (N=30) also reported no difference in the number of participants who experienced any adverse event (40% vs. 53%, $P=0.46$) between xenon gas and sevoflurane gas (Stoppe et al. 2013). There was also no difference in the mean number of complications in one trial of femoral nerve block versus conventional pain management in hip fracture surgery (N=236, mean 5.6 vs. 5.7, $P=0.841$ [Unneby et al. 2020]). There were no differences in adverse events (Hu et al. 2021; Szwed et al. 2021; Tang et al. 2021) or in "intervention-related" adverse events (Khera et al. 2021) between intervention and control groups post-operatively. One trial reported that intra-operative hypotension was more likely with combined general and epidural anesthesia, whereas intra-operative and post-operative hypertension was more likely with general anesthesia alone in patients undergoing noncardiac surgery (Li et al. 2021).

### *GABAergic Anticonvulsant Medications*

Among post-operative populations, four trials (N=1,042) assessed gabapentin (3 trials; Dighe et al. 2014; Leung et al. 2006, 2017) and pregabalin (1 trial; Farlinger et al. 2018) compared with placebo. For two of the studies (Dighe et al. 2014; Farlinger et al. 2018), data on delirium was obtained through chart review and post-hoc analysis of trials intended to assess pain (Clarke et al. 2014, 2015). The patients were all undergoing orthopedic surgeries, with three enrolling patients with a mean age 60 to 63 (Dighe et al. 2014; Farlinger et al. 2018; Leung et al. 2006), and one enrolling patients over 65 years (mean 73 years [Leung et al. 2017]). Gabapentin was dosed at 600 mg to 900 mg daily, and pregabalin was dosed at 100 mg daily given 1 to 2 hours pre-operatively, and then for 3 to 4 days post-operatively.

All four trials reported delirium incidence, with two trials using the CAM instrument (Leung et al. 2006, 2017) and two using unspecified methods of chart review (Dighe et al. 2014; Farlinger et al. 2018). Assessment time was 3 to 4 days after surgery. The incidence of delirium was not different compared with placebo (18% vs. 17%, RR 1.00, 95% CI 0.62–1.63, $I^2$=18%). In one trial of gabapentin, analyses stratified by type of surgery or anesthesia did not alter the findings on incidence of delirium (Leung et al. 2017). In patients who developed delirium, its duration was 1 day in the two post-hoc analyses that reported it (Dighe et al. 2014; Farlinger et al. 2018). None of the studies reported severity of delirium. Three trials reported on hospital length of stay, with no difference between groups (MD 0.16 days, 95% CI -0.13–0.46, $I^2$=0% [Dighe et al. 2014; Farlinger et al. 2018; Leung et al. 2017]). Regarding mortality and adverse events in post-operative populations, there were no deaths in any of the trials. Incidences of sedation and dizziness were reported as not significantly different in all four trials (data could not be pooled due to heterogeneous reporting). Two trials reported lower rates of nausea and vomiting in the gabapentin groups than placebo, but there were also differences in other post-operative treatments (e.g., opioids).

### *Cholinesterase Inhibitors*

Three moderate risk of bias trials (N=232) assessed cholinesterase inhibitors compared with placebo or no treatment to prevent delirium in post-operative patients (Gamberini et al. 2009; Sampson et al. 2007; Youn et al. 2017). One enrolled older patients undergoing elective cardiac surgery (Gamberini et al. 2009), and two enrolled patients undergoing orthopedic surgeries (1 hip replacement, 1 hip fracture in patients with cognitive impairment at baseline) (Sampson et al. 2007; Youn et al. 2017). Rivastigmine was used in two trials—one with oral dosing of 1.5 mg 3 times a day starting the evening before surgery and continuing for 6 days, and the other used a transdermal patch (4.6 mg) daily, starting 2 to 3 days prior to surgery and continuing for 7 days (Gamberini et al. 2009; Youn et al. 2017). The third trial used donepezil 5 mg daily starting immediately following surgery and continuing for 3 days (Sampson et al. 2007). In the trial of rivastigmine patch, patients ages 65 and older were included if their cognitive status was judged to be impaired, as reflected by scores of 10 to 26 on the MMSE and 3 to 5 on the Global Deterioration Scale (Youn et al. 2017).

A pooled analysis of the three trials did not find a significant impact on incidence of delirium (24% vs. 35%, RR 0.56, 95% CI 0.23–1.37, $I^2$=66%). A subgroup analysis by type of surgery found reduction in incidence based on the combined estimate from the two orthopedic surgery studies (14% vs. 42%, RR 0.34, 95% CI 0.16–0.73, $I^2$=0% [Sampson et al. 2007; Youn et al. 2017]); however, the *P*-value for the subgroup interaction term was not statistically significant (*P*=0.25) and it is not clear whether there is a meaningful difference between orthopedic and cardiac surgery.

Two trials reported on the duration of delirium, with only small, non-significant differences between groups (Gamberini et al. 2009; Sampson et al. 2007). In one trial, rivastigmine resulted in a median duration of 2.5 days (range 1 to 5) compared with 3 days (range 1 to 6) in the placebo group (Gamberini et al. 2009). In the other, donepezil resulted in a median duration of 1.5 days compared with 1.8 days in the placebo group (MD -0.3 days, 95% CI -0.38–1.41 [Sampson et al. 2007]).

The trial of rivastigmine patch in orthopedic surgery patients with cognitive impairment at baseline reported on the severity of delirium (Youn et al. 2017). Using the DRS, this trial found that severity was significantly lower in the rivastigmine group (DRS 2.2 vs. 6.2, *P*=0.03).

Rivastigmine and placebo groups did not differ in length of ICU stay or overall hospital stay in older cardiac surgery patients (median 2 days for ICU stay and median 13 days for hospital stay [Gamberini et al. 2009]). The trial of patients undergoing hip replacement (mean age 68) found a significantly lower length of hospital stay with donepezil than placebo (mean 9.9 days vs. 12.1 days, MD -2.19, 95% CI -0.39–4.78 [Sampson et al. 2007]). However, this study was conducted in England, from 2003 to 2004, and the clinical relevance of this finding to the United States is limited.

Similar numbers of patients in the trial of rivastigmine in cardiac surgery patients required rescue medication treatment with haloperidol (32% vs. 30%, RR 0.96, 95% CI 0.55–1.67 [Gamberini et al. 2009]). This trial also reported no differences between groups on measures of cognition, such as the MMSE change from baseline to day 2 or minimum value, or the Clock Drawing test.

Mortality was rare in the one trial that reported it (1 of 59 vs. 1 of 61 [Gamberini et al. 2009]). All three trials reported on adverse events that are typical with cholinesterase inhibitors, mainly gastrointestinal effects, with no differences between groups (Gamberini et al. 2009; Sampson et al. 2007; Youn et al. 2017). One trial reported there were no serious adverse events (Sampson et al. 2007).

### *Opioid Medications*

Three trials (N=297) assessed the effect of opioids on post-operative delirium (Beaussier et al. 2006; Liu et al. 2017; Wang et al. 2019). Trials enrolled an older population undergoing major surgery. Incidence of delirium was not significantly different between pre-operative intrathecal morphine 300 µg followed by post-operative PCA systemic morphine 0.3 mg and subcutaneous saline in a trial (N=52) of patients over 70 years undergoing major abdominal surgery (34.6% vs. 38.5%, RR 0.90, 95% CI 0.44–1.85 [Beaussier et al. 2006]). Length of hospital stay and mortality were also not different between groups in this study (length of stay MD -0.50 days, 95% CI -1.51–0.51; and mortality 0% vs. 3.7%, RR 0.35, 95% CI 0.02–0.12 [Beaussier et al. 2006]). Delirium incidence was not significantly different between post-operative flurbiprofen axetil 300 mg plus sufentanil 150 µg in a PCA pump for 3 days and sufentanil 150 µg alone in a PCA pump in patients over 65 years undergoing major noncardiac surgery (N=140, 12.9% vs. 18.6%, RR 0.69, 95% CI 0.32–1.51 [Wang et al. 2019]). In a comparison of fentanyl versus remifentanil versus placebo, where all three groups received midazolam, there was no difference in delirium incidence between fentanyl versus placebo (n=70; 40% vs. 57%, RR 0.70, 95% CI 0.42–1.15) or between fentanyl and remifentanil (n=70; 40% vs. 23%, RR 1.75, 95% CI 0.84–3.64), but there was less delirium with remifentanil compared with placebo (n=70; 23% vs. 57%, RR 0.40, 95% CI 0.20–0.78) (Liu et al. 2017). There was no difference between fentanyl, remifentanil, and placebo on duration of delirium or on length of hospital stay (Liu et al. 2017).

### *Steroid Medications*

Four placebo-controlled trials in patients undergoing cardiac surgery (N=5,151)—three of dexamethasone (N=4,654; Dieleman et al. 2012; Kluger et al. 2021; Mardani and Bigdelian 2012) and

one of methylprednisolone (N=498; Royse et al. 2017)—assessed steroids for decreasing inflammation and preventing delirium. The first dose of steroids was given pre-operatively (Kluger et al. 2021; Mardani and Bigdelian 2012), at induction (Royse et al. 2017), or intra-operatively (Dieleman et al. 2012). Dose regimens consisted of 1 dose (Dieleman et al. 2012), 1 dose (Royse et al. 2017), or 1 dose pre-operatively followed by 3 days of steroid therapy (Mardani and Bigdelian 2012). Two trials were rated as having a moderate risk of bias, one as having a low risk of bias, and one as having a high risk of bias.

The pooled analysis of delirium incidence was significantly lower with steroids compared with placebo (5 trials, N=5,269; 9.2% vs. 12.0%, RR 0.76, 95% CI, 0.65–0.89, $I^2$=0%); however, these results are driven by one large trial (N=4,482) of a single dose of dexamethasone 1 mg/kg given intra-operatively in patients having cardiac surgery with cardiopulmonary bypass (Dieleman et al. 2012). In one of the sites that participated in this large multicenter trial (n=737), patients who developed delirium showed no significantly difference in its duration regardless of whether they received dexamethasone or placebo (median 2 days vs. 2 days, *P*=0.45 [Sauer et al. 2014]). One trial in hip fracture patients found severity of delirium, measured with the MDAS, was significantly lower in the dexamethasone group (N=14; median 5 vs. 9, *P*=0.010) but no difference in delirium incidence at post-operative day 3 (15% vs. 23%, *P*=0.360 [Kluger et al. 2021]). An additional trial (N=117) of a single, pre-operative IV dose of 125 mg methylprednisolone in older hip fracture patients showed no significant difference in delirium severity score over the first 3 post-operative days as measured by the CAM ([range]) cumulative between the methylprednisolone and placebo groups (median 1 [IQR 0–6] vs. median 2 [IQR 0–10], *P*=0.294) (Clemmesen et al. 2018).

Two trials of dexamethasone reported duration of ICU stay. One trial (N=4,482) of a single dose of intra-operative dexamethasone 1 mg/kg versus placebo found a statistically shorter ICU stay with dexamethasone (MD -0.013 days, 95% CI, -0.023 to -0.004), but the difference is very small (19 minutes [Dieleman et al. 2012]) and not likely to be clinically significant. The second trial of dexamethasone 8 mg pre-operatively and 24 mg daily for 3 days post-operatively also found shorter ICU stays with dexamethasone (N=93; MD -0.82 days, 95% CI -1.36 to -0.29 [Mardani and Bigdelian 2012]). The same two trials also reported shorter hospital stays with dexamethasone (N=4,482, MD -0.33 days, 95% CI -0.59 to -0.07 [Dieleman et al. 2012]; and N=93, MD -0.71 days, 95% CI -1.28 to -0.14 [Mardani and Bigdelian 2012]). The pooled analysis indicated a small but significant difference, favoring steroids (4 trials, N=4,561; MD -0.40, 95% CI -0.63 to -0.1, $I^2$=0%). Stratifying by surgery type (cardiac vs. orthopedic) did not alter the findings.

A single site analysis from a large multicenter trial (Dieleman et al. 2012) reported on mortality and found no significant difference with a single dose of dexamethasone 1 mg/kg versus placebo (1.1% vs. 0.54%, RR 2.02, 95% CI 0.37–10.94 [Sauer et al. 2014]). The overall multicenter trial of single-dose dexamethasone reported a primary composite outcome of death, stroke, renal failure, and respiratory failure, finding no significant difference (7% vs. 8.5%, RR 0.83, 95% CI 0.67–1.01 [Dieleman et al. 2012]). Infection risk was reported in two studies of dexamethasone, with different regimens and different results. In the large multicenter trial, there was a statistically significantly lower risk of any post-operative infection with dexamethasone (9.5% vs. 14.8%, RR 0.64, 95% CI 0.54–0.75) than with placebo (Dieleman et al. 2012). A second trial of dexamethasone (pre-operative 8 mg and 24 mg daily post-

operatively for 3 days) did not find a significant difference in infection risk (N=93; 7.0% vs. 4.0%, RR 1.74, 95% CI 0.31–9.96 [Mardani and Bigdelian 2012]). The study in hip fracture patients reported low incidence of mortality at 30 days (0 in dexamethasone, 1 in placebo) and between 1 and 6 months (1 dexamethasone, 0 placebo [Kluger et al. 2021]). Although adverse events occurred more frequently in the dexamethasone group, differences were not statistically significant (hyperglycemia 15% vs. 11%, *P*=0.526; and infection 20% vs. 8%, *P*=0.193 [Kluger et al. 2021]).

### *Additional Medications*

Thirteen trials (N=1,916) in post-operative patients studied other drugs, with generally one trial per specific drug class or type of intervention (Bielza et al. 2020; Deng et al. 2020; Kim et al. 1996; Y.N. Li et al. 2017; Mohammadi et al. 2016; Moslemi et al. 2020; Nakamura et al. 2021; Papadopoulos et al. 2014; Robinson et al. 2014; Rubino et al. 2010; Saager et al. 2015; Spies et al. 2021; Xin et al. 2017). The classes of drugs were calcium channel blocker, nonsteroidal anti-inflammatory drug, antiemetic, antihistamine (1 histamine-1 and 1 histamine-2 blocker), central alpha agonist, an amino acid, hypertonic saline, insulin clamping, iron, thiamine, physostigmine, and methylene blue. All but one study compared the drug with a placebo or usual care (insulin clamp); the study of histamine-1 blockers was a head-to-head trial. These trials are summarized in Table G-2 below.

Table G-2. Miscellaneous drugs for prevention of delirium in surgical patients post-operatively

| Study<br>Risk of Bias<br>Sample size | Drug and dose | Duration (follow-up time) | Population | Delirium incidence[a] |
|---|---|---|---|---|
| Study: Kim et al. 1996<br>RoB: Moderate<br>N: 127 | Cimetidine 900 mg/day IV vs. ranitidine 150 mg/day IV | Post-operative until discharge (mean 8.8 days) | Age: Adults<br>Surgery type: Cardiac | 25% vs. 25%, adjusted OR 0.72, 95% CI 0.29–1.80 |
| Study: Rubino et al. 2010<br>RoB: Moderate<br>N: 30 | Clonidine 0.5 mcg/kg IV bolus followed by 1-2 mcg/kg/h infusion vs. placebo | During weaning from mechanical ventilation (POD 7) | Age: Adults<br>Surgery type: Cardiothoracic | 40% vs. 33.3% (*P*>0.05) |
| Study: Mohammadi et al. 2016<br>RoB: Moderate<br>N: 45 | Cyproheptadine 4 mg three times daily vs. placebo | 7 days (POD 7) | Age: Adults<br>Surgery type: Noncardiac, ICU | 15% vs. 35%, adjusted OR 0.14, 95% CI 0.09–0.86, *P*=0.04;<br>severity DRS: NSD on days 1-7 |
| Study: Saager et al. 2015<br>RoB: Low<br>N: 203 | Insulin clamp, titrated to blood glucose 80–110 mg/dL vs. usual care | Intra-operatively only (POD 5) | Age: Adults<br>Surgery type: Cardiac | 28% vs. 14%, RR 1.89, 95% CI 1.06–3.37, *P*=0.03 |

| Study<br>Risk of Bias<br>Sample size | Drug and dose | Duration (follow-up time) | Population | Delirium incidence[a] |
|---|---|---|---|---|
| Study: Xin et al. 2017<br>RoB: Moderate<br>N: 120 | Hypertonic saline (7.5%) 4 ml/kg vs. normal saline | Pre-operatively only (POD 3) | Age: >65 years<br>Surgery type: Orthopedic, hip fracture | 12% vs. 38%, OR 0.13, 95% CI 0.04–0.41, *P*=0.001 |
| Study: Robinson et al. 2014<br>RoB: Low<br>N: 301 | L-tryptophan 1 gm three times daily vs. placebo | 3 days (mean POD 5) | Age: >60 years<br>Surgery type: Miscellaneous, with ICU stay | 40% vs. 37% (*P*=0.60); duration: 2.9 days vs. 2.4 days (*P*=0.17) |
| Study: Li Y.N. et al. 2017<br>RoB: High<br>N: 30 | Nimodipine 7.5 mg/kg/hour IV vs. saline | Pre-operatively only (POD 7) | Age: Adults<br>Surgery type: Orthopedic, spine | 7% vs. 17% (*P*=0.017) (from graph) |
| Study: Papadopoulos et al. 2014<br>RoB: Moderate<br>N: 106 | Ondansetron 8 mg IV daily vs. placebo | 5 days (POD 5) | Age: >40 years<br>Surgery type: Orthopedic, hip fracture | POD 2: 36% vs. 53% (*P*=0.07);<br>POD 3: 16% vs. 42% (*P*=0.003);<br>POD 4: 2% vs. 27% (*P*<0.001);<br>POD 5: 0% vs. 27% (*P*<0.001) |
| Study: Bielza et al. 2020<br>RoB: Low<br>N: 253 | Iron sucrose 200 mg IV days 1,3,5) vs. normal saline | 5 (POD 5) | Age: >70 years<br>Surgery type: Orthopedic, hip fracture | 12.8% vs. 13.5% (*P*=0.871) |
| Study: Moslemi et al. 2020<br>RoB: Moderate<br>N: 96 | Thiamine 200 mg IV daily vs. saline | 3 days (POD 3) | Age: Adults<br>Surgery type: Gastrointestinal, ICU | 6.2% vs. 14.6% (*P*=0.15) |
| Study: Nakamura et al. 2021<br>RoB: Moderate<br>N: 64 | Thiamine 200 mg IV vs. placebo | 30 days (post-transplantation) | Age: Adults<br>Surgery type: Post-operative, cancer | 28% vs. 21% (*P*=0.73) |

| Study<br>Risk of Bias<br>Sample size | Drug and dose | Duration (follow-up time) | Population | Delirium incidence[a] |
|---|---|---|---|---|
| Study: Deng et al. 2020<br>RoB: Moderate<br>N: 248 | Methylene blue 2 mg/kg IV vs. normal saline | 5 (POD 5) | Age: Elderly<br>Surgery type: Noncardiac, non-neurosurgical | 7.4% vs. 24.2% (*P*<0.001) |
| Study: Spies et al. 2021<br>RoB: Low<br>N: 261 | Physostigmine 0.02 mg/kg IV bolus, then 0.01 mg/kg infusion vs. placebo | 1 year (POD 7, 90, and 365) | Age: Adults<br>Surgery type: Intra-operative, liver | 20% vs. 15% (*P*=0.334) |

[a] Results as reported by study authors.

*Abbreviations.* CI=confidence interval; DRS=Delirium Rating Scale; ICU=intensive care unit; IV=intravenous; NSD=no significant difference; OR=odds ratio; POD=post-operative day; RoB=risk of bias; RR=risk ratio.

*Sources*. Bielza et al. 2020; Deng et al. 2020; Kim et al. 1996; Y.N. Li et al. 2017; Mohammadi et al. 2016; Moslemi et al. 2020; Nakamura et al. 2021; Papadopoulos et al. 2014; Robinson et al. 2014; Rubino et al. 2010; Saager et al. 2015; Spies et al. 2021; Xin et al. 2017.

## Additional Pharmacological Interventions for Treatment of Delirium

### *Cholinesterase Inhibitors*

In a single study of the cholinesterase inhibitor rivastigmine, the trial was halted after enrolling 104 of a planned 440 patients because of higher mortality compared with placebo, when each were used in addition to usual care with haloperidol in an ICU setting (22% vs. 8%, *P*=0.07 [van Eijk et al. 2010]). However, mortality at 90-day follow-up did not show a statistically significant increase with rivastigmine (33% vs. 22%, *P*=0.14). In the patients who were enrolled prior to study cessation, delirium duration seemed longer with the cholinesterase inhibitor (median 5 days vs. 3 days, *P*=0.06), and severity was greater when measured by the ratio of Delirium Severity Index and days with delirium (2.3 vs. 2.0, *P*=0.004). Rivastigmine was also associated with longer ICU stays (median 15 days vs. 8 days, *P*<0.0001) and a trend towards longer hospital stays (median 29 days vs. 25 days, *P*=0.06). Rescue medication use did not differ between groups.

In general inpatients, a very small study (N=15) with high risk of bias compared rivastigmine with placebo and reported a statistically significant difference in delirium response (100% vs. 43% became CAM-negative, *P*=0.03 [Overshott et al. 2010]). Mortality was also lower in the treatment arm (0 vs. 4 deaths, *P*=0.03). In this trial, there was no significant difference with rivastigmine in delirium duration, and only one adverse event occurred. Three patients in the placebo group needed rescue medication, while none were reported in the treatment group.

### *Benzodiazepine Antagonist*

Twenty-two ICU patients were included in a placebo-controlled trial of the benzodiazepine antagonist flumazenil (Schomer et al. 2020). Eligible patients had hypoactive delirium associated with benzodiazepine treatment in the ICU and also responded with decreased sedation to a test dose of flumazenil before random assignment. The study suggested a higher rate of delirium resolution with

flumazenil compared with placebo, but the difference was not statistically significant (90% vs. 70%, *P*=0.2). The effect of flumazenil on delirium- and coma-free days was also not significant (median 12.7 vs. 9.2 out of 14 days, *P*=0.079). ICU length of stay and adverse events were similar with and without treatment.

# Appendix H. Evidence Tables for Additional Studies Reviewed

## Additional Non-Pharmacological Interventions for Prevention of Delirium

### *Red Blood Cell Transfusion*

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Gregersen et al. 2015); Blandfort et al. (2017) (post hoc analysis) | Design: RCT<br>Setting: Postop, hip<br>Country: Denmark<br>Funding: University | Randomized N: 179<br>Analyzed N: 179<br>Intervention 1 (N=90): Liberal red blood cell transfusion strategy (hemoglobin <11.3 g/dL; 7 mmol/L)<br>Intervention 2 (N=89): Restrictive red blood cell transfusion strategy (hemoglobin <9.7 g/dL; 6 mmol/L)<br>Duration: Hemoglobin measured for 30 days after surgery with transfusions performed as necessary<br>Follow-up (days): 90 | Inclusion: ≥65 years, admitted from nursing homes for hip fracture surgery, and postop hemoglobin levels between 9.7 (6 mmol/L) and 11.3 g/dL (7 mmol/L) during the first 6 postop days<br>Exclusion: Active cancer, pathological fracture, fluid overload, or irregular erythrocyte antibodies | Mean (SD) age: 87.6 (6.5)<br>Female %: 75<br>Race %: NR<br>Delirium %: Unclear<br>Modified Barthel Index:<br>100 to 90: 12%<br>89 to 50: 68%<br>49 to 0: 20%<br>Dementia %: 56<br>Postop %: 100<br>Cancer %: NR (active cancer excluded) | Main outcomes: Liberal blood transfusion prevents development of delirium on day 10, compared to restrictive blood transfusion (OR 0.41, 95 % CI 0.17 to 0.96).<br>Attrition: 9% vs. 9% | Moderate |
| Gruber-Baldini et al. (2013) | Design: RCT<br>Setting: Postop, hip<br>Country: U.S.<br>Funding: Mixed | Randomized N: 139<br>Analyzed N: 138<br>Intervention 1 (N=67): Liberal; 1 unit of packed red blood cells and additional blood given to hemoglobin >10 g/dL<br>Intervention 2 (N=72): Restrictive; blood given to hemoglobin >8 g/dL | Inclusion: ≥50 years undergoing hip fracture surgery with a hemoglobin of <10 g/dL within 3 days after surgery<br>Exclusion: Unable to walk without human assistance prior to hip fracture, declined blood transfusions, multiple trauma, pathologic hip fracture, clinically recognized | Mean (SD) age: 81.46 (9.09)<br>Female %: 73<br>Race %:<br>Caucasian: 90.6<br>Black/African American: 8.7<br>Asian: NR<br>Other: NR<br>Delirium %: 24.2<br>Mean ASA: 2.9<br>Dementia %: 31.9<br>Postop %: 100 hip fracture | Main outcomes: There were no significant differences in the prevalence of delirium at any time point during the study with the largest difference on day 1 post randomization (31% vs. 40%, p>0.29).<br>Attrition: 1% vs. 0% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Duration: Postop<br>Follow-up (days): Delirium assessed multiple times within 5 days of randomization or discharge | acute myocardial infarction within 30 days prior to randomization, previously participated in the trial, symptoms associated with anemia, or actively bleeding | surgery<br>Cancer %: 0 (16% had chart history of cancer) | | |

*Abbreviations.* ASA=American Society of Anesthesiologists; CI=confidence interval; N=number; NR=not reported; OR=odds ratio; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

### *Fluid Therapy*

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Bruera et al. (2013) | Design: RCT<br>Setting: Palliative care<br>Country: U.S.<br>Funding: Government | Randomized N: 129<br>Analyzed N: 102<br>Intervention 1 (N=63): 1,000 mL of normal saline<br>Intervention 2 (N=66): Placebo; 100 mL of normal saline<br>Duration: Over 4 hours daily<br>Follow-up (days): Until patient was unresponsive, developed progressive coma, or died | Inclusion: ≥18 years with advanced cancer, admitted to hospice, a reduced oral intake of fluids with evidence of mild or moderate dehydration, intensity of ≥1 on 0-10 scale for fatigue and 2 of 3 target symptoms (hallucinations, sedation, and myoclonus), life expectancy of ≥1 week, and MDAS score <13<br>Exclusion: Severe dehydration, decreased levels of consciousness, no urine output for 12 hours, history of evidence of renal failure with creatinine >1.5 X upper normal limit, history of evidence of congestive heart failure, and history of bleeding disorder or active bleeding | Median age: 67 (range: 41-92)<br>Female %: 47<br>Race %:<br>Caucasian: 60<br>Black/African American: 26<br>Asian: NR<br>Other: 1<br>Hispanic: 13<br>Median (IQR) MDAS score at baseline: 6 (3-9)<br>Median (IQR) NuDESC at baseline, day: 1 (0-3)<br>Median (IQR) FACIT-F at baseline: 72 (59-84)<br>Median (IQR) ESAS, depression scale: 2 (0-5)<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: 100 | Main outcomes: MDAS and RASS scores significantly worsened from baseline in both groups at days 4 and 7 ($p<0.001$). There was a trend for less deterioration in the hydration group as compared with the placebo group (RASS $p=0.065$, MDAS $p=0.085$). By day 4, the placebo group showed significantly more deterioration from baseline in night-time NuDESC scores as compared with the hydration group ($p=0.028$).<br>Attrition: 22% vs. 20% | Low |

*Abbreviations.* ESAS=Edmonton Symptom Assessment Scale; FACIT-F=Functional Assessment of Chronic Illness Therapy–Fatigue; IQR=interquartile range; MDAS=Memorial Delirium Assessment Scale; N=number; NR=not reported; NuDESC=Nursing Delirium Screening Scale; OR=odds ratio; postop=post-operative; RASS=Richmond Agitation Sedation Scale; RCT=randomized controlled trial.

*Mechanical Ventilation in Intensive Care Unit Setting*

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Girard et al. (2008) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: Mixed | Randomized N: 336<br>Analyzed N: 335<br>Intervention (N=168): Spontaneous waking trials along with spontaneous breathing trial protocols<br>Control (N=168): Usual care with spontaneous breathing trial protocols followed<br>Duration: MV<br>Follow-up (days): Discharge 365 | Inclusion: ≥18 years who required MV for ≥12 hours; receiving full support or support was being weaned<br>Exclusion: Admission after cardiopulmonary arrest, continuous MV ≥2 weeks, moribund state, withdrawal of life support, profound neurological deficits (e.g., large stroke or severe dementia), or current enrolment in another trial | Median age: 60 vs. 64<br>Female %: 47.8<br>Race %: NR<br>Delirium %: NR<br>Median APACHE II: 26<br>Dementia %: NR, severe dementia excluded<br>Postop %: NR<br>Cancer %: 1.5 | Main outcomes: The duration of coma was significantly shorter in the intervention group than in the control group, whereas the duration of delirium was similar between the 2 groups. Of the assessable patients, delirium occurred in 124 (74%) in the intervention group and 119 (71%) in the control group (p=0·66).<br>Attrition: 1% vs. 4% | Moderate |
| Luo et al. (2015) | Design: RCT<br>Setting: ICU<br>Country: China<br>Funding: Government | Randomized N: 40<br>Analyzed N: 40<br>Intervention 1 (N=20): Synchronized intermittent mandatory ventilation with pressure support<br>Intervention 2 (N=20): Assist/Control ventilation<br>Duration: MV<br>Follow-up (days): 28 or discharge | Inclusion: ≥18 years receiving invasive MV for acute respiratory distress syndrome<br>Exclusion: Pregnancy, severe arrhythmia or acute myocardial ischemia, pneumothorax or mediastinal emphysema, intracranial hypertension, neuromuscular diseases that could impair spontaneous breathing, severe COPD, severe multiple organs dysfunction, end-stage malignant carcinoma with an estimated 6-month mortality risk exceeding 50%, sickle cell disease, immunosuppression conditions, attending confounding trials within 30 days before | Mean (SD) age: 54.55 (16.3)<br>Female %: 60<br>Race %: NR<br>Delirium %: NR<br>APACHE II %: 18.0<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: Excluded end-stage malignant carcinoma | Main outcomes: There was no significant difference in incidence of delirium based on ventilation techniques (0% vs. 20%, p=0.106).<br>Attrition: NR; 14 patients died during the follow-up (6 in the intervention group vs. 8 in control group) | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | | enrollment, or unwilling or refusing the use of full life support | | | |
| Mehta et al. (2012) | Design: RCT<br>Setting: ICU<br>Country: Canada<br>Funding: Government | Randomized N: 430<br>Analyzed N: 423<br>Intervention 1 (N=218): Daily interrupted continuous infusion of midazolam or lorazepam and morphine or fentanyl<br>Intervention 2 (N=212): Continuous infusion of midazolam or lorazepam and morphine or fentanyl without interruption<br>Duration: MV<br>Follow-up (days): Delirium assessed daily | Inclusion: Critically ill adults admitted to ICU who were expected to require MV for at least 48 hours<br>Exclusion: Admitted to ICU after cardiac arrest or traumatic brain injury, receiving neuromuscular blocking agents, enrolled in another trial or previously enrolled in the current study, or a lack of commitment | Mean (SD) age: 58<br>Female %: 44<br>Race %: NR<br>Delirium %: NR<br>APACHE II: 28.4<br>Dementia %: NR<br>Postop %: 12.3<br>Cancer %: NR | Main outcomes: The incidence of delirium was not different between interrupted sedation and continuous sedation (53.3% vs. 54.1%, p=0.83).<br>Attrition: 2% vs. 1% | Moderate |
| Nassar Junior and Park (2014) | Design: RCT<br>Setting: ICU<br>Country: Brazil<br>Funding: None | Randomized N: 60<br>Analyzed N: 60<br>Intervention (N=30): Daily interruption of sedation protocol, along with spontaneous breathing trial protocols<br>Control (N=30): Usual care with spontaneous breathing trial protocols followed<br>Duration: MV<br>Follow-up (days): Discharge, 28 | Inclusion: ≥18 years who required MV within the last 24 hours and were expected to need MV for >24 hours<br>Exclusion: Those needing deep levels of sedation, previously cognitively impaired (e.g., advanced dementia), or readmitted to the ICU after participating in the trial | Median age: 47 vs. 51<br>Female %: 50<br>Race %: NR<br>Delirium %: NR<br>Median APACHE II: 22 vs. 18<br>Dementia %: NR, severe dementia excluded<br>Postop %: NR<br>Cancer %: 1.5 | Main outcomes: There were no differences in ICU mortality (40% vs. 23.3%, p=0.165), hospital mortality (43.3% vs. 30%, p=0.284), incidence of delirium (30% vs. 40%, p=0.472).<br>Overall attrition: 0% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Olsen et al. (2020) | Design: RCT<br>Setting: ICU<br>Country: Denmark, Norway, and Sweden<br>Funding: Government | Randomized N: 710<br>Analyzed N: 700<br>Intervention 1 (N=354): No sedation<br>Intervention 2 (N=356): Light sedation with daily interruption<br>Duration: Until discharge from ICU<br>Follow-up (days): 90 | Inclusion: ≥18 years, had undergone endotracheal intubation within 24 hours before screening, and were expected to receive MV for >24 hours<br>Exclusion: Severe head trauma, therapeutic hypothermia, status epilepticus, participated in a previous trial, transferred from another ICU with a LOS >48 hours, comatose on admission, brain-dead, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen of <9, or sedation anticipated to be necessary for oxygenation or for the patient to remain in a prone position | Median age: 72 vs. 70<br>Female %: 39<br>Race %: NR<br>Delirium %: NR<br>Median APACHE II: 26 vs. 25<br>Dementia %: 0 (excluded)<br>Postop %: 31.5<br>Cancer %: NR | Main outcomes: The patients in the no sedation group had a median of 27 days free from coma or delirium, and those in the sedation group had a median of 26 days free from coma or delirium.<br>Attrition: 1% vs. 1% | Moderate |
| Strøm et al. (2010) | Design: RCT<br>Setting: ICU<br>Country: Denmark<br>Funding: Mixed | Randomized N: 140<br>Analyzed N: 113<br>Intervention 1 (N=70): No sedation<br>Intervention 2 (N=70): Interrupted sedation of propofol IV 20 mg/mL; after 48 hours propofol discontinued and midazolam IV 1 mg/mL begun<br>Duration: MV<br>Follow-up (days): Discharge | Inclusion: ≥18 years critically ill patients expected to need MV for > 24 hours<br>Exclusion: Increased intracranial pressure, sedation needed (e.g., for status epilepticus, or hypothermia after cardiac arrest), pregnancy, meeting criteria for weaning from ventilation ($FiO_2$ ≤40% and positive end-expiratory pressure of 5 cm $H_2O$), or no cerebral contact | Mean age: 66<br>Female %: 33<br>Race %: NR<br>Delirium %: NR<br>APACHE II: 26<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR | Main outcomes: Agitated delirium was more common in the patients who had no sedation compared with interrupted sedation (20% vs. 7%, p=0.040).<br>Attrition: 21% vs. 17% | Moderate |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; COPD=chronic obstructive pulmonary disease; ICU=intensive care unit; IV=intravenous; LOS=length of stay; MV=medical ventilation; N=number; NR=not reported; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

4507 *Mechanical Interventions in Surgical Setting*

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Brown et al. (2019) | Design: RCT<br>Setting: Intra-operative, cardiothoracic<br>Country: U.S.<br>Funding: Mixed | Randomized N: 215<br>Analyzed N: 199<br>Intervention (N=112): Autoregulation group; targeting MAP during CPB to be greater than the patient's the lower limit of autoregulation<br>Control (N=103): Usual care; the patient's MAP during CPB was maintained using usual MAP targets, typically greater than 60 mmHg, using the same protocol.<br>Duration: During surgery<br>Follow-up (days): 4 | Inclusion: ≥55 years undergoing primary or preop CABG with or without valvular surgery or ascending aorta surgery that required CPB, and high-risk of neurologic complications<br>Exclusion: Patients with delirium at baseline or emergency surgery | Mean (SD) age: 70.3 (7.5)<br>Female %: 24.6<br>Race %:<br>Caucasian: 81.4<br>Black/African American: 13.1<br>Asian: NR<br>Other: 5.5<br>Delirium %: 0 (excluded)<br>Functioning: NR<br>Median (IQR) MMSE: 27 (26 to 29) vs. 28 (26 to 29)<br>Postop %: 100<br>Cancer: NR<br>Reoperation %: 8 | Main outcomes: Excluding 5 patients with coma, delirium occurred in 48/91 (53%) in usual care group vs. 39/103 (38%) in the intervention group (p=0.04). The odds of delirium were reduced by 45% in patients randomized to the autoregulation group (OR 0.55, 95% CI 0.31 to 0.97, p=0.04).<br>Attrition: 6% vs. 9% | Low |
| Fu et al. (2020) | Design: RCT<br>Setting: Postop, cardiac<br>Country: China<br>Funding: Industry | Randomized N: 63<br>Analyzed N: 55<br>Intervention (N=27): Mild hyperthermia: after DHCA patients were gradually rewarmed to a nasopharyngeal temperature of 34$^{o}$C and maintained at this temperature for 24 hours after surgery<br>Control (N=28): Usual care: after DHCA patients were gradually rewarmed to a nasopharyngeal temperature of 36$^{o}$C and maintained at this | Inclusion: Age 18-75 years, acute Stanford type A aortic dissection involving the aortic arch, confirmed by computed tomography angiography and echocardiography, and requiring surgical treatment<br>Exclusion: Immediate death after surgery, history of nervous system disease or mental illness, long-term use of hormones or immunosuppressive agents, confirmed infection, and history of malignant tumors, | Mean (SD) age: 52 (11)<br>Female %: 21.8<br>Race %: NR<br>Delirium %: NR<br>Mean (SD) APACHE II: 15.5 (4.11)<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Cerebral tissue oxygen saturation, incidence of delirium or permanent neurological dysfunction, duration of hospital stay, and 28-day mortality showed no statistical difference.<br>Attrition: 13% vs. 13% | High |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | temperature for 24 hours after surgery<br>Duration: During surgery<br>Follow-up (days): Discharge, 28 | other immune diseases, or organ transplants | | | |
| Gao et al. (2018) | Design: RCT<br>Setting: Intra-operative, spine<br>Country: China<br>Funding: Government | Randomized N: 64<br>Analyzed N: 64<br>Intervention (N=32): TEAS at acupoints Hegu and Neiguan bilaterally; disperse-dense waves, frequency 2/100 Hz, and maximum tolerated current<br>Control (N=32): Sham TEAS; electrodes placed at acupoints Hegu and Neiguan bilaterally and no current<br>Duration: Preop (30 minutes before anesthesia) through end of surgery<br>Follow-up (days): POD 3 | Inclusion: ≥65 years, undergoing spine surgery, assessed for lacunar infarction by MRI<br>Exclusion: MMSE < 24, dementia, preop delirium, history of neurological illness, current use of antidepressants, history of endocrine or metabolic disorder, recent use of glucocorticoids or other hormones, infections, chronic inflammatory conditions, or anti-inflammatory drugs | Mean (SD) age: 72 (5)<br>Female %: 48<br>Race %: NR<br>Delirium %: 0 (excluded)<br>ASA physical status ≥3 %: 0<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer: NR | Main outcomes: Incidence of delirium was lower with TEAS than sham treatment (6.3% vs 25.0%, p=0.039).<br>Attrition: NR | Moderate |
| Jia et al. (2014) | Design: RCT<br>Setting: Preop and postop, cancer<br>Country: China<br>Funding: Government | Randomized N: 240<br>Analyzed N: 233<br>Intervention (N=120): Fast track surgery, with preop and postop management<br>Control (N=120): Usual care<br>Intervention duration: Preop and postop through day 3<br>Control duration: During hospitalization | Inclusion: Age 70-88 years undergoing open curative resection for colorectal carcinoma<br>Exclusion: History of dementia, alcohol intake ≥250 g/day, long-term use of sleeping pills or anxiolytics, received anesthesia within the past 30 days, given intra- | Mean age: 75.18<br>Female %: 37.5<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: 100 | Main outcomes: The incidence of POD was significantly lower in patients with the fast-track therapy (4/117, 3.4 %) than with the traditional therapy (15/116, 12.9 %; p=0.008).<br>Attrition: 3% vs. 3% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Follow-up (days): Until discharge | operative blood transfusion, or admitted to ICU | | | |
| Lei et al. (2017) | Design: RCT<br>Setting: Postop, cardiac surgery<br>Country: Canada<br>Funding: Industry | Randomized N: 250<br>Analyzed N: 249<br>Intervention (N=124): Cerebral oximetry monitoring with rScO2 desaturation to baseline values<br>Control (N=126): Usual care<br>Intervention duration: Postop 12-hour intervals for 7 days<br>Control duration: Pre-operatively (baseline) and post-operatively every 12 hours or as needed until discharge<br>Follow-up (days): 7 | Inclusion: ≥60 years, combined valve and coronary re-vascularization, repeat cardiac surgery, multiple valve replacement or repair, or surgery of ascending aorta and aortic arch with or without circulatory arrest<br>Exclusion: History of serious mental illness, delirium, or undergoing either emergency or surgery without bypass | Mean (SD) age: 73.5 (6.4)<br>Female %: 29<br>Race %: NR<br>Delirium %: NR<br>Regional cerebral oxygenation (rScO2):10%<br>Dementia: NR<br>Cancer: NR<br>Medications taken at baseline:<br>Beta-blockers %: 54.5 vs. 54.7<br>Calcium channel blockers %: 26.8 vs. 26.9<br>ACE inhibitors %: 33.3 vs. 40.5<br>Statins %: 63.4 vs. 68.2<br>Aspirin %: 65.8 vs. 66.6<br>Antidepressants %: 5.7 vs. 8.7<br>Benzodiazepines %: 7.3 vs. 11.1<br>Lorazepam premedication %: 48.8 vs. 52.3 | Main outcomes: POD occurred in 30/123 (24.4%) vs. 31/126 (24.6%) patients in the intervention and control groups, respectively (OR 0.98, 95% CI 0.55 to 1.76, p=0.97). POD was present in 20/28 (71%) patients with baseline regional cerebral oxygen saturation ≤ 50%, compared with 41/221 (18%) patients with baseline regional cerebral oxygen saturation > 50% (p=0.0001).<br>Attrition: 1% vs. 0% | Moderate |
| Nadler et al. (2017) | Design: RCT<br>Setting: Postop, ortho<br>Country: U.S.<br>Funding: Industry | Randomized N: 135<br>Analyzed N: 114<br>Intervention (N=68): CPAP used any time patient slept before surgery and on postop days 0, 1, and 2<br>Control (N=67): Usual Care<br>Duration: During hospitalization | Inclusion: ≥50 years, at risk of obstructive sleep apnea, and scheduled for elective knee or hip arthroplasty<br>Exclusion: Severe tracheal or lung disease or previous obstructive sleep apnea | Mean (SD) age: 65.7 (8.9)<br>Female %: 60.7<br>Race %: NR<br>Delirium %: NR<br>Depression %: 43.8<br>Dementia or significant cognitive impairment %: 2<br>Postop %: 100<br>Cancer %: NR<br>Alcohol abuse %: 5.3 | Main outcomes: Delirium was equally common in both groups: 21% (12/58) in the CPAP group and 16% (9/56) in the routine care group (OR 1.36,95% CI 0.52 to 3.54, p=0.53). Delirious subjects were slightly older (mean [SD] age 68.9 [10.7] vs. 64.9 [8.2], p=0.07), but had nearly | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Follow-up (days): Until discharge | | | identical preop STOP-Bang scores (4.19 [1.1] vs. 4.27 [1.3], p=0.79).<br>Attrition: 15% vs. 16% | |
| Wang et al. (2015) | Design: RCT<br>Setting: Intra-operative, GI surgery<br>Country: China<br>Funding: Industry | Randomized N: 174<br>Analyzed N: 162<br>Intervention (N=87): Variable lung protective MV during surgery<br>Control (N=87): Conventional lung protective MV<br>Duration: Intra-operative<br>Follow-up (days): 7 | Inclusion: ≥60 years undergoing elective gastrointestinal tumor resection via laparotomy<br>Exclusion: MMSE<24 or history of dementia | Mean (SD) age: 67.44 (7.28)<br>Female %: 61<br>Race %: NR<br>Delirium %: 0<br>ASA II, III %: 100<br>Dementia %: 0 (excluded)<br>Postop %: GI surgery 100<br>Cancer: NR | Main outcomes: There was less POD in the group that received variable ventilation than conventional ventilation (16.5% vs. 28.9%, p=0.036).<br>Attrition: 6% vs. 2% | Moderate |
| Wang J. et al. (2020) | Design: RCT<br>Setting: Intra-operative, mixed<br>Country: China<br>Funding: Industry | Randomized N: 71<br>Analyzed N: 64<br>Intervention (N=35): Lung protective ventilation<br>Control (N=36): Usual care; MV<br>Duration: Intra-operative<br>Follow-up (days): 1,2,3 | Inclusion: ≥65 years, BMI <28, ASA status ≤III, and MMSE ≥23<br>Exclusion: History of anemia, hypoalbuminemia, CNS disorders, mental illness, hypoxemia, chronic lung disease, asthma, or treatment with antidepressants or sedatives; baseline $rSO_2$ <60% before anesthesia induction; change in surgical plan; refused blood donations; >4 hours of operation time; >800 ml of intra-operative blood loss | Mean (SD) age: 69.1 (2.6)<br>Female %: 64<br>Race %: NR<br>Delirium: NR<br>ASA II %: 59<br>Dementia %: NR<br>Mean (SD) MMSE: 26.6 (1.7)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: The incidences of cerebral desaturation and POD were significantly lower in the lung protective ventilation group (p<0.05).<br>Attrition: 9% vs. 11% | Moderate |
| Xu et al. (2020) | Design: RCT<br>Setting: Intra-operative, ortho | Randomized N: 156<br>Analyzed N: 150<br>Intervention 1 (N=52): MAP maintained from 10% to 20% | Inclusion: Age 65-80 years undergoing elective hip replacement with ASA status II or III and New York Heart | Mean (SD) age: 68.6 (7.4)<br>Female %: 60<br>Race %: NR<br>Delirium %: NR | Main outcomes: Patients in Intervention 3 showed a lower incidence of POD on the 1st day than those in | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Country: China<br>Funding: None | below baseline level<br>Intervention 2 (N=52): MAP maintained from baseline to 10% below baseline level<br>Intervention 3 (N=52): MAP maintained from baseline to 10% above the baseline level<br><br>Duration: Intra-operative<br>Follow-up (days): 1, 2, 3 | Association Functional Classification class II or III<br>Exclusion: Diseases of brain tumor disease, history of cerebrovascular accident, history of mental diseases and taking psychotropic drugs within 6 months before admission, visual auditory, or language communication disorder, liver and kidney dysfunction, and long-term alcohol abuse | ASA III: 25%<br>Dementia %: NR, but implied excluded<br>Postop %: 100<br>Cancer %: NR | Intervention 1 and Intervention 2 (22% and 16% vs. 4%, p=0.031). There is no difference of incidence of POD on the 2nd and 3rd days post-operatively.<br>Attrition at follow-up: 4% vs. 4% vs. 4% | |

*Abbreviations.* AAAD=acute Stanford type A aortic dissection; APACHE II=Acute Physiology and Chronic Health Evaluation II; ASA=American Society of Anesthesiologists; BMI=body mass index; CABG=coronary artery bypass graf; CI=confidence interval; CNS=central nervous system; CPAP=continuous positive airway pressure; CPB=cardiopulmonary bypass; DHCA=deep hypothermic circulatory arrest; GI=gastrointestinal; ICU=intensive care unit; IQR=interquartile range; MAP=mean arterial pressure; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; MV=medical ventilation; N=number; NR=not reported; OR=odds ratio; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; SD=standard deviation; TEAS=Transcutaneous electrical acupoint stimulation.

## Additional Pharmacological Interventions for Prevention of Delirium

### *Electroencephalography-Guided Anesthesia vs. Usual Anesthesia*

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Chan et al. (2013); Chan and Gin (2014); CODA | Design: RCT<br>Setting: Intra-operative, colorectal<br>Country: Hong Kong<br>Funding: Government | Randomized N: 921<br>Analyzed N: Week 1 N=783; 3 months N=835<br>Intervention (N=462): BIS-guided anesthesia (a BIS value between 40 and 60)<br>Control (N=459): Usual anesthesia care | Inclusion: ≥60 years scheduled for elective major colorectal surgery with general anesthesia expected to last for at least 2 hours with an anticipated hospital stay of at least 4 days<br>Exclusion: Patients with | Mean (SD) age: 67.85 (8.25)<br>Female %: 39<br>Race %: NR<br>Delirium %: 0<br>ASA I, II %: 83.7<br>Dementia %: 0<br>Postop %: 100<br>Gastrointestinal surgery | Main outcomes: There were fewer patients with delirium in the BIS group compared with usual anesthesia care (15.6% vs. 24.1%, p=0.01).<br>Attrition at 1 week: 17% vs. 13% | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Duration: Intra-operative<br>Follow-up (days): 7, 90, discharge | suspected dementia or memory impairment or MMSE score of <24 | Cancer %: 76 gastrointestinal cancer | | |
| Cotae et al. (2021) | Design: RCT<br>Setting: Intra-operative, trauma surgery<br>Country: Romania<br>Funding: No external funding | Randomized N: 95<br>Analyzed N: 74<br>Intervention (N=48): Standard anesthesia monitoring plus assessment of anesthesia depth and nociception (Surgical Pleth Index)<br>Control (N=47): Standard anesthesia monitoring<br>Duration: Intra-operative<br>Follow-up (days): 1, 2, 3 | Inclusion: ≥18 years and noncardiac trauma surgery expected to last at least 2 hours<br>Exclusion: Neurotrauma, chronic use of psychoactive substances or alcohol, impaired preop cognitive function pre-existing psychopathological symptoms, neurological deficits, or expected surgery time less than 2 hours | Mean age: 44.5<br>Female %: 43.2<br>Race %: NR<br>Delirium %: NR<br>ASA II-IV %: 100<br>Dementia %: NR<br>Postop %: 100<br>Abdominal surgery: NR<br>Orthopedic surgery: NR | Main outcomes: Fewer patients experienced POD in the intervention group compared with the control group, but the results were not statistically significant (p<0.08).<br>Attrition: 21% vs. 23% | Moderate |
| Kunst et al. (2020) | Design: RCT<br>Setting: Intra-operative, cardiac<br>Country: U.K.<br>Funding: University | Randomized N: 90 (2 patients withdrawn before surgery)<br>Analyzed N: 82<br>Intervention (N=45): BIS-guided anesthesia plus regional cerebral tissue oxygenation optimization<br>Control (N=43): Usual anesthesia care<br>Duration: Intra-operative<br>Follow-up (days): 3 to 5 | Inclusion: ≥65 years undergoing elective CABG surgery on CPB<br>Exclusion: Dementia | Mean (SD) age: 71.8 (4.67)<br>Female %: 18<br>Race %:<br>Caucasian: 87<br>Black/African American: 0<br>Asian: 13<br>Other: 0<br>Delirium %: NR<br>MMSE< 24 %: 0<br>Dementia %: 0<br>Postop %: 100 cardiac surgery<br>Cancer %: 0 | Main outcomes: There was a reduction in the incidence of delirium in the intervention group compared with the control group (2.4% vs. 20%, p=0.01).<br>Attrition: 7% vs. 7% | Moderate |
| Radtke et al. (2013) | Design: RCT<br>Setting: Intra-operative, | Randomized N: 1,277<br>Analyzed N: 1,155<br>Intervention (N=638): BIS-guided | Inclusion: ≥60 years undergoing elective surgery | Mean (SD) age: 69.9 (6.4)<br>Female %: 46<br>Race %: NR | Main outcomes: POD was detected in 95 patients (16.7%) in the intervention | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | mixed<br>Country: Germany<br>Funding: Mixed | anesthesia<br>Control (N=639): Usual care<br>Duration: During surgery<br>Follow-up (days): Until discharge, 90 | expected to last ≥60 minutes<br>Exclusion: <24 on MMSE | Delirium %: NR<br>ASA I-II %: 52<br>Dementia %: 0 (excluded)<br>Mean (SD) MMSE: 28.8 (1.5)<br>Postop %: 100<br>Cancer %: NR | group compared with 124 patients (21.4%) in the control group (p=0.036).<br>Attrition: 10% vs. 9% | |
| Sieber et al. (2010) | Design: RCT<br>Setting: Intra-operative, hip<br>Country: U.S.<br>Funding: Unclear | Randomized N: 114<br>Analyzed N: 114<br>Intervention 1 (N=57): Light Sedation (BIS approximately 50)<br>Intervention 2 (N=57): Deep Sedation (BIS ≥ 80)<br>Duration: Intra-operative<br>Follow-up (days): Discharge | Inclusion: ≥65 years undergoing hip fracture repair with spinal anesthesia and propofol<br>Exclusion: Preop delirium | Mean (SD) age: 81.5 (7.16)<br>Female %: 73<br>Race %: NR<br>Delirium %: 0<br>ASA: Median 3<br>MMSE: 24.7<br>Living independently %: 65<br>Dementia %: 35<br>Postop %: 100<br>Cancer %: NR | Main outcomes: POD was significantly lower in the light sedation group compared with the deep sedation (19% vs. 40%, p=0.02).<br>Overall attrition: 0% | Low |
| Sieber et al. (2018, 2019); STRIDE | Design: RCT<br>Setting: Intra-operative, hip<br>Country: U.S.<br>Funding: Government | Randomized N: 200<br>Analyzed N: 200<br>Intervention 1 (N=100): Light Sedation (OAA/S 3-5)<br>Intervention 2 (N=100): Deep Sedation (OAA/S 0-2)<br>Duration: Intra-operative<br>Follow-up (days): POD 5 | Inclusion: ≥65 years undergoing hip fracture repair with spinal anesthesia and propofol<br>Exclusion: Preop delirium and severe dementia | Mean (SD) age: 81.8 (7.7)<br>Female %: 73<br>Race %: White: 97<br>Delirium %: 0<br>Subsyndromal Delirium %: 6.5<br>ASA≥3 %: 69.5<br>MMSE: 24.3<br>Assisted living/nursing home %: 7<br>Clinical Dementia Rating Score=0 %: 41.4<br>Postop %: 100<br>Cancer %: NR | Main outcomes: There was no difference in the incidence of delirium between lighter compared with deeper sedation (34% vs. 39%, p=0.46).<br>Attrition: 4% vs. 3% | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Tang C. J. et al. (2020); ADAPT-2 | Design: RCT<br>Setting: Intra-operative, mixed<br>Country: U.S.<br>Funding: None | Randomized N: 223<br>Analyzed N: 102<br>Intervention (N=109): Processed EEG-guided anesthetic management<br>Control (N=114): Standard anesthesia care<br>Duration: Intra-operative<br>Follow-up (days): 3 | Inclusion: ≥65 years undergoing major elective, noncardiac surgery, with an anticipated hospital stay of ≥2 days<br>Exclusion: Preop delirium, inability to perform neurocognitive testing, history of intra-operative recall, or undergoing surgery of the brain | Mean (SD) age: 71.9 (5.4)<br>Female %: 52<br>Race %:<br>Caucasian: 89<br>Black/African American: NR<br>Asian: NR<br>Other: NR<br>Delirium %: 0 (excluded)<br>ASA III or IV %: 53.4<br>Dementia %: NR<br>Preop cognitive impairment %: 10.3<br>Postop %: 100<br>Cancer %: NR | Main outcomes: The incidence of delirium was not found to be different between the intervention (17%) and the standard care groups (20%) (RR 0.85, 95% CI 0.47 to 1.5).<br>Attrition: 6% vs. 11% | Moderate |
| Wildes et al. (2016, 2019) | Design: RCT<br>Setting: Intra-operative, mixed<br>Country: U.S.<br>Funding: Government | Randomized N: 1,232<br>Analyzed N: 1,213<br>Intervention (N=614): EEG/BIS-guided anesthesia (≥40)<br>Control (N=618): Usual care<br>Duration: During surgery<br>Follow-up (days): POD 1-5, 30 | Inclusion: ≥60 years, undergoing major surgery with general anesthesia<br>Exclusion: Delirious, history of intra-operative awareness, or scheduled for a second surgery within 5 days of initial surgery | Median age: 69<br>Female %: 45.7<br>Race %:<br>White: 90<br>Black: 8.7<br>Other: 1<br>Delirium %: 0 (excluded)<br>History of Delirium %: 12.8<br>ASA >III %: 15<br>History of depression %: 13.6<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: POD occurred in 26.0% of the EEG-guided anesthetic group and 23.0% of the usual care group; a difference that was not statistically significant.<br>Attrition: 2% vs. 1% | Low |
| Zhou et al. (2018) | Design: RCT<br>Setting: Intra-operative, colorectal cancer | Randomized N: 89<br>Analyzed N: 81<br>Intervention (N=44): BIS-guided anesthesia (40 to 60) | Inclusion: Age 65-75 years undergoing surgery for colon cancer with surgery expected to last at least 2 hours | Mean (SD) age: 68.59 (2.90)<br>Female %: 69<br>Race %: NR<br>Delirium %: 0<br>ASA I-III %: 100 | Main outcomes: The incidence of delirium was lower in the group who received BIS-guided anesthesia compared with | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Country: China<br>Funding: University | Control (N=45): Usual anesthesia care<br>Duration: Intra-operative<br>Follow-up (days): Through POD 5 | Exclusion: MMSE≤27, Parkinson, or Alzheimer's | Parkinson, Alzheimer's Dementia %: 0<br>MMSE: 29.08<br>Postop %: 100 colon surgery<br>Cancer %: 100 colon cancer | usual anesthesia care (17% vs. 27.5%, p<0.001).<br>Attrition at 5 days assessments: 7% vs. 11% | |

*Abbreviations.* ASA=American Society of Anesthesiologists; BIS=bispectral index; CABG=coronary artery bypass graf; CI=confidence interval; CPB=cardiopulmonary bypass; EEG=electroencephalogram; MMSE=Mini-Mental State Examination; N=number; NR=not reported; OAA/S=modified observer's assessment of alertness/sedation score; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; RR=relative risk; SD=standard deviation

## *Additional Anesthetic Comparisons*

### Xenon Gas vs. Sevoflurane Gas

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Al Tmimi et al. (2020) | Design: RCT<br>Setting: Intra-operative, cardiac surgery<br>Country: Belgium<br>Funding: Non-profit | Randomized N: 190<br>Analyzed N: 190<br>Intervention 1 (N=96): Xenon 40%-60% in oxygen<br>Intervention 2 (N=94): Sevoflurane 1.0%-1.4% in oxygen<br>Duration: Intra-operative<br>Follow-up (days): 90, 180, 365 | Inclusion: ≥65 years scheduled for cardiac surgery on CPB<br>Exclusion: Severe COPD, disabling neuropsychiatric illness (dementia, schizophrenia, epilepsy, intellectual disability), signs or symptoms of increases cranial pressure, history of stroke or TBI with residual neurological signs, risk factors for or history of malignant hyperthermia, or delirium at baseline | Mean (SD) age: Median: 76<br>Female %: 48<br>Race %: NR<br>Delirium %: 0% (excluded)<br>ASA status IV %: 93.6<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Overall incidence of POD was 41% (78/190), with no statistically significant difference between the xenon and sevoflurane groups (42.7% [41/96] vs. 39.4% [37/94], p=0.583, OR 1.18, 95% CI 0.65 to 2.16).<br>Overall attrition: 0% | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Coburn et al. (2018); HIPELD | Design: RCT<br>Setting: Intra-operative, hip<br>Country: 6 European countries Funding: Industry | Randomized N: 256<br>Analyzed N: 256<br>Intervention 1 (N=124): Xenon gas 5%<br>Intervention 2 (N=132): Sevoflurane 1.0%-1.4% in oxygen<br>Duration: Intra-operative<br>Follow-up (days): Up to day 4 | Inclusion: ≥75 years with planned surgery within 48 hours of hip fracture<br>Exclusion: Delirium, severe dementia, Alzheimer's, moderate to severe depression, recent brain trauma, history of stroke, or MMSE<24 | Mean (SD) age: 84.11 (4.85)<br>Female %: 75<br>Race %: NR<br>Delirium %: 0<br>ASA I, II %: 62.9<br>MMSE: 27.1<br>Severe Dementia %: 0<br>Postop %: 100<br>Cancer %: 0 | Main outcomes: The incidence of delirium with xenon 9.7% (95% CI 4.5 to 14.6) vs. sevoflurane 13.6% (95% CI 7.8 to 18.5) was not significantly different (p=0.33). Incidence of serious adverse events and fatal adverse events was 8.0% vs. 15.9% (p=0.05) and 0% vs. 3.8% (p=0.06), respectively.<br>Attrition: 11% vs. 9% | Moderate |
| Stoppe et al. (2013) | Design: RCT<br>Setting: Intra-operative, cardiac<br>Country: Germany Funding: Government | Randomized N: 30<br>Analyzed N: 30<br>Intervention 1 (N=15): Xenon gas<br>Intervention 2 (N=15): Sevoflurane gas<br>Duration: Intra-operative<br>Follow-up (days): Until discharge | Inclusion: >50 years undergoing elective CABG without severe comorbidity<br>Exclusion: Cardiac, respiratory, liver, or renal Failure; acute coronary syndrome within 24 hours before surgery; haemodynamic instability; emergency operations; lack of informed consent; severe neurological dysfunction; depression; GDS >5; MMSE <24; and patients with predisposition to malignant hyperthermia and/or hypersensitivity to the study drugs | Mean age: 67<br>Female %: 20<br>Race %: NR<br>Delirium %: NR<br>ASA II-IV %: 100<br>Dementia %: NR<br>Postop %: 100 cardiac surgery<br>Cancer %: 0 | Main outcomes: There was no difference between use of xenon and sevoflurane in incidence of POD (20% vs. 27%, p=0.666).<br>Overall attrition: 0% | Moderate |

*Abbreviations.* ASA=American Society of Anesthesiologists; CI=confidence interval; COPD=chronic obstructive pulmonary disease; CPB=cardiopulmonary bypass; GDS=Geriatric Depression Score; MMSE=Mini-Mental State Examination; N=number; NR=not reported; OR=odds ratio; POD=post-operative delirium; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation; TBI=traumatic brain injury.

## Propofol vs. Dexmedetomidine

### In Surgical Settings

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Chang et al. (2018) | Design: RCT<br>Setting: Postop, major<br>Country: Taiwan<br>Funding: Unclear | Randomized N: 60<br>Analyzed N: 60<br>Intervention 1 (N=31): Dexmedetomidine IV 0.1-0.7 µg/kg/hour<br>Intervention 2 (N=29): Propofol IV 0.3-1.6 mg/kg/hour<br>Duration: Postop<br>Follow-up (days): 0-24 hours postop | Inclusion: Age 20-99 years undergoing major abdominal surgery<br>Exclusion: Refractory bradycardia <60bpm, high degree atrioventricular block (second or third degree), refractory shock despite resuscitation (MAP <60 mm Hg), new onset of MI, New York Heart Association Class IV heart failure, acute physiology and chronic health evaluation II score >30, severe liver cirrhosis (ChildePugh class B or C), organ transplantation within 1 year, pregnancy, known allergic history to dexmedetomidine or propofol, enrolled in other clinical trial of dexmedetomidine or propofol within 1 month, signed consent of do not resuscitate, other conditions determined by surgeon or | Mean (SD) age: 70.52 (11.08)<br>Female %: 42<br>Race %: NR<br>Delirium %: NR<br>APACHE II score > 30 %: 0<br>Dementia %: NR<br>Postop %: 100 abdominal surgery<br>Cancer %: NR | Main outcomes: There were no instances of delirium within 24 hours after abdominal surgery.<br>Overall attrition: 0% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | | primary intensivist, and non-native speaker | | | |
| Djaiani et al. (2016) | Design: RCT<br>Setting: Postop, cardiac<br>Country: Canada<br>Funding: Mixed | Randomized N: 185<br>Analyzed N: 183<br>Intervention 1 (analyzed N=91): Dexmedetomidine continuous IV infusion of 0.4 µg/kg bolus followed by 0.2-0.7 µg/kg/hour; if MV needed beyond 24 hours, patients switched to propofol<br>Intervention 2 (analyzed N=92): Propofol continuous IV infusion 25-50 µg/kg/minute<br>Intervention 1 duration: Postop during MV, maximum 24 hours<br>Intervention 2 duration: Intra-operative<br>Follow-up (days): Through day 5 | Inclusion: ≥60 years undergoing complex cardiac surgery or ≥70 years undergoing coronary revascularization or single-valve repair/replacement with the use of CPB<br>Exclusion: Serious mental illness, delirium, or severe dementia | Mean (SD) age: 72.55 (6.3)<br>Female %: 25<br>Race %: NR<br>Delirium %: 0<br>Function: NR<br>Severe Dementia %: 0<br>Postop %: 100 cardiac surgery<br>Cancer %: 0 | Main outcomes: POD was present in 16 of 91 (17.5%) and 29 of 92 (31.5%) patients in dexmedetomidine and propofol groups, respectively (p=0.028). Duration of POD was 2 days vs. 3 days (p=0.04).<br>Overall attrition: 1% | Moderate |
| Liu X. et al. (2016) | Design: RCT<br>Setting: Postop, cardiac<br>Country: China<br>Funding: Unclear | Randomized N: 68<br>Analyzed N: 61<br>Intervention 1 (N=34): Dexmedetomidine IV 0.2-1.5 µg/kg/hour<br>Intervention 2 (N=34): Propofol IV 5-50 µg/kg/minute<br>Duration: Postop | Inclusion: ≥18 years undergoing elective cardiac valve surgery admitted to ICU<br>Exclusion: Patients who received 2 or more sedatives after randomization and had a sedation time <4 hours or ≥24 hours | Median age: 54<br>Female %: 59<br>Race %: NR<br>Delirium %: NR<br>Median APACHE II: 15 or 16<br>Dementia %: NR<br>Postop %: 100 cardiac surgery<br>Cancer %: 0 | Main outcomes: The incidence of delirium was not different in those who received dexmedetomidine vs. propofol (0% vs. 6%, p=0.493).<br>Attrition: 12% vs. 6% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Follow-up (days): Unclear (delirium listed as an adverse event) | | | | |
| Maldonado et al. (2009) | Design: RCT<br>Setting: Postop, cardiac<br>Country: U.S.<br>Funding: Unclear | Randomized N: 118<br>Analyzed N: 90<br>Intervention 1 (N=40): Dexmedetomidine IV 0.4 µg/kg bolus followed by 0.2-0.7 µg/kg/hour<br>Intervention 2 (N=38): Propofol IV 25-50 µg/kg/minute<br>Intervention 3 (N=40): Midazolam IV 0.5-2.0 mg/hour<br>Duration: Postop<br>Follow-up (days): Through POD 3 | Inclusion: Age 18-90 years undergoing elective cardiac valve operation<br>Exclusion: Preexisting dementia | Mean (SD) age: 57 (17)<br>Female %: 36<br>Race %: NR<br>Delirium %: NR<br>Mean ASA: 3.4<br>MMSE: 29.4<br>Dementia %: 0<br>Postop %: 100 cardiac surgery<br>Cancer %: 0 | Main outcomes: Postop sedation with dexmedetomidine was associated with significantly lower rates of POD than propofol or midazolam (3% vs. 50% vs. 50%).<br>Attrition: 10% vs. 18% vs. 20% | Moderate |
| Mei et al. (2018) | Design: RCT<br>Setting: Intra-operative, hip<br>Country: China<br>Funding: Government | Randomized N: 336<br>Analyzed N: 296<br>Intervention 1 (N=167): Dexmedetomidine IV 0.8-1.0 µg/kg bolus followed by 0.1-0.5 µg/kg/hour until end of surgery<br>Intervention 2 (N=169): Propofol IV 0.8-1.0 µg/mL<br>Duration: Intra-operative<br>Follow-up (days): Through POD 3 | Inclusion: ≥65 years undergoing total hip arthroplasty with nerve block<br>Exclusion: Cognitive impairment and/or preop delirium | Mean (SD) age: 75 (7)<br>Female %: 54<br>Race %: NR<br>Delirium %: 0<br>Mean ASA: 3<br>MMSE: 26<br>Dementia %: 0<br>Postop %: 100 hip arthroplasty<br>Cancer %: 0 | Main outcomes: Patients sedated with dexmedetomidine had a lower incidence of POD than patients sedated with propofol (7% vs. 16%, p=0.030).<br>Attrition: 9% vs. 11% | Low |
| Mei B. et al. (2020) | Design: RCT | Randomized N: 415*<br>Analyzed N: 366 | Inclusion: ≥65 years undergoing total hip | Mean (SD) age: 72.5 (10)<br>Female %: 60 | Main outcomes: Patients sedated with | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Setting: Intra-operative, hip<br>Country: China<br>Funding: Government | *The study noted 207 and 208 patients were assigned to the groups but it is not clear which group had which number of patients.<br>Intervention 1 (N=unclear): Dexmedetomidine IV 0.8-1.0 µg/kg bolus followed by 0.1-0.5 µg/kg/hour until end of surgery<br>Intervention 2 (N=unclear): Propofol IV 0.8 -1.0 µg/mL<br>Duration: Intra-operative<br>Follow-up (days): Through POD 7 | arthroplasty with nerve block<br>Exclusion: Cognitive impairment and/or preop delirium | Race %: NR<br>Delirium %: 0<br>Mean ASA: 2<br>MMSE: 26.9<br>Dementia %: 0<br>Postop %: 100 knee arthroplasty<br>Cancer %: 0 | dexmedetomidine had a lower incidence of POD than patients sedated with propofol (14% vs. 23%, p=0.032).<br>Attrition: 5% vs. 8% | |
| Sheikh et al. (2018) | Design: RCT<br>Setting: Intra-operative, cardiac<br>Country: India<br>Funding: None | Randomized N: 60<br>Analyzed N: 60<br>Intervention 1 (N=30): Dexmedetomidine IV 1.0 µg/kg bolus followed by 0.2-0.6 µg/kg/hour<br>Intervention 2 (N=30): Propofol IV 0.25-1.0 µg/kg/hour<br>Duration: Intra-operative<br>Follow-up (days): Discharge | Inclusion: Age 15-60 years undergoing elective open-heart surgery<br>Exclusion: Patients with neurological/psychological disorders | Mean (SD) age: 34.58 (10.74)<br>Female %: NR<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR<br>Postop %: 100 cardiac surgery<br>Cancer %: NR | Main outcomes: The risk of delirium was significantly less in the dexmedetomidine group compared with the propofol group (3.3% vs. 23.3%, p=0.02).<br>Attrition: NR | High |
| Susheela et al. (2017) ; O'Neal et al. (2015) | Design: RCT<br>Setting: Postop, cardiac<br>Country: U.S.<br>Funding: Government | Randomized N: 12<br>Analyzed N: 12<br>Intervention 1 (N=3): Dexmedetomidine IV 0.1-1.0 µg/kg/hour<br>Intervention 2 (N=3): | Inclusion: ≥60 undergoing CABG and/or valve surgery<br>Exclusion: Preexisting cognitive impairment or medications for cognitive decline | Mean (SD) age: NR<br>Female %: NR<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Cognitive Impairment %: 0 | Main outcomes: The incidence of delirium was 2/3 in the dexmedetomidine and the propofol groups, 1/3 in the dexmedetomidine plus | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Propofol IV 25-100 µg/kg/minute<br>Intervention 3 (N=3): Dexmedetomidine IV 0.1-1.0 µg/kg/hour plus IV acetaminophen 1 g/6 hours<br>Intervention 4 (N=3): Propofol IV 25-100 µg/kg/minute plus IV acetaminophen 1 g/6 hours<br>Duration: Postop<br>Follow-up (days): Discharge | | Postop %: 100<br>Cancer %: 0 | acetaminophen group, and 0/3 in the group receiving propofol plus acetaminophen.<br>Overall attrition: 0% | |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; ASA=American Society of Anesthesiologists; CABG=coronary artery bypass graf; CPB=cardiopulmonary bypass; IV=intravenous; MI=myocardial infarction; MMSE=Mini-Mental State Examination; MV=medical ventilation; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; SD=standard deviation.

## In Intensive Care Unit Setting

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Jakob et al. (2012); PRODEX | Design: RCT<br>Setting: ICU<br>Country: Europe and Russia<br>Funding: Industry | Randomized N: 500<br>Analyzed N: 498<br>Intervention 1 (N=251): Dexmedetomidine IV 0.2-1.4 µg/kg/hour<br>Intervention 2 (N=249): Propofol IV 0.3-4.0 mg/kg/hour<br>Duration: MV<br>Follow-up (days): Delirium assessed 48 hours after discontinuing sedation | Inclusion: ≥18 years requiring MV with light to moderate sedation for at least 24 hours<br>Exclusion: Acute severe neurological disorder, MAP <55 mm Hg, heart rate <50/minute, atrioventricular-conduction grade II or III (unless pacemaker installed), and | Median age: 65<br>Female %: 35<br>Race %: NR<br>Delirium %: NR<br>Simplified Acute Physiology Score II: 46.3<br>Dementia %: NR<br>Postop %: 56.2<br>Cancer %: NR | Main outcomes: There was no difference in the incidence of delirium between the dexmedetomidine group and the propofol group at 48 hours post sedation (9.6% vs. 13.7%, p=0.231).<br>Attrition: 28% vs. 24% | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | | use of $\alpha_2$ agonists or antagonists within 24 hours prior to randomization | | | |
| Li et al. (2019) | Design: RCT<br>Setting: ICU<br>Country: China<br>Funding: Mixed | Randomized N: 126<br>Analyzed N: 126<br>Intervention 1 (N=64): Dexmedetomidine IV 0.8 µg/kg/hour<br>Intervention 2 (N=62): Midazolam IV 0.06 mg/kg/hour or propofol IV 0.5-2 mg/kg/hour<br>Duration: During ICU stay<br>Follow-up (days): Delirium assessed twice daily until discharged from ICU | Inclusion: ≥18 years admitted to general ICU for more than 96 hours under continuous sedation and analgesia for 48 hours or longer<br>Exclusion: GCS <13 at baseline in ED | Mean (SD) age: 43.98 (14.05)<br>Female %: 44<br>Race %: NR<br>Delirium %: NR<br>APACHE II: 20.5<br>Dementia %: NR<br>Postop %: 0 within 24 hours of study<br>Cancer %: 0 | Main outcomes: The rate of delirium was significantly lower in the dexmedetomidine group than in the control group (28% vs. 55%, p=0.0023).<br>Attrition: NR | Moderate |
| Ruokonen et al. (2009) | Design: RCT<br>Setting: ICU<br>Country: Finland<br>Funding: Industry | Randomized N: 85<br>Analyzed N: 85<br>Intervention 1 (N=41): Dexmedetomidine 0.8 µg/kg/hour for 1 hour, then adjusted stepwise at 0.25, 0.5, 0.8, 1.1, and 1.4 µg/kg/hour<br>Intervention 2 (N=44): Standard care: 1) propofol 2.4 mg/kg/hour for 1 hour, then adjusted stepwise at 0.8, 1.6, 2.4, 3.2, and 4.0 mg/kg/hour OR 2) midazolam IV bolus 1-2 mg starting at 3 boluses/hour for 1 hour, thereafter 1-4 boluses/hour; if not sufficient | Inclusion: ≥18 years, MV, need for sedation for ≥24 hours after randomization, and an expected ICU stay ≥48 hours<br>Exclusion: Acute severe neurological disorder, MAP <55 mmHg despite volume and vasopressors, heart rate <50 beats/minute, atrioventricular-conduction block II to III (unless pacemaker installed), hepatic SOFA score >2, bilirubin >101 lmol/L, muscle relaxation, loss of hearing or | Median age: 64 vs. 68<br>Female %: 17.6<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR | Main outcomes: Delirium was more common in the dexmedetomidine group than in the standard care group (43.9% vs. 25.0%, p=0.035) when analyzed as the combined endpoint of CAM-ICU and adverse events of delirium and confusion. However, more CAM-ICU assessments were performed in the dexmedetomidine group than in the standard care group (106 vs. 84), and the proportion of positive CAM- | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | as continuous infusion of 0.2 mg/kg/hour for 1 hour followed by adjustment at 0.04, 0.08, 0.12, 0.16, and 0.20 mg/kg/hour<br>Duration: During ICU stay<br>Follow-up (days): 45 | vision, any other condition interfering with RASS assessment, or use of $\alpha_2$ agonists or antagonists at the time of randomization | | ICU results was comparable (17.0% vs. 17.9%, p=NS).<br>During the follow-up to ICU discharge, no significant difference was observed in the occurrence rate of positive RASS scores (26% vs. 32%).<br>Attrition: 24% vs. 16% | |
| Winings et al. (2021) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: None | Randomized N: 57<br>Analyzed N: 57<br>Intervention 1 (N=28): Dexmedetomidine mean dose of 0.48 mcg/kg/hour<br>Intervention 2 (N=29): Propofol mean dose of 24.6 mcg/kg/minute<br>Duration: During ICU stay<br>Follow-up (days): 4 | Inclusion: ≥18 years, MV, placed on the institutional sedation protocol, expected to require sedation lasting 24 hours after randomization, and admitted to the TSICU and followed by the TSICU Service<br>Exclusion: ≥72 hours since sedation protocol initiation, treatment per the institutional TBI protocol, concomitant continuous infusion of a neuromuscular blocking agent, heart rate <50 beats/minute, MAP <55 mmHg despite fluid resuscitation and vasopressors, and/or use of other $\alpha_2$ agonists within 24 hours of randomization | Mean (SD) age: 50.6 (19.2)<br>Female %: 28.9<br>Race %: NR<br>Delirium %: NR<br>Mean (SD) APACHE II: 17.5 (7.4)<br>Dementia %: NR<br>Postop %: 29.8<br>Cancer %: NR | Main outcomes: There was no difference between the groups in ICU mortality, ICU and hospital LOS, or incidence of delirium.<br>Attrition: NR | Moderate |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; CAM-ICU=Confusion Assessment Method for the ICU; ED=emergency department; GCS=Glasgow Coma Scale; ICU=intensive care unit; LOS=length of stay; MAP=mean arterial pressure; MV=medical ventilation; N=number; NS=not significant; NR=not reported; postop=post-operative; RASS=Richmond Agitation Sedation Scale; RCT=randomized controlled trial; SD=standard deviation; SOFA=Sequential Organ Failure Assessment; TBI=traumatic brain injury; TSICU=trauma/surgical ICU.

## Propofol vs. Sevoflurane Gas

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Ishii et al. (2016) | Design: RCT<br>Setting: Intra-operative, mixed<br>Country: Japan<br>Funding: NR | Randomized N: 59<br>Analyzed N: 59<br>Intervention 1 (N=29): Propofol IV 1.5-3 µg/mL<br>Intervention 2 (N=30): Sevoflurane 1-1.5 minimum alveolar concentration<br>Duration: During surgery<br>Follow-up (days): Until discharge | Inclusion: ≥70 years with ASA status I or II, scheduled to undergo elective gastrectomy, colectomy, or rectectomy under general anesthesia combined with epidural anesthesia<br>Exclusion: History of dementia, depression, alcoholism, and liver cirrhosis; history of using benzodiazepine, major tranquilizers, or steroids; an ineffective postop analgesia via epidural anesthesia | Mean (SD) age: 76.9 (4.5)<br>Female %: 32.2<br>Race %: NR<br>Delirium %: NR<br>ASA I or II %: 100<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: The incidence of POD in the propofol anesthesia (6.9%) was significantly less than that observed in the sevoflurane anesthesia (26.7%) (p=0.038).<br>Attrition: NR | Moderate |
| Lurati Buse et al. (2012) | Design: RCT<br>Setting: Intra-operative, cardiothoracic<br>Country: Switzerland<br>Funding: Unclear | Randomized N: 385<br>Analyzed N: 385<br>Intervention 1 (N=184): Sevoflurane dose not restricted by study protocol<br>Intervention 2 (N=201): Propofol dose not restricted by study protocol<br>Duration: Intra-operative<br>Follow-up (days): POD 1, ,2, 7 | Inclusion: Proven coronary artery disease and scheduled for major surgery or at risk for coronary artery disease and scheduled for major vascular surgery<br>Exclusion: Current medication with sulfonylurea derivatives or theophylline unless stopped ≥2 days before surgery, current congestive heart | Mean (SD) age: 72.5 (8)<br>Female %: 24<br>Race %: NR<br>Delirium %: NR<br>ASA III, IV %: 86.2<br>Dementia %: NR<br>Postop %: 100 major surgery<br>Cancer %: NR | Main outcomes: There was no difference between sevoflurane and propofol on POD (11.4% vs. 14.4%, p=0.379).<br>Overall attrition: 0% | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | | failure, current unstable angina pectoris, preop hemodynamic instability, hepatic disease, renal insufficiency, emergent surgery, severe COPD, prior enrollment in the study, concurrent enrollment in another RCT, pregnancy, or absence of written informed consent | | | |
| Mei X. et al. (2020) | Design: RCT<br>Setting: Intra-operative, mixed<br>Country: China<br>Funding: Government | Randomized N: 240<br>Analyzed N: 209<br>Intervention 1 (N=118): Sevoflurane anesthesia<br>Intervention 2 (N=122): Propofol anesthesia<br>Duration: Intra-operative<br>Follow-up (days): 1, 2, 3 | Inclusion: ≥60 years scheduled for surgery under general anesthesia, ASA class I to III, and normal cognitive function (MMSE >24)<br>Exclusion: Pre-existing delirium, prior diagnoses of neurologic diseases (e.g., stroke and Parkinson's disease), or history of mental disorders | Mean (SD) age: 71.2 (6.75)<br>Female %: 71<br>Race %: NR<br>Delirium %: 0 (excluded)<br>ASA II %: 80.4<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: POD was 33.0% (propofol) vs. 23.3% (sevoflurane), (p=0.119). Days of POD per person were higher with propofol (0.5±0.8) vs. sevoflurane (0.3±0.5) (p=0.049).<br>Attrition at follow-up: 13% vs. 13% | Moderate |
| Nishikawa et al. (2004) | Design: RCT<br>Setting: Intra-operative, mixed<br>Country: Japan<br>Funding: NR | Randomized N: 50<br>Analyzed N: 50<br>Intervention 1 (N=25): Propofol induction of 4 µg/mL<br>Intervention 2 (N=25): Sevoflurane gas<br>Duration: During surgery<br>Follow-up (days): 1, 2, 3 | Inclusion: >65 years, ASA status I or II, or scheduled for elective laparoscope-assisted surgical procedures which would last >3 hours under combined general and epidural anesthesia<br>Exclusion: Anticoagulation, symptomatic coronary | Mean (SD) age: 71 (7.5)<br>Female %: 42.1<br>Race %: NR<br>Delirium %: NR<br>ASA I %: 26<br>ASA II %: 74<br>Dementia %: NR, excluded cognitive impairment | Main outcomes: There was no significant difference between the incidences of POD in the 2 groups during the first 3 days after surgery. The scores for DRS on day 2 and 3 after surgery, however, were significantly higher in the propofol group than in | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | | artery disease, cardiac valvular regurgitation or stenosis, CNS or neuromuscular disorders, major or minor tranquilizer medication, or psychotic symptoms or cognitive impairment | Postop %: 100<br>Cancer %: NR | the sevoflurane group (p<0.01).<br>Attrition: NR | |

*Abbreviations.* ASA=American Society of Anesthesiologists; CNS=central nervous system; DRS=Delirium Rating Scale; MMSE=Mini-Mental State Examination; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; SD=standard deviation.

## Propofol vs. Desflurane

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Tanaka et al. (2017) | Design: RCT<br>Setting: Intra-operative, knee<br>Country: U.S.<br>Funding: Industry | Randomized N: 100<br>Analyzed N: 90<br>Intervention 1 (N=45 analyzed): Desflurane maintenance anesthesia<br>Intervention 2 (N=45 analyzed): Propofol maintenance anesthesia<br>Duration: Intra-operative<br>Follow-up (days): 1, 2 | Inclusion: ≥65 years undergoing total knee replacement<br>Exclusion: Neurocognitive disorders and MMSE score ≤23 | Mean age: 70.2<br>Female %: 56<br>Race %: NR<br>Delirium %: 0<br>MMSE≤ 23 %: 0<br>ASA III %: 46.7<br>Dementia %: NR (neurocognitive disorders excluded)<br>Postop %: 100 knee replacement surgery<br>Cancer %: 0 | Main outcomes: There was no difference in incident delirium in patients whose anesthesia was maintained with desflurane compared with propofol (0% vs. 2.2%, p=0.315).<br>Overall attrition: 21% | Moderate |

*Abbreviations.* ASA=American Society of Anesthesiologists; COPD=chronic obstructive pulmonary disease; MMSE=Mini-Mental State Examination; N=number; NR=not reported; postop=post-operative; RCT=randomized controlled trial.

4538 Propofol vs. Midazolam

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Chen (2020) | Design: RCT<br>Setting: ICU<br>Country: China<br>Funding: None | Randomized N: 120<br>Analyzed N: 120<br>Intervention 1 (N=60): Midazolam IV 0.05-0.2 mg/kg/hour<br>Intervention 2 (N=60): Propofol IV 0.5-4 mg/kg/hour<br>Duration: During MV<br>Follow-up (days): 28 | Inclusion: Age 18-60 years with expected sedation time of ≤72 hours and required continuous sedation with MV<br>Exclusion: Cerebral surgery; history of CNS and mental illness (including Alzheimer's disease); long-term use of antidepressants or sedatives, and alcoholics; serious liver and kidney dysfunction, internal environment disorder, or hyper-lipidaemia; in a coma; obvious abnormal blood glucose and great fluctuations; sepsis, unstable circulation, severe complicated hypoproteinaemia, anemia, and thrombocytopenia; allergic to midazolam or propofol | Mean age: 41 to 60 years; 51%<br>Female %: 30<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: 0 (excluded)<br>Postop %: NR<br>Cancer %: NR | Main outcomes: The difference in the incidence of delirium, adverse reactions, ICU LOS, and mortality in 28 days between the groups was not statistically significant (p>0.05). However, time to spontaneous eye opening was longer in the midazolam group (p<0.05). The onset effect time of sedatives was slightly longer in the midazolam group, compared with the propofol group (p<0.05). The difference in the time to reach the optimal level of sedation between these 2 groups was not statistically significant (p>0.05).<br>Attrition: NR | High |
| Li et al. (2019) | Design: RCT<br>Setting: ICU<br>Country: China<br>Funding: Mixed | Randomized N: 126<br>Analyzed N: 126<br>Intervention 1 (N=64): Dexmedetomidine IV 0.8 µg/kg/hour<br>Intervention 2 (N=62): Midazolam IV 0.06 | Inclusion: ≥18 years admitted to general ICU for more than 96 hours under continuous sedation and analgesia for 48 hours or longer | Mean (SD) age: 43.98 (14.05)<br>Female %: 44<br>Race %: NR<br>Delirium %: NR<br>APACHE II: 20.5<br>Dementia %: NR<br>Postop %: 0 within 24 hours of | Main outcomes: The rate of delirium was significantly lower in the dexmedetomidine group than in the control group (28% vs. 55%, p=0.0023).<br>Attrition: NR | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | mg/kg/hour or propofol IV 0.5-2 mg/kg/hour<br>Duration: During ICU stay<br>Follow-up (days): Delirium assessed twice daily until discharged from ICU | Exclusion: GCS <13 at baseline in ED | study<br>Cancer %: 0 | | |
| Maldonado et al. (2009) | Design: RCT<br>Setting: Postop, cardiac<br>Country: U.S.<br>Funding: Unclear | Randomized N: 118<br>Analyzed N: 90<br>Intervention 1 (N=40): Dexmedetomidine IV 0.4 µg/kg bolus followed by 0.2-0.7 µg/kg/hour<br>Intervention 2 (N=38): Propofol IV 25-50 µg/kg/minute<br>Intervention 3 (N=40): Midazolam IV 0.5-2.0 mg/hour<br>Duration: Postop<br>Follow-up (days): Through POD 3 | Inclusion: Age 18-90 years undergoing elective cardiac valve operation<br>Exclusion: Preexisting dementia | Mean (SD) age: 57 (17)<br>Female %: 36<br>Race %: NR<br>Delirium %: NR<br>Mean ASA: 3.4<br>MMSE: 29.4<br>Dementia %: 0<br>Postop %: 100 cardiac surgery<br>Cancer %: 0 | Main outcomes: Postop sedation with dexmedetomidine was associated with significantly lower rates of POD than propofol or midazolam (3% vs. 50% vs. 50%).<br>Attrition: 10% vs. 18% vs. 20% | Moderate |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; ASA=American Society of Anesthesiologists; CNS=central nervous system; ED=emergency department; GCS=Glasgow Coma Scale; ICU=intensive care unit; IV=intravenous; LOS=length of stay; MMSE=Mini-Mental State Examination; MV=medical ventilation; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

## Propofol vs. No Sedation

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Strøm et al. (2010) | Design: RCT | Randomized N: 140<br>Analyzed N: 113<br>Intervention 1 (N=70): No | Inclusion: ≥18 years critically ill patients expected to need MV for more than 24 hours | Mean (SD) age: 66<br>Female %: 33<br>Race %: NR | Main outcomes: Agitated delirium was more common in the patients who had no | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Setting: ICU<br>Country: Denmark<br>Funding: Mixed | sedation<br>Intervention 2 (N=70): Interrupted sedation of propofol IV 20mg/mL; after 48 hours propofol discontinued and midazolam IV 1 mg/mL begun<br>Duration: MV<br>Follow-up (days): Discharge | Exclusion: Increased intracranial pressure, sedation needed (e.g., for status epilepticus, or hypothermia after cardiac arrest), pregnancy, meeting criteria for weaning from ventilation ($FiO_2$ ≤40% and positive end-expiratory pressure of 5 cm $H_2O$), or no cerebral contact | Delirium %: NR<br>APACHE II: 26<br>Dementia %: NR<br>Postop %: NR<br>Cancer %: NR | sedation compared with interrupted sedation (20% vs. 7%, p=0.040).<br>Attrition: 21% vs. 17% | |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; ICU=intensive care unit; IV=intravenous; MV=medical ventilation; N=number; NR=not reported; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

### Ketamine (Low/High) vs. Normal Saline

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Avidan et al. (2017); PODCAST trial | Design: RCT<br>Setting: Intra-operative, mixed<br>Country: U.S.<br>Funding: Mixed | Randomized N: 672<br>Analyzed N: 654<br>Intervention 1 (N=227): Ketamine, low-dose (0.5 mg/kg)<br>Intervention 2 (N=223): Ketamine, high-dose (1.0 mg/kg)<br>Intervention 3 (N=222): Placebo; normal saline<br>Duration: During surgery<br>Follow-up (days): POD 3 | Inclusion: ≥60 years undergoing major open cardiac or non-cardiac surgeries under general anesthesia<br>Exclusion: Patients with delirium prior to surgery or with a weight outside of the range of 50-200 kg | Mean (SD) age: 70 (7.1)<br>Female %: 38<br>Race %: NR<br>Delirium %: 0 (excluded)<br>Median (IQR) Charlson Comorbidity index: 5 (3-6)<br>History of depression %: 11<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: No difference was found in POD incidence between those in the combined ketamine groups and those who received placebo (19.45% vs. 19.82%, respectively; absolute difference 0.36%, 95% CI −6.07% to 7.38%, p=0.92).<br>Attrition: 2% vs. 2% vs. 3% | Low |
| Hollinger et al. (2021) | Design: RCT<br>Setting: Intra-operative, | Randomized N: 192<br>Analyzed N: 182<br>Intervention 1 (N=48): | Inclusion: ≥65 years scheduled for visceral, orthopedic, vascular, | Mean (SD) age: 73.7 (6.1)<br>Female %: 43.4<br>Race %: NR | Main outcomes: None of the 3 study arms – haloperidol, ketamine, or both drugs | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | mixed<br>Country: Switzerland<br>Funding: Non-profit | Haloperidol 5 µg/kg<br>Intervention 2 (N=49): Ketamine 1 mg/kg<br>Intervention 3 (N=49): Haloperidol 5 µg/kg plus ketamine 1 mg/kg<br>Intervention 4 (N=47): Placebo<br>Duration: Once before induction of anesthesia<br>Follow-up (days): 3 | gynecological, cardiac, or thoracic surgery<br>Exclusion: Delirium at admission or prior to surgery, MMSE <24, DOS ≥3, dementia, high risk for postop treatment in the ICU, QT interval prolongation, or drugs influencing QT interval, Parkinson's disease, intake of dopaminergic drugs, epilepsy, delay of surgery for >72 hours after set indication for surgery, or weight >100 kg | Delirium %: 0 (excluded)<br>Function: NR<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR | combined – was significantly superior to placebo for prevention of postop brain dysfunction and delirium (p=0.39).<br>Attrition: 6% vs. 4% vs. 4% vs. 6% | |
| Hudetz et al. (2009) | Design: RCT<br>Setting: Intra-operative, cardiac<br>Country: U.S.<br>Funding: Government | Randomized N: 58<br>Analyzed N: 58<br>Intervention 1 (N=29): Ketamine IV 0.5 mg/kg bolus<br>Intervention 2 (N=29): Placebo; normal saline<br>Duration: Intra-operative<br>Follow-up (days): Up to day 5 or discharge | Inclusion: ≥55 years, U.S. veteran having elective CABG or valve replacement/repair with CPB<br>Exclusion: Patients with previous defined cognitive difficulty | Mean (SD) age: 64 (8)<br>Female %: 0<br>Race %:<br>Caucasian: 90<br>Black/African American: NR<br>Asian: NR<br>Other: NR<br>Delirium %: NR (0% assumed)<br>Function: NR<br>History of cognitive impairment %: 0<br>Postop %: 100 cardiac surgery<br>Cancer %: 0 | Main outcomes: The incidence of POD was lower in patients receiving ketamine compared with placebo (3% vs. 31%, p=0.01).<br>Overall attrition: 0% | Moderate |

*Abbreviations.* CABG=coronary artery bypass graf; CI=confidence interval; CPB=cardiopulmonary bypass; DOS=Delirium Observation Scale; ICU=intensive care unit; IQR=interquartile range; IV=intravenous; MMSE=Mini-Mental State Examination; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

4548 Forms of Reginal Anesthesia vs. Placebo/General Anesthesia/Opioid Therapy

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Jin L. et al. (2020) | Design: RCT<br>Setting: Intra-operative, esophageal cancer<br>Country: China<br>Funding: Mixed | Randomized N: 180<br>Analyzed N: 167<br>Intervention 1 (N=90): Ultrasound-guided continuous thoracic PVB<br>Intervention 2 (N=90): PCA as usual care<br><br>Intervention 1 duration: Before induction of anesthesia<br>Intervention 2 duration: Postop<br>Follow-up (days): 4 | Inclusion: Age 65-75 years undergoing elective esophagectomy for stage III or IV esophageal cancer<br>Exclusion: Brain injury or neurosurgery, cardiovascular or cerebrovascular disease, COPD, neurological or psychiatric disorders, hepatic and/or kidney dysfunction, or BMI >35 | Mean (SD) age: 71.1 (5.4)<br>Female %: 54<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR (most likely excluded, but unclear)<br>Postop %: 100<br>Cancer %: 100 | Main outcomes: The incidence of POD was significantly lower in the PVB group than in the PCA group.<br>Attrition: 7% vs. 8% | Moderate |
| Li et al. (2021) | Design: RCT<br>Setting: Intra-operative, thoracic or abdominal<br>Country: China<br>Funding: University | Randomized N: 1,802<br>Analyzed N: 1,720<br>Intervention (N=901): General anesthesia plus epidural<br>Control (N=901): General anesthesia<br>Duration: During surgery<br>Follow-up (days): 7 | Inclusion: Age 60-90 years and scheduled for noncardiac thoracic or abdominal surgery expected to last ≥2 hours<br>Exclusion: Severe neurologic conditions, acute MI or stroke within 3 months, any contraindication for epidural anesthesia, severe heart dysfunction, severe liver dysfunction (Child–Pugh grade C), or renal failure | Mean age: 69.5<br>Female %: 65.3<br>Race %: NR<br>Delirium %: 0<br>ASA I-III %: 100<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: 92 | Main outcomes: Delirium was less common in the general anesthesia plus epidural group than in the general anesthesia only group (1.8% vs. 5.0%, p<0.001).<br>Attrition: 5% vs. 4% | Moderate |
| Mann et al. (2000) | Design: RCT<br>Setting: Intra-operative, abdominal<br>Country: France<br>Funding: Unclear | Randomized N: 70<br>Analyzed N: 70<br>Intervention 1 (N=35): Sufentanil 1 µg/ml plus bupivacaine 0.25% mixture epidural anesthesia | Inclusion: >70 years undergoing major abdominal surgery for cancer with ASA status I or II and normal preop mental status, absence of contraindications to epidural anesthesia, and absence of extreme | Mean (SD) age: 76.45 (5.17)<br>Female %: 46<br>Race %: NR<br>Delirium %: 0<br>ASA I, II %: 100<br>Dementia %: 0 | Main outcomes: There was no difference in POD between the treatment groups (26% vs. 24%, p>0.05). | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | continuous infusion intra-operatively followed by sufentanil 0.5 µg/ml plus bupivacaine mixture by PCA epidural pump during postop<br>Intervention 2 (N=35): Sufentanil IV 0.5 µg/kg bolus followed by 0.2-0.4 µg/kg intra-operatively as necessary followed by PCA with morphine 1.5 mg per dose during postop<br>Duration: Intra-operatively, postop<br>Follow-up (days): Until discharge | malnutrition or cerebral vascular insufficiency<br>Exclusion: NR | Postop %: 100 abdominal surgery<br>Cancer %: 100 | Attrition: 11% vs. 6% | |
| Mouzopoulos et al. (2009) | Design: RCT<br>Setting: Preop and postop, hip<br>Country: Greece<br>Funding: Unclear | Randomized N: 219<br>Analyzed N: 207<br>Intervention 1 (N=108): FICB<br>Intervention 2 (N=111): Placebo<br>Duration: Preop, postop<br>Follow-up (days): Discharge | Inclusion: ≥70 years undergoing surgery for hip fracture with intermediate or high risk for POD<br>Exclusion: Patients with delirium at presentation, Parkinsonism, or profound dementia | Mean (SD) age: 72.71 (3.95)<br>Female %: 74<br>Race %: NR<br>Delirium %: 0<br>APACHE II: 15.3<br>MMSE: 21.2<br>Profound Dementia %: 0<br>Postop %: 100 hip arthroplasty<br>Cancer %: 0 | Main outcomes: The incidence of delirium was lower in the FICB group (10.78%, 11/102) than the placebo group (23.8%, 25/105) (RR 0.45, 95% CI 0.23 to 0.87).<br>Attrition: 6% vs. 5% | Moderate |
| Papaioannou et al. (2005) | Design: RCT<br>Setting: Intra-operative, mixed<br>Country: Greece<br>Funding: Government | Randomized N: 50<br>Analyzed N: 47<br>Intervention (N=25): Regional anesthesia<br>Control (N=25): General anesthesia | Inclusion: ≥60 years, scheduled for elective surgery that could be performed under regional or general anesthesia<br>Exclusion: ≤23 on MMSE, indicating | Mean age:<br>60-69: 62%<br>≥70: 38%<br>Female %: 36<br>Race %: NR<br>Delirium at baseline: NR | Main outcomes: 9 patients developed delirium, but the type of anesthesia did not affect its incidence. The only important | High |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Duration: During surgery<br>Follow-up (days): Until discharge | dementia, and those with CNS disorders | ASA I-II %: 91<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR<br>Cardiovascular disease %: 53<br>Orthopedic surgery %: 34 | factor for the development of delirium was preexisting cardiovascular disease irrespective of anesthesia type (p<0.025).<br>Attrition at follow-up: 24% vs. 4% | |
| Strike et al. (2019) | Design: RCT<br>Setting: Intra-operative, cardiac<br>Country: Canada, Latvia Funding: Unclear | Randomized N: 50<br>Analyzed N: 44<br>Intervention 1 (N=25): PVB<br>Intervention 2 (N=25): PCA<br>Intervention 1 duration: Preop, intra-operative, postop<br>Intervention 2 duration: Postop<br>Follow-up (days): POD 7 or discharge | Inclusion: Patients undergoing transcatheter aortic valve replacement surgery<br>Exclusion: Patients with delirium or severe dementia | Mean (SD) age: 82 (5.9)<br>Female %: 57<br>Race %: NR<br>Delirium %: 0<br>Function: NR<br>Severe Dementia %: 0<br>Postop %: 100<br>Cancer %: 0 | Main outcomes: There was no difference in the incidence of delirium between the groups (PVB 23% vs. PCA 32%, p=0.73).<br>Attrition: 12% vs. 12% | Moderate |
| Unneby et al. (2020) | Design: RCT<br>Setting: Intra-operative, mixed<br>Country: Sweden<br>Funding: Non-profit | Randomized N: 277<br>Analyzed N: 236<br>Intervention (N=116): Femoral nerve block<br>Control (N=120): Conventional pain management<br>Intervention duration: Preop<br>Control duration: During hospitalization<br>Follow-up (days): 5 | Inclusion: ≥70 years with radiographically verified hip fracture who were admitted consecutively to an orthopedic ward<br>Exclusion: Infection or previous vascular surgery in the inguinal area | Mean (SD) age: 84.1 (6.7)<br>Female %: 66.1<br>Race %: NR<br>Delirium %: NR<br>Mean (SD) Barthel Index score: 15.7 (4.6)<br>ASA III-IV %: 61.7<br>Dementia %: 46.2<br>Postop %: 100<br>Cancer %: NR | Main outcomes: The intervention group had 20% lower incidence of POD compared with the control group. However, there was no significant difference between the groups regarding the number of patients suffered | High |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | | | | preop and postop delirium or the duration of delirium.<br>Overall attrition: 16% | |
| Uysal et al. (2020) | Design: RCT<br>Setting: Preop, orthopedic<br>Country: Turkey<br>Funding: None | Randomized N: 110<br>Analyzed N: 96<br>Intervention 1 (N=55): Femoral nerve block with bupivacaine 0.5mL/kg 0.25% every 8 hours<br>Intervention 2 (N=55): Paracetamol IV 15 mg/kg<br>Duration: Preop<br>Follow-up (days): NR | Inclusion: ≥65 years admitted to the ED with trochanteric femur fracture<br>Exclusion: Patients with preexisting delirium and fracture due to cancer | Mean (SD) age: 81.72 (7.48)<br>Female %: 53<br>Race %: NR<br>Delirium %: 0<br>ASA II-IV %: 100<br>Dementia %: NR<br>Postop %: 0<br>Cancer %: 0 | Main outcomes: The incidence of delirium was similar between those who received the femoral nerve block and those who received paracetamol (20% vs. 10.9%, p=0.227).<br>Attrition: 16% vs. 18% | Moderate |
| Williams-Russo et al. (1995) | Design: RCT<br>Setting: Intra-operative, knee<br>Country: U.S.<br>Funding: Mixed | Randomized N: 262<br>Analyzed N: 262<br>Intervention (N=134): Epidural anesthesia<br>Control (N=128): General anesthesia<br>Duration: Intra-operative<br>Follow-up (days): Until discharge | Inclusion: >40 years undergoing elective unilateral total knee replacement surgery<br>Exclusion: History of surgery performed with either a regional or general anesthetic in the 3 months or contraindication to either epidural or general anesthesia | Median age: 69<br>Female %: 70<br>Race %: NR<br>Delirium %: NR<br>Comorbidity score=0 %: 46.2<br>Dementia %: NR<br>Postop %: 100 knee surgery<br>Cancer %: 0 | Main outcomes: There was no difference between epidural anesthesia and general anesthesia in the incidence of delirium (12% vs. 9.4%, p=0.50).<br>Attrition: 2% vs. 2%<br>Attrition at 6-month postop neuropsychological testing: 12% (including 2 deaths) | Moderate |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; ASA=American Society of Anesthesiologists; BMI=body mass index; CI=confidence interval; CNS=central nervous system; ED=emergency department; FICB=fascia iliaca compartment block; IV=intravenous; MI=myocardial infarction; MMSE=Mini-Mental State Examination; N=number; NR=not reported; PCA=patient-controlled analgesia; POD=post-operative delirium; postop=post-operative; preop=pre-operative; PVB=paravertebral block; RCT=randomized controlled trial; RR=relative risk; SD=standard deviation.

## Pecto-intercostal fascial plane block vs. Placebo

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Khera et al. (2021) | Design: RCT<br>Setting: Postop, cardiac<br>Country: U.S.<br>Funding: NR | Randomized N: 80<br>Analyzed N: 80<br>Intervention 1 (N=40): PIFB with 0.25% bupivacaine<br>Intervention 2 (N=40): PIFB with placebo<br>Duration: During surgery<br>Follow-up (days): 2 | Inclusion: ≥18 years requiring median sternotomy<br>Exclusion: Hemodynamic instability (left ventricular ejection fraction <30%, on ventricular assist device); surgical factors, such as emergency procedures; minimally invasive procedure; aortic surgery; use of chronic pain medications or neuromodulatory medications; receiving other regional anesthetic modality | Mean age: 65.8<br>Female %: 23.8<br>Race %:<br>White: 81.3<br>Asian: 2.5<br>Unknown: 17.5<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR<br>Postop %: 100<br>Isolated CABG %: 60<br>CABG + additional surgery %: 20<br>Valve surgery %: 28.5<br>Solid tumor, metastic %: 2.5 | Main outcomes:<br>There was no difference in the incidence of POD between groups (p=0.45).<br>Overall attrition: 0% | Moderate |

*Abbreviations.* CABG=coronary artery bypass graf; N=number; NR=not reported; PIFB=pecto-intercostal fascial plane block; POD=post-operative delirium; postop=post-operative; RCT=randomized controlled trial.

## Deep vs. Standard Neuromuscular Blockade

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Oh C.S. et al. (2021) | Design: RCT<br>Setting: Intra-operative, orthopedic<br>Country: South Korea<br>Funding: Industry | Randomized N: 82<br>Analyzed N: 82<br>Intervention (N=41): Deep neuromuscular blockade (rocuronium)<br>Control (N=41): Standard neuromuscular blockade<br>Duration: During surgery<br>Follow-up (days): 7 | Inclusion: >50 years having total hip replacement with general anesthesia<br>Exclusion: Preexisting cognitive dysfunction, other concurrent surgery, underlying liver dysfunction, kidney dysfunction, or neuromuscular disease, and use of any medication that could | Mean age: 73.5<br>Female %: 34.1<br>Race %: NR<br>Delirium %: 0 (excluded)<br>ASA I-III %: 100<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Hip replacement surgery %: | Main outcomes:<br>There was no difference in the incidence of POD between groups (17% vs. 34%, p=0.129).<br>Overall attrition: 0% | Low |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | potentially interfere with neuromuscular transmission | 100<br>Cancer %: NR | | |

*Abbreviations.* ASA=American Society of Anesthesiologists; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; RCT=randomized controlled trial.

### Anaortic Off-Pump Coronary Bypass With Total Arterial Revascularization vs. Carbon Dioxide Field Flooding or Use of Vein Grafts

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Szwed et al. (2021) | Design: RCT<br>Setting: Intra-operative, cardiac<br>Country: Poland<br>Funding: Government | Randomized N: 192<br>Analyzed N: 191<br>Intervention 1 (N=64): Anaortic OPCAB with total arterial revascularization<br>Intervention 2 (N=64): OPCAB with carbon dioxide surgical field flooding<br>Intervention 3 (N=64): Conventional OPCAB with vein grafts<br>Duration: During surgery<br>Follow-up (days): 7 | Inclusion: Patients scheduled for elective isolated OPCAB<br>Exclusion: History of neurologic or psychiatric illness, use of tranquilizers or antipsychotics, previous cardiac surgery, left ventricular ejection fraction <31%, and carotid artery stenosis >70% in an obligatory preop ultrasound; scoring below age- and education-adjusted MMSE cutoffs; HADS >7 | Mean (SD) age: 65.8 (8.4)<br>Female %: 26.7<br>Race %: NR<br>Delirium %: NR<br>New York Heart Association class I-II %: 25.6<br>New York Heart Association class III %: 2.6<br>Dementia %: NR (most likely excluded)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: The incidence of POD was 35.9% in the conventional OPCAB arm, 32.8% in the OPCAB with carbon dioxide arm, and 12.5% in the anaortic OPCAB arm (p=0.006). Post hoc tests revealed that the incidence of POD In the anaortic OPCAB arm differed from that in the OPCAB arm (OR 0.26, 95% CI 0.09 to 0.68, p=0.002).<br>Attrition: 2% vs. 5% vs. 5% | Low |

*Abbreviations.* CI=confidence interval; HADS=Hospital Anxiety and Depression Scale; MMSE=Mini-Mental State Examination; N=number; NR=not reported; OPCAB=off-pump coronary artery bypass; OR=odds ratio; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; SD=standard deviation.

### Unilateral Spinal Anesthesia vs. Combined Lumbar-Sacral Plexus Block Plus General Anesthesia

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|

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|---|---|---|---|---|---|---|
| Tang et al. (2021) | Design: RCT<br>Setting: Intra-operative, orthopedic<br>Country: China<br>Funding: Government | Randomized N: 124<br>Analyzed N: 110<br>Intervention 1 (N=62): Unilateral spinal anesthesia<br>Intervention 2 (N=62): Combined lumbar-sacral plexus block plus general anesthesia<br>Duration: During surgery<br>Follow-up (days): 7 | Inclusion: >65 years, ASA I-IV, undergoing elective unilateral hip fracture surgeries<br>Exclusion: Dementia or severe cognitive dysfunction, unstable mental state or mental disease, use of psychotropic drugs or abuse of narcotic sedation analgesics, being delirious or history of delirium, anesthesia and surgery within 6 months, other surgeries at the same time, cerebrovascular accidents within 3 months, and prosthesis fracture repair surgery | Mean (SD) age: 77.3 (6.72)<br>Female %: 67<br>Race %: NR<br>Delirium %: 0 (excluded)<br>Charlson Comorbidity index score of ≤2 %: 90<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: There were no significant differences in incidence of POD, postop nausea and vomiting, and other complications.<br>Attrition at follow-up: 11% vs. 11% | Moderate |

*Abbreviations.* ASA=American Society of Anesthesiologists; N=number; NR=not reported; POD=post-operative delirium; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

## High vs. Low Mean Arterial Pressure/Pressure Perfusion

| **Author (year); trial name** | **Study characteristics** | **Study protocol including numbers of participants, interventions, duration, and follow-up** | **Study population including main inclusion and exclusion criteria** | **Sample demographics** | **Results including main outcomes and attrition rates** | **Risk of Bias** |
|---|---|---|---|---|---|---|
| Hu et al. (2021) | Design: RCT<br>Setting: Intra-operative, mixed<br>Country: China<br>Funding: Unclear | Randomized N: 322<br>Analyzed N: 298<br>Intervention 1 (N=161): High MAP (90-100 mmHg)<br>Intervention 2 (N=161): Low MAP (60-70 mmHg)<br>Duration: Intra-operative<br>Follow-up (days): 7 | Inclusion: ≥65 years, non-cardiothoracic surgery with general anesthesia of ≥2 hours<br>Exclusion: Preop history of schizophrenia, epilepsy, parkinsonism, diabetes, hypertension, severe sinus bradycardia (<50 bpm), or a second-degree or greater atrioventricular block without a pacemaker; use of a cholinesterase inhibitor or levodopa; severe hepatic dysfunction (Child-Pugh class C); severe renal dysfunction (dialysis before surgery); brain injury or previous neurosurgery; severe cognitive | Mean (SD) age: 72.5<br>Female %: 58.4<br>Race %: NR<br>Delirium %: NR<br>ASA I-II %: 100<br>MMSE score ≥15 %: 100<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Fewer patients in the high MAP group than the low MAP group experienced POD (11.9% vs. 24.5%, p=0.02).<br>Attrition: 4% vs. 11% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | | impairment (MMSE score < 15); use of haloperidol or other neuroleptics during or after anesthesia; previous participation in this study; or patients who were unlikely to survive for >24 hours. | | | |
| Siepe et al. (2011) | Design: RCT<br>Setting: Intra-operative, cardiac<br>Country: Germany<br>Funding: Unclear | Randomized N: 105<br>Analyzed N: 92<br>Intervention 1 (N=44 analyzed): High-pressure perfusion (80-90 mmHg)<br>Intervention 2 (N=48 analyzed): Low-pressure perfusion (60-70 mmHg)<br>Duration: Intra-operative<br>Follow-up (days): POD 2 | Inclusion: Undergoing elective or urgent CABG surgery<br>Exclusion: Patients with psychiatric disorders | Mean (SD) age: 66.87 (9.0)<br>Female %: 20<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR<br>Postop %: 100 cardiac surgery<br>Cancer %: NR | Main outcomes: Significantly fewer patients in the high-pressure group developed POD than in the low-pressure group (0% vs. 13%, p=0.017).<br>Overall attrition: 12% | Moderate |

*Abbreviations.* ASA=American Society of Anesthesiologists; CABG=coronary artery bypass graf; MAP=mean arterial pressure; MMSE=Mini-Mental State Examination; N=number; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; SD=standard deviation.

### *GABAergic Anticonvulsant Medications*

#### Gabapentin vs. Placebo

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Clarke et al. (2014); Dighe et al. (2014) | Design: RCT<br>Setting: Postop, orthopedic<br>Country: Canada<br>Funding: University/Government | Randomized N: 179<br>Analyzed N: 150 (Day 4), 157 (6 weeks), 155 (3 months)<br>Intervention 1 (N=95): Gabapentin 600 mg orally 2 hours pre-operatively x 1 dose (in addition to celecoxib 400 | Inclusion: Ages 18-75 years with an ASA physical status score of I, II, or III undergoing total knee arthroplasty<br>Exclusion: Diabetes with impaired renal function or | Mean (SD) age: 63 (6.84)<br>Female %: 50<br>Race %: NR<br>Delirium %: NR<br>TUG seconds: 12.3<br>6MWT meters: 357<br>WOMAC physical | Main outcomes: No difference was found between gabapentin and placebo regarding the incidence or duration of POD among elective total knee arthroplasty patients. | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | mg), then 200 mg three times daily for 4 days<br>Intervention 2 (N=84): Placebo 2 hours pre-operatively (in addition to celecoxib 400 mg), then three times daily for 4 days<br>Duration: Preop, postop<br>Follow-up (days): 1, 4, 42, 90 | unable or unwilling to use PCA devise | function (0-68): 33.6<br>Dementia %: NR<br>Postop %: 96<br>Cancer %: NR | Attrition at POD 4: 16% vs. 17% | |
| Leung et al. (2006) | Design: RCT<br>Setting: Postop, orthopedic<br>Country: U.S.<br>Funding: University/Government | Randomized N: 21<br>Analyzed N: 21 (Days 0, 1), 20 (Day 2), 17 (Day 3)<br>Intervention 1 (N=9): Gabapentin 900 mg orally 1-2 hours pre-operatively then daily for 3 days<br>Intervention 2 (N=12): Placebo orally 1-2 hours pre-operatively, then daily for 3 days<br>Duration: Preop and 3 days postop<br>Follow-up (days): 3 | Inclusion: ≥45 years, undergoing surgery involving the spine, requiring general anesthesia, and expected to remain in the hospital for 72 hours<br>Exclusion: Couldn't complete the delirium testing, already taking gabapentin, or sensitive to gabapentin | Mean (SD) age: 59.6 (10.88)<br>Female %: 48<br>Race %:<br>Caucasian: 90<br>Black/African American: NR<br>Asian: NR<br>Other: 10<br>Delirium %: NR<br>ASA I-II %: 52<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: POD occurred in 5/12 patients (42%) who received placebo vs. 0/9 patients who received gabapentin (p=0.045). The reduction in delirium appears to be secondary to the opioid-sparing effect of gabapentin.<br>Attrition: NR | Moderate |
| Leung et al. (2017) | Design: RCT<br>Setting: Postop, orthopedic<br>Country: U.S.<br>Funding: Government | Randomized N: 750<br>Analyzed N: 697<br>Intervention 1 (N=376): Gabapentin 900 mg orally 1-2 hours pre-operatively then daily for 3 days<br>Intervention 2 (N=374): Placebo orally 1-2 hours pre-operatively, then daily for 3 days | Inclusion: >65 years undergoing surgery involving the spine or arthroplasty of hips or knees with an anticipated hospital LOS of at least 3 days<br>Exclusion: Known sensitivity to gabapentin, use of preop gabapentin, | Mean (SD) age: 73 (6)<br>Female %: 50<br>Race %:<br>Caucasian: 92<br>Black/African American: NR<br>Asian: NR<br>Other: 8<br>Delirium %: NR<br>ASA I-II %: 52 | Main outcomes: The overall incidence of POD in any of the first 3 days was 22.4% (24.0% in the gabapentin and 20.8% in the placebo groups; the difference was 3.20%, 95% CI 3.22 to 9.72, p=0.30). The incidence of delirium did not differ between the 2 groups when | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Duration: Preop and 3 days Postop<br>Follow-up (days): 3 | pregabalin, or other anti-epileptics, spinal surgery that involved more than 1 surgical procedure to be performed within the same hospitalization period, emergency surgery, preop renal dialysis, or opioid tolerance | Dementia %: NR<br>Postop %: 99<br>Cancer %: NR | stratified by surgery type, anesthesia type, or preop risk status.<br>Attrition: 6% vs. 8% | |

*Abbreviations.* ASA=American Society of Anesthesiologists; CI=confidence interval; LOS=length of stay; 6MWT=six-minute walk test; N=number; NR=not reported; PCA=patient-controlled analgesia; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; SD=standard deviation; TUG=timed up and go; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

## Pregabalin vs. Placebo

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Farlinger et al. (2018); Clarke et al. (2015) | Design: RCT<br>Setting: Postop, orthopedic<br>Country: Canada<br>Funding: University/Government | Randomized N: 184<br>Analyzed N: 163 (4 days), 162 (6 weeks, 130 (3 months)<br>Intervention 1 (N=84 analyzed): Pregabalin 150 mg orally 2 hours pre-operatively x 1 dose (in addition to celecoxib 400 mg), then 75 mg twice daily<br>Intervention 2 (N=79 analyzed): Placebo 2 hours pre-operatively (in addition to celecoxib 400 mg), then twice daily for 4 days<br>Duration: In hospital and 7 days after discharge<br>Follow-up (days): 1, 7, 42, 90 | Inclusion: Ages 18-75 years, ASA physical status score of I, II, or III undergoing total knee arthroplasty<br>Exclusion: DM with impaired renal function or unable or unwilling to use patient-controlled analgesia devise | Mean (SD) age: 60 (9.15)<br>Female %: 43<br>Race %: NR<br>Delirium %: NR<br>WOMAC physical function (0 to 68): 33.85 (10.98)<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: No effect of pregabalin was found on POD following elective total hip arthroplasty.<br>Overall attrition: 11% | Moderate |

*Abbreviations.* ASA=American Society of Anesthesiologists; CI=confidence interval; LOS=length of stay; 6MWT=six-minute walk test; N=number; NR=not reported; PCA=patient-controlled analgesia; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; SD=standard deviation; TUG=timed up and go; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

### *Cholinesterase Inhibitors*

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Gamberini et al. (2009) | Design: RCT<br>Setting: Postop, cardiac<br>Country: Switzerland<br>Funding: Industry and University | Randomized N: 120<br>Analyzed N: 113<br>Intervention 1 (N=59): Rivastigmine 1.5 mg 3 times daily<br>Intervention 2 (N=61): Placebo 3 times daily<br>Duration: From the evening before surgery to the evening of POD 6<br>Follow-up (days): NR | Inclusion: ≥65 years, elective cardiac surgery with CPB<br>Exclusion: Urgent or emergency surgery, previous cardiac surgery, cardiac surgery combined with noncardiac procedures, sensory impairment interfering with neuropsychological testing, preop MMSE <15, preexisting neurologic deficits, or previous or ongoing treatment with cholinesterase inhibitor | Mean (SD) age: 74.3 (5.6)<br>Female %: 32<br>Race %: NR<br>Delirium %: NR<br>SAPS II: NR overall<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Trial does not support short-term oral rivastigmine to prevent POD in elderly patients undergoing elective cardiac surgery (RR 1.08, 95% CI 0.62 to 1.90).<br>Attrition at follow-up: 24% vs. 25% | Moderate |
| Sampson et al. (2007) | Design: RCT<br>Setting: Postop, hip<br>Country: U.K.<br>Funding: Industry | Randomized N: 50<br>Analyzed N: 33<br>Intervention 1 (N=19 analyzed): Donepezil 5mg<br>Intervention 2 (N=14 analyzed): Placebo<br>Duration: Immediately following surgery and daily for 3 more days<br>Follow-up (days): POD 5 for delirium | Inclusion: All patients undergoing elective total hip replacement<br>Exclusion: MMSE <26, patients with sensory impairment who could not undertake neuropsychological testing | Mean (SD) age: 67.7 (9.6)<br>Female %: 48.5<br>Race %: NR<br>Delirium %: NR<br>Baseline scale of function: NR<br>Dementia %: NR (MMSE <26 excluded)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Donepezil did not significantly reduce the incidence of delirium compared to placebo (unadjusted RR 0.29, 95% CI 0.06 to 1.30).<br>Attrition at follow-up: 34% | Moderate |
| Youn et al. (2017) | Design: RCT<br>Setting: Postop, hip<br>Country: South Korea | Randomized N: 62<br>Analyzed N: 62<br>Intervention 1 (N=31): Rivastigmine patch, 4.6 mg | Inclusion: Older patients undergoing hip fracture surgery, with cognitive impairment (MMSE score 10-26 and GDS score 3-5) | Mean (SD) age: 79.3 (6.1)<br>Female %: 58<br>Race %: NR<br>Delirium %: 0 (excluded)<br>Baseline scale of function: | Main outcomes: POD occurred in 5 patients in the rivastigmine group vs. 14 patients in the control group (p=0.013). The mean | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Funding: None | Intervention 2 (N=31): No rivastigmine patch<br>Duration: From 2 or 3 days before surgery to 7 days after<br>Follow-up (days): POD 7 | Exclusion: Delirium or depression at baseline | NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | severity of delirium in the 2 groups as determined by DRS was 2.2 and 6.2, respectively (p=0.033).<br>Adjusted OR for POD was 0.259 (95% CI 0.074 to 0.905, p=0.034).<br>Attrition: NR | |

*Abbreviations.* CI=confidence interval; CPB=cardiopulmonary bypass; DRS=Delirium Rating Scale; GDS=Global Deterioration Scale; MMSE=Mini-Mental State Examination; N=number; NR=not reported; OR=odds ratio; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; RR=relative risk; SAPS III=Simplified Acute Physiology Score III; SD=standard deviation.

### *Opioid Medications*

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Beaussier et al. (2006) | Design: RCT<br>Setting: Preop, colorectal<br>Country: Switzerland<br>Funding: Mixed | Randomized N: 59<br>Analyzed N:52<br>Intervention (N=29): Intrathecal morphine 300 µg<br>Control (N=30): Subcutaneous saline<br>Duration: Preop<br>Follow-up (days): NR | Inclusion: >70 years undergoing major colorectal surgery for colon cancer<br>Exclusion: ASA physical status III and IV, BMI >30 kg/m$^2$, inflammatory bowel disease, contraindications to intrathecal morphine administration, preop mental dysfunction, chronic pain, preop opioid consumption, psychiatric disorders, and inability to use the PCA device | Mean (SD) age: 77.5 (5.00)<br>Female %: 48<br>Race %: NR<br>Delirium %: 0<br>ASA I and II %: 100<br>Preop mental dysfunction %: 0<br>Postop %: 100 colorectal surgery<br>Cancer %: 100 | Main outcomes: Episodes of POD occurred similarly in the morphine and control groups (35% vs. 38%, p>0.05).<br>Attrition: 10% vs. 13% | Low |
| Liu et al. (2017) | Design: RCT<br>Setting: Postop, mixed<br>Country: China | Randomized N: 105<br>Analyzed N: 105<br>Intervention 1 (N=35): Fentanyl 1 µg/kg/hour and midazolam | Inclusion: Age 18-85 years, admitted to the surgical ICU, required MV for an anticipated time >24 hours, and required | Mean (SD) age: 64.2 (10.7)<br>Female %: 47.6<br>Race %: NR<br>Delirium %: 0 (excluded) | Main outcomes: Remifentanil has a significant effect on reducing the | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Funding: Government | loading dose of 0.05 mg/kg followed by 0.02-0.1 mg/kg/hour<br>Intervention 2 (N=35): Remifentanil 1 µg/kg/hour and midazolam loading dose of 0.05 mg/kg followed by 0.02-0.1 mg/kg/hour<br>Intervention 3 (N=35): Normal saline and midazolam loading dose of 0.05 mg/kg followed by 0.02-0.1 mg/kg/hour<br>Duration: During ventilation<br>Follow-up (days): Until discharge, 28 | midazolam sedation<br>Exclusion: Intracranial lesions, neurosurgical intervention, mental disabilities or coma, alcohol abuse, or history of delirium or antipsychotic use at home | Mean (SD) APACHE II: 20.2 (5.4)<br>Dementia %: NR, mental disabilities excluded<br>Postop %: 100<br>Cancer %: NR | occurrence of delirium (p=0.007). The logistic regression analysis of delirium demonstrated that remifentanil (OR 0.230, 95% Cl 0.074 to 0.711, p=0.011) is independent protective factors for delirium, and high APACHE II score (OR 1.103, 95% Cl 1.007 to 1.208, p=0.036) is the independent risk factor for delirium.<br>Overall attrition: 0% | |
| Mann et al. (2000) | Design: RCT<br>Setting: Intra-operative, abdominal<br>Country: France<br>Funding: Unclear | Randomized N: 70<br>Analyzed N: 70<br>Intervention 1 (N=35): Sufentanil 1 µg/ml plus bupivacaine 0.25% mixture epidural anesthesia continuous infusion intra-operatively followed by sufentanil 0.5 µg/ml plus bupivacaine mixture by PCA epidural pump during postop<br>Intervention 2 (N=35): Sufentanil IV 0.5 µg/kg bolus followed by 0.2-0.4 µg/kg intra-operatively as necessary | Inclusion: >70 years undergoing major abdominal surgery for cancer with ASA status I or II and normal preop mental status; absence of contraindications to epidural anesthesia and absence of extreme malnutrition or cerebral vascular insufficiency<br>Exclusion: NR | Mean (SD) age: 76.45 (5.17)<br>Female %: 46<br>Race %: NR<br>Delirium %: 0<br>ASA I, II %: 100<br>Dementia %: 0<br>Postop %: 100 abdominal surgery<br>Cancer %: 100 | Main outcomes: There was no difference in POD between treatment groups (26% vs. 24%, p>0.05).<br>Attrition: 11% vs. 6% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | followed by PCA with morphine 1.5 mg per dose during postop<br>Duration: Intra-operatively, postop<br>Follow-up (days): Until discharge | | | | |
| Park et al. (2014) | Design: RCT<br>Setting: Postop, cardiac<br>Country: South Korea<br>Funding: None | Randomized N: 142<br>Analyzed N: 142<br>Intervention 1 (N=67): Dexmedetomidine loading dose, 0.5 µg/kg; maintenance dose, 0.2-0.8 µg/kg/hour<br>Intervention 2 (N=75): Remifentanil range, 1,000-2,500 µg/hour<br>Duration: Daily<br>Follow-up (days): 3 | Inclusion: Age 18-90 years undergoing cardiac surgery on CPB<br>Exclusion: Re-do and emergency surgery, severe pulmonary, or systemic disease, left ventricular ejection fraction <40%, pre-existing renal dysfunction, surgery requiring deep hypothermic circulatory arrest involving thoracic aorta, and documented preop dementia, Parkinson disease, or recent stroke | Mean (SD) age: 52.8 (15)<br>Female %: 44<br>Race %: NR<br>Delirium %: NR<br>ASA III-IV %: 17<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR<br>Mean (SD) length of operation, minutes: 344.7 (107) | Main outcomes: Delirium incidence was significantly less in dexmedetomidine group (6/67 patients, 8.96%) vs. remifentanil group (17/75 patients, 22.67%) (p<0.05).<br>Attrition: NR | Moderate |
| Shehabi et al. (2009) | Design: RCT<br>Setting: Postop, cardiac<br>Country: Australia<br>Funding: Mixed | Randomized N: 306<br>Analyzed N: 299<br>Intervention 1 (N=154): Dexmedetomidine IV 0.1-0.7 µg/kg/hour<br>Intervention 2 (N=152): Morphine IV 10-70 µg/kg/hour<br>Duration: Postop<br>Follow-up (days): Discharge | Inclusion: ≥60 years undergoing pump cardiac surgery (e.g., CABG, valve surgery)<br>Exclusion: Documented preop dementia and Parkinson disease | Median age: 71.3<br>Female %: 25<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: 0<br>Postop %: 100<br>Cancer %: 0 | Main outcomes: Delirium incidence was comparable between dexmedetomidine and morphine (8.6% vs. 15.0%, p=0.088).<br>Attrition: 1% vs. 3% | Low |
| Tang C. et al. (2020) | Design: RCT<br>Setting: Postop, esophageal cancer<br>Country: China | Randomized N: 60<br>Analyzed N: 53<br>Intervention 1 (N=30): Dexmedetomidine 2.5 µg/mL plus sufentanil 1 µg/mL PCA | Inclusion: Age 18-80 years with ASA status I-III and undergoing thoracoscopic-laparoscopic esophagectomy<br>Exclusion: Obstructive or restrictive lung disease with | Mean (SD) age: 61.5 (7.7)<br>Female %: 47.2<br>Race %: NR<br>Delirium %: NR<br>ASA I %: 32.1<br>ASA II %: 62.3 | Main outcomes: The simultaneous administration of dexmedetomidine and sufentanil significantly reduced plasma | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Funding: Government | Intervention 2 (N=30): Sufentanil 1 µg/mL PCA<br>Duration: During post anesthesia care unit stay<br>Follow-up (days): 1, 2 | FEV1/FVC% < 70% and 50% predict FEV1 < 80% predict, asthma and sleep apnea syndrome, liver or urinary bladder disorders, regular use of pain perception-modifying drugs and opioids or sedative medications in the week prior to surgery, known history of second- or third-degree heart block and ischemic heart diseases, difficulties with the use of PCA, known cognitive dysfunction/dementia, and BMI >35 kg/$m^2$ | ASA III %: 5.7<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: 100 | interleukin-6 and tumor necrosis factor-α concentrations and increased interleukin-10 level (p<0.0001, p=0.0003, and p=0.0345, respectively), accompanied by better POD categories and health statuses of patients (p=0.024 and p<0.05, respectively). There was no hypotension, bradycardia, respiratory depression, or over sedation in the dexmedetomidine group.<br>Attrition: 10% vs. 13% | |
| Wang et al. (2019) | Design: RCT<br>Setting: Postop, noncardiac<br>Country: China<br>Funding: Government, university | Randomized N: 142<br>Analyzed N: 140<br>Intervention 1 (N=71): PCA pump with 0.5 µg/ ml sufentanil + 1 mg/ml flurbiprofen axetil (150 µg sufentanil + 300 mg flurbiprofen axetil in 300 ml of 0.9% saline); continuous infusion dose of 4 ml/hour plus bolus dose of 3 ml if needed | Inclusion: >65 years, ASA I to III, undergoing major noncardiac surgeries (thoracic, general, genitourinary, gynecologic, and orthopedic)<br>Exclusion: Regular use of opioids or NSAIDs, severe visual and hearing disorders, history of myasthenia gravis, coma or profound dementia, brain injury or | Mean (SD) age: 69.4 (4.4)<br>Female %: Unclear (n and % for control group inconsistent)<br>Race %: NR<br>Delirium %: NR<br>ASA I, II %: 95<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Incidence of POD was not significantly different between groups (12.9% with flurbiprofen vs. 18.6% without).<br>Attrition at follow-up: 1% vs. 1% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Intervention 2 (N=71): PCA pump with 0.5 µg/ml sufentanil (150 µg sufentanil in 300 ml of 0.9% saline); continuous infusion dose of 4 ml/hour plus bolus dose of 3 ml if needed<br>Duration: PCA pump used for ≤72 hours after surgery, until solution ran out, and was not refilled<br>Follow-up (days): POD 7 | history of neurosurgery, serious hepatic or renal dysfunction, and preop MMSE below thresholds varying by education level | | | |
| Zhao et al. (2020) | Design: RCT<br>Setting: Intra-operative, noncardiac<br>Country: China<br>Funding: Government | Randomized N: 432<br>Analyzed N: 416<br>Intervention 1 (N=111): Dexmedetomidine 1 µ/kg then dexmedetomidine 100 µg plus sufentanil 150 µg in PCA pump<br>Intervention 2 (N=107): Dexmedetomidine 1 µ/kg then dexmedetomidine 200 µg plus sufentanil 150 µg in PCA pump<br>Intervention 3 (N=108): Dexmedetomidine 1 µ/kg then dexmedetomidine 400 µg plus sufentanil 150 µg in PCA pump<br>Intervention 4 (N=106): Sufentanil 150 µg in PCA pump<br>Intervention 1, Intervention 2, Intervention 3 duration: 10 minutes before anesthesia induction, then post-operatively<br>Intervention 4 duration: Postop | Inclusion: >65 years scheduled to undergo non-cardiac major surgery with ASA I-III<br>Exclusion: Regular use of opioids, sedatives, antidepressants, or anxiolytic drugs prior to the surgery; drug addiction; preop history of schizophrenia, epilepsy, Parkinsonism, or myasthenia gravis; brain injury or a history of neurosurgery; serious hepatic dysfunction (Child-Pugh class C); serious renal dysfunction (undergoing dialysis before surgery); a preop left ventricular ejection fraction <50%; sick sinus syndrome, severe sinus bradycardia (<50/minute), or a ≥second-degree atrioventricular block without a pacemaker; and a preop MMSE scores <17 in | Mean (SD) age: 69.5 (4.2)<br>Female %: 44<br>Race %: NR<br>Delirium %: NR<br>ASA II %: 97<br>Median (IQR) MMSE score: 27 (24-30)<br>Postop %: 100<br>-Thoracic: 15.9<br>-Abdominal: 83.9<br>-Orthopedic: 0.2<br>Cancer %: NR | Main outcomes: Incidence rates of POD and early postop cognitive dysfunction 7 days after surgery were lower in the dexmedetomidine 200 mg and 400 mg groups than in the dexmedetomidine 0 mg and 100 mg groups ($p<0.05$). Compared with dexmedetomidine 200 mg, dexmedetomidine 400 mg reduced early postop cognitive dysfunction in patients who underwent open surgery ($p<0.05$).<br>There were no | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | Follow-up (days): 1, 2, 3, 7 | uneducated patients, <20 for patients with education of ≤6 years, and <24 for patients with education of >6 years | | intergroup differences in the postop sedation level, pain intensity, and side effects.<br>Attrition: 3% vs. 1% vs. 6% vs. 4% | |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; ASA=American Society of Anesthesiologists; BMI=body mass index; CABG=coronary artery bypass graf; CI=confidence interval; CPB=cardiopulmonary bypass; ICU=intensive care unit; IQR=interquartile range; IV=intravenous; MMSE=Mini-Mental State Examination; MV=medical ventilation; N=number; NR=not reported; NSAIDs=nonsteroidal anti-inflammatory drugs; OR=odds ratio; PCA=patient-controlled analgesia; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; SD=standard deviation.

### *Steroid Medications*

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Clemmesen et al. (2018) | Design: RCT<br>Setting: Preop, orthopedic<br>Country: Denmark<br>Funding: None | Randomized N: 120<br>Analyzed N: 117<br>Intervention 1 (N=60): Methylprednisolone IV 125 mg<br>Intervention 2 (N=60): Placebo<br>Duration: Single preop dose on admission<br>Follow-up (days): 90 | Inclusion: ≥65 years and admitted for acute hip fracture<br>Exclusion: Severe dementia, peptic ulcer disease, cancer, glaucoma, insulin-dependent diabetes, positive for HIV, HBV, or HCV, immunoinflammatory disease, or currently receiving systemic glucocorticoids or immunosuppressive therapy | Mean (SD) age: 80 (9)<br>Female %: 64<br>Race %: NR<br>Delirium %: NR<br>ASA physical status ≥3 (severe systemic disease) %: 37<br>Dementia %: NR (severe dementia excluded)<br>Postop %: 100<br>Cancer %: 0 (excluded) | Main outcomes: POD (single-day CAM-S ≥5) between the placebo and drug groups was: OR 2.39, 95% CI 1.00 to 5.72, p=0.048.<br>Attrition: 2% vs. 3% | Low |
| Dieleman et al. (2012 ); Sauer et al. (2014); DECS | Design: RCT<br>Setting: Postop, cardiac<br>Country: The Netherlands<br>Funding: | Randomized N: 4,494<br>Analyzed N: 4,482<br>Intervention 1 (N=2,239): Dexamethasone IV 1 mg/kg; maximum 100 mg<br>Intervention 2 (N=2,255): Placebo; normal saline IV | Inclusion: ≥18 years undergoing cardiac surgery requiring CPB<br>Exclusion: Emergency or off-pump procedure or life expectancy <6 months | Mean (SD) age: 66.1 (10.9)<br>Female %: 27<br>Race %: NR<br>Delirium %: NR<br>Baseline scale of function: NR<br>Dementia %: NR | Main outcomes: Incidence of POD (need for neuroleptics) was RR 0.79 (95% CI 0.66 to 0.94).<br>Attrition: 4/2,239 vs. 8/2,255 | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | Government and nonprofit | Duration: Single dose at induction of anesthesia<br>Follow-up (days): 30 | | Postop %: 100<br>Cancer %: NR | | |
| Kluger et al. (2021); STRIDE | Design: RCT<br>Setting: Preop, orthopedic<br>Country: New Zealand<br>Funding: Government | Randomized N: 79<br>Analyzed N: 78<br>Intervention 1 (N=40): Dexamethasone IV 20 mg<br>Intervention 2 (N=39): Placebo<br>Duration: 1 dose at induction of anesthesia and one dose before bypass<br>Follow-up (days): POD 3 | Inclusion: >65 years undergoing surgery for hip fracture<br>Exclusion: Uncontrolled diabetes, cognitive impairment, or delirium | Mean (SD) age: 81 (8.05)<br>Female %: 23<br>Race %: NR<br>Delirium %: 0 (excluded)<br>ASA I-III %: 91<br>Dementia %: 0 (excluded)<br>Postop %: 100 hip fracture surgery<br>Cancer %: NR | Main outcomes: Delirium incidence did not differ between the groups: 6/40 (15%) in the dexamethasone group vs. 9/39 (23%) in the placebo group (RR 0.65, 95% CI 0.22 to 1.65, p=0.360).<br>Attrition: 0% vs. 3% | Low |
| Mardani and Bigdelian (2012) | Design: RCT<br>Setting: Postop, cardiac<br>Country: Iran<br>Funding: None | Randomized N: 110<br>Analyzed N: 93<br>Intervention 1 (N=55): Dexamethasone IV 8 mg<br>Intervention 2 (N=55): Placebo<br>Duration: Given before induction of anesthesia and every 8 hours for 3 days<br>Follow-up (days): NR (POD 3 for delirium) | Inclusion: ≤80 years undergoing cardiac surgery<br>Exclusion: Prolonged intubation, CPB of >3 hours, ejection fraction <20%, hemodynamic instability, history of delirium, and emergency operation | Mean (SD) age: 62.13 (12.03)<br>Female %: 14<br>Race %: NR<br>Delirium %: 0 (excluded)<br>Baseline scale of function: NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes:<br>No statistically significant difference was found between dexamethasone and placebo in the number of patients with delirium on POD 3 (2.3% vs. 2%, p=1.0).<br>Attrition: 22% vs. 9% | High |
| Royse et al. (2017); SIRS sub-study (companion to Whitlock (2015 which was excluded | Design: RCT<br>Setting: Postop, cardiac<br>Country: Australia, Canada, U.S.<br>Funding: Government | Randomized N: 555<br>Analyzed N: 498<br>Intervention 1 (N=277): Methylprednisolone, 2 x 250 mg doses during surgery<br>Intervention 2 (N=278): Placebo<br>Duration: 1 dose at induction of anesthesia and 1 dose before bypass | Inclusion: >18 years and EuroScOrE ≥ 6<br>Exclusion: Known cognitive impairment, taking or expected to receive systemic steroids in the immediate postop period, expected to receive aprotinin, or history of bacterial or fungal infection in the preceding 30 days | Mean (SD) age: 73.9 (9.9)<br>Female %: 48.5<br>Race %: NR<br>Delirium %: NR<br>Baseline scale of function: NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Incidence of delirium was 8% in the methylprednisolone group vs. 10% in the control group (p=0.357).<br>Attrition: 10% vs. 11% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| from the review) | | Follow-up (days): POD 3 for delirium | | | | |
| Sauer et al. (2014 ); Dieleman et al. (2012); DECS sub-study | Design: RCT<br>Setting: Postop, cardiac<br>Country: The Netherlands<br>Funding: Government and nonprofit | Randomized N: 768<br>Analyzed N: 737<br>Intervention 1 (N=367 analyzed): Dexamethasone IV 1 mg/kg; maximum 100 mg<br>Intervention 2 (N=370 analyzed): Placebo; normal saline IV<br>Duration: Single dose at induction of anesthesia<br>Follow-up (days): POD 4 | Inclusion: ≥18 years undergoing cardiac surgery requiring CPB<br>Exclusion: Emergency or off-pump procedure or life expectancy <6 months | Mean (SD) age: 66 (12)<br>Female %: 35<br>Race %: NR<br>Delirium %: NR<br>Baseline scale of function: NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Incidence of delirium was similar between groups (adjusted OR 0.85, 95% CI 0.55 to 1.31).<br>Attrition: 13% vs. 12% | Moderate |

*Abbreviations.* ASA=American Society of Anesthesiologists; CAM-S=Confusion Assessment Method-Severity; CI=confidence interval; CPB=cardiopulmonary bypass; EuroScOrE=European System for cardiac risk Evaluation; IV=intravenous; N=number; NR=not reported; OR=odds ratio; POD=post-operative delirium; postop=post-operative; RCT=randomized controlled trial; RR=relative risk; SD=standard deviation.

## *Additional Medications*

### Clonidine

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Rubino et al. (2010) | Design: RCT<br>Setting: Postop, cardiothoracic<br>Country: Italy<br>Funding: Unclear | Randomized N: 30<br>Analyzed N: 30<br>Intervention 1 (N=15): Clonidine 0.5 µg/kg bolus followed by 1-2 µg/kg/hour<br>Intervention 2 (N=15): Placebo; normal saline<br>Duration: Postop<br>Follow-up (days): Discharge | Inclusion: Conscious and hemodynamically stable requiring repair of an acute type-A aortic dissection<br>Exclusion: NR | Mean (SD) age: 62.6 (7.71)<br>Female %: 40<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: 0 | Main outcomes: There was no difference in incident delirium between treatment with clonidine vs. placebo for POD (40% vs. 33.3%, p>0.05).<br>Attrition: NR | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Shokri and Ali (2020) | Design: RCT<br>Setting: Intra- and post-operative, cardiac<br>Country: Egypt<br>Funding: None | Randomized N: 294<br>Analyzed N: 286<br>Intervention 1 (N=147): Dexmedetomidine; initial continuous infusion of 0.7-1.2 µg/kg/hour, then adjusted based on sedation and analgesia adequacy to a maximum dose of 1-1.4 µg/kg/hour<br>Intervention 2 (N=147): Clonidine IV 0.5 µg/kg slowly over 10-15 minutes, followed by a continuous IV infusion of 1-2 µg/kg/hour<br>Intervention 1 duration: During surgery, then weaned off slowly after surgery<br>Intervention 2 duration: During surgery<br>Follow-up (days): 8 | Inclusion: Age 60-70 years with ASA status II and III, scheduled for elective isolated CABG, and absence of any associated comorbidities or history of MI<br>Exclusion: History of mental illness, severe dementia, delirium, or undergoing emergency procedures, or treated with haloperidol impaired renal or hepatic functions. | Mean (SD) age: 64.1 (4.1)<br>Female %: 51.4<br>Race %: NR<br>Delirium %: NR, severe delirium excluded<br>ASA II %: 62.6<br>ASA III %: 37.4<br>Dementia %: NR, severe dementia excluded<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Dexmedetomidine was associated with lower risk and duration of delirium, shorter MV duration and ICU stay, lower mortality rate, and lower morphine consumption than the clonidine group. Dexmedetomidine significantly decreased heart rates after ICU admission.<br>Attrition at follow-up: 2% vs. 3% | Low |
| Sultan (2010) | Design: RCT<br>Setting: Preop, hip<br>Country: Egypt<br>Funding: None | Randomized N: 222<br>Analyzed N: 203<br>Intervention 1 (N=53 analyzed): Melatonin 5 mg, 2 oral doses<br>Intervention 2 (N=50 analyzed): Midazolam 7.5 mg, 2 oral doses<br>Intervention 3 (N=51 analyzed): Clonidine 100 µg, 2 oral doses<br>Intervention 4 (N=49 analyzed): No sedation | Inclusion: >65 years, scheduled for hip arthroplasty under spinal anesthesia, and ASA I to III<br>Exclusion: Sensory impairment (blindness, deafness); dementia; severe infections; severe anemia (hematocrit<30%); intracranial events (stroke, bleeding, infection); fluid or electrolyte | Mean (SD) age: 71.01 (36.8)<br>Female %: 51<br>Race %: NR<br>Delirium %: 0 (excluded)<br>ASA I-III: inclusion criterion<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: NR | Main outcomes: The melatonin group showed a statistically significant decrease in the percentage of POD (9.43% vs. 32.65% in controls).<br>Overall attrition: 9% | High |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Duration: One dose the night before surgery and another 90 minutes before surgery<br>Follow-up (days): POD 3 | disturbances; acute cardiac events; acute pulmonary events; and medications including anticonvulsants, antihistamines, and benzodiazepines | | | |

4590 *Abbreviations.* ASA=American Society of Anesthesiologists; CABG=coronary artery bypass graf; ICU=intensive care unit; IV=intravenous; MI=myocardial infarction; MV=medical ventilation; N=number;
4591 NR=not reported; POD=post-operative delirium; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

4592 ## Other Medications

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Bielza et al. (2020) | Design: RCT<br>Setting: Intra-operative, hip<br>Country: Spain<br>Funding: Non-profit | Randomized N: 253<br>Analyzed N: 253<br>Intervention (N=126): Iron IV 200 mg in 100 mL saline<br>Control (N=127): Normal saline<br>Duration: On days 1, 3, and 5 of hospital stay<br>Follow-up (days): Discharge | Inclusion: ≥70 years undergoing hip fracture surgery admitted to the orthogeriatric care share service<br>Exclusion: Asthma or severe atopic disease, hemochromatosis, inability to walk prior to the fracture, dependency for all basic daily living activities, severe dementia, or known terminal illness (life expectancy of <6 months) | Median age: 87<br>Female %: 72.7<br>Race %: NR<br>Delirium %: 6.3<br>Median (IQR) Charlson comorbidity index: 2 (1-3)<br>Dementia %: 26.9<br>Postop %: 100<br>Cancer %: NR | Main outcomes: IV iron did not show significant effects in any of the secondary end points: mortality, functional recovery at 3 months, postop transfusion requirements, hemoglobin levels at 3 months, and proportion of nosocomial infections or incidence of POD.<br>Attrition: 21% vs. 22% | Low |
| Deng et al. (2020) | Design: RCT<br>Setting: Intra-operative, noncardiac<br>Country: China | Randomized N: 248<br>Analyzed N: 248<br>Intervention 1 (N=124): Methylene blue IV continuous infusion of 2 | Inclusion: Age 60-80 years undergoing noncardiac and non-neurosurgical major surgery<br>Exclusion: Preexisting | Median age: 67 vs. 68.5<br>Female %: 40.3<br>Race %: NR<br>Delirium %: NR<br>ASA I %: 13.7 | Main outcomes: The incidence of POD in methylene blue group was significantly less than that in control group (7.3% vs. 24.2%, OR 0.24, 95% | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | Funding: Government | mg/kg diluted with normal saline into total 50 mL<br>Control (N=124): Normal saline<br>Duration: Immediately after anesthetic induction<br>Follow-up (days): Discharge 90 | dementia, major depression, or other serious mental or neurological disorders; history of major head trauma; emergency surgery; serious medical diseases; planned postop intubation | ASA II %: 83.9<br>ASA III %: 2.4<br>Dementia %: 0 (excluded)<br>Postop %: 100<br>Cancer %: 72.2 | CI 0.11 to 0.53, p<0.001). The incidence of early POCD at postop 7th day in methylene blue group was also less than that in control group (16.1% vs. 40.2%, OR 0.30, 95% CI 0.16 to 0.57, p<0.001). The adverse events were comparable in both groups.<br>Attrition at follow-up: 2% vs. 4% | |
| Kim et al. (1996) | Design: RCT<br>Setting: Postop, cardiac<br>Country: U.S.<br>Funding: Industry and nonprofit | Randomized N: 127<br>Analyzed N: 111<br>Intervention 1 (N=53 analyzed): Cimetidine IV 900 mg/day adjusted according to creatinine clearance<br>Intervention 2 (N=58 analyzed): Ranitidine IV 150 mg/day adjusted according to creatinine clearance<br>Duration: Postop until ICU discharge<br>Follow-up (days): NR | Inclusion: cardiac surgery patients<br>Exclusion: Taking an H-2 antagonist pre-operatively, taking a drug that adversely interacts with cimetidine (warfarin, lidocaine, phenytoin, and theophylline) | Mean (SD) age: 65.9 (10.7)<br>Female %: 28<br>Race %: NR<br>Delirium %: NR<br>Baseline scale of function: NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: The incidence of delirium did not differ according to whether patients received cimetidine or ranitidine (adjusted OR 0.72, 95% CI 0.29 to 1.80).<br>Overall attrition: 13% | Moderate |
| Li Y.N. et al. (2017) | Design: RCT<br>Setting: Intra-operative, spine<br>Country: China<br>Funding: Government | Randomized N: 60<br>Analyzed N: 30<br>Intervention (N=NR): Nimodipine, calcium channel blocker 7.5mg/kg/ hour injected continually 30 minutes before anesthesia induction | Inclusion: Spine surgery patients<br>Exclusion: Traumatic brain injury, neurological diseases and alcohol abuse, or no severe hearing and visual impairment | Mean (SD) age: 69.5 (4)<br>Female %: 54<br>Race %: NR<br>Delirium %: 0<br>MMSE %: 0<br>Dementia %: 0<br>Postop %:100<br>Cancer %: NR | Main outcomes: Compared with the control group, S100β and glial fibrillary acidic protein decreased, and incidence of POD reduced at T3-T4 (from 1 hour after skin incision to the time the surgery was completed) in the | High |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | | Control (N=NR): Saline 7.5mg/kg/hour injected continually 30 minutes before anesthesia induction<br>Duration: Preop<br>Follow-up (days): 1 to 7 | | Hepatic or renal impairment %: 0<br>Alcohol abuse %: 0<br>Drug use %: 0<br>Medications taken at baseline: NR | nimodipine group; the difference was statistically significant (p<0.05).<br>Attrition: NR; 7 patients were lost because of non-cooperation and 4 patients by not receiving operation. | |
| Mohammadi et al. (2016) | Design: RCT<br>Setting: Postop, noncardiac<br>Country: Iran<br>Funding: University | Randomized N: 45<br>Analyzed N: 40<br>Intervention 1 (N=23): Cyproheptadine 4 mg 3 times per day<br>Intervention 2 (N=22): Placebo<br>Duration: Duration 7 days<br>Follow-up (days): 7 | Inclusion: Age 16-65 years admitted to the ICU after noncardiac surgery<br>Exclusion: History of seizure, Alzheimer's disease, schizophrenia, asthma, cardiac arrhythmia, urinary retention, or active GI bleeding or obstruction | Mean (SD) age: 59.7 (15.6)<br>Female %: 35<br>Race %: NR<br>Delirium %: NR<br>APACHE II: 15.1 (6.2)<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Cyproheptadine co-treatment compared with placebo significantly decreased the incidence of delirium (adjusted OR 0.14, 95% CI 0.09 to 0.86).<br>Attrition: 13% vs. 9% | Moderate |
| Moslemi et al. (2020) | Design: RCT<br>Setting: Intra-operative, GI surgery<br>Country: Iran<br>Funding: None | Randomized N: 102<br>Analyzed N: 96<br>Intervention 1 (N=51): Thiamine IV 200 mg<br>Intervention 2 (N=51): Saline IV<br>Duration: 3 days in ICU<br>Follow-up (days): 3 | Inclusion: ≥18 years admitted to the ICU after GI surgery<br>Exclusion: History of any neuropsychiatric disorder, severe renal or liver impairment, substance or alcohol abuse, diabetic ketoacidosis, or delirious patients at time of ICU admission | Mean (SD) age: 54 (12.1)<br>Female %: 58.8<br>Race %: NR<br>Delirium %: NR<br>Function: NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: The incidence rate of delirium was significantly lower in the thiamine group vs. placebo group on the first day (8.3% vs. 25%, OR 0.27, 95% CI 0.08 to 0.92, p=0.026) and on the second day (4.2% vs. 20.8%, OR 0.16, 95% CI 0.03 to 0.81, p=0.014).<br>Attrition: 6% vs. 6% | Moderate |
| Nakamura et al. (2021) | Design: RCT<br>Setting: Postop, cancer<br>Country: U.S. | Randomized N: 64<br>Analyzed N: 61<br>Intervention 1 (N=30): Thiamine IV 200 mg | Inclusion: >18 years, allogenic hematopoietic stem cell transplantation<br>Exclusion: Delirium | Mean (SD) age: 54.7 (13.6)<br>Female %: 39<br>Race %:<br>White: 85<br>Black 15 | Main outcomes: Delirium incidence (25% vs. 21%, Chi-square [df=1] 0.12, p=0.73), time to onset, duration, and | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
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| | Funding: Non-profit | Intervention 2 (N=34): Placebo (saline)<br>Duration: Three times daily for 7 days<br>Follow-up (days): 30 days or discharge | | Delirium %: 0 (excluded)<br>ECOG-PS: 0-1 98%<br>Dementia %: NR<br>Postop %:100<br>Cancer %: 100 | severity were not different between the study arms.<br>Attrition at follow-up: 13% vs. 3% | |
| Papadopoulos et al. (2014) | Design: RCT<br>Setting: Postop, orthopedic<br>Country: Greece<br>Funding: NR | Randomized N: 106<br>Analyzed N: 106<br>Intervention 1 (N=51): Ondansetron 8 mg IV<br>Intervention 2 (N=55): Placebo<br>Duration: Daily starting postop for 5 days<br>Follow-up (days): 30 | Inclusion: >40 years and femoral or hip fracture surgery<br>Exclusion: Prior neuropsychiatric testing, dementia (Alzheime''s), multiple injuries, or second surgery within 30 days | Mean (SD) age: 71<br>Female %: 56<br>Race %: NR<br>Delirium %: NR<br>ASA III %: 25<br>Dementia %: 0 (excluded)<br>Postop %: NR<br>Cancer %: NR | Main outcomes: Delirium % was 36% (18/51) vs. 53% (29/55) (p=0.07) on POD 2 (days 3 to 5: p=0.003, p<0.001, and p<0.001, respectively; day 5=0 in both groups).<br>Attrition: NR | Moderate |
| Robinson et al. (2014) | Design: RCT<br>Setting: Postop, mixed<br>Country: U.S.<br>Funding: Mixed | Randomized N: 301<br>Analyzed N: 301<br>Intervention 1 (N=152): L-Tryptophan 1 gm<br>Intervention 2 (N=149): Placebo<br>Duration: Three times daily, 9 doses<br>Follow-up (days): ICU discharge | Inclusion: >60 years undergoing elective surgery with planned postop ICU admission (general, vascular, urological, or thoracic surgery)<br>Exclusion: Drugs that increase serotonin | Mean (SD) age: 69<br>Female %: 2<br>Race %: NR<br>Delirium %: NR<br>TUG: 12 seconds<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Delirium occurred in 40% and 37% of patients with tryptophan and placebo, respectively (p=0.60). Duration of delirium was 2.9 to 1.8 days for tryptophan and 2.4 to 1.6 days for placebo (p=0.17).<br>Overall attrition: 0% | Low |
| Saager et al. (2015) | Design: RCT<br>Setting: Postop, cardiac<br>Country: U.S.<br>Funding: Government | Randomized N: 203<br>Analyzed N: 198<br>Intervention (N=95): Hyperinsulinemic-normoglycemic clamp; a constant infusion of insulin (5 mU/kg/minute) was | Inclusion: ≥18 years undergoing cardiac surgery with CPB<br>Exclusion: NR | Mean (SD) age: 65.5 (13.5)<br>Female %: 27.3<br>Race %: NR<br>Delirium %: NR<br>ASA IV-V %: 81<br>Dementia %: NR<br>Postop %: 100 | Main outcomes: Patients randomized to tight glucose control were more likely to be diagnosed as being delirious than those assigned to routine glucose control (26/93 vs. | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | given with a concomitant variable infusion of 20% dextrose titrated to target blood glucose concentrations 80-110 mg/dl<br>Control (N=108): Usual care<br>Duration: During surgery<br>Follow-up (days): Until discharge or POD 5 | | Cancer %: NR<br>Diabetes %: 31.8 | 15/105, RR 1.89, 95% CI 1.06 to 3.37, p=0.03).<br>Attrition: 2% vs. 3% | |
| Spies et al. (2021) | Design: RCT<br>Setting: Intra-operative, liver<br>Country: Germany<br>Funding: Industry | Randomized N: 281<br>Analyzed N: 261<br>Intervention 1 (N=139): Physostigmine 0.02 mg/kg IV bolus, then 0.01 mg/kg infusion<br>Intervention 2 (N=142): Placebo<br>Duration: 24 hours after start of anesthesia<br>Follow-up (days): 7 | Inclusion: >18 years undergoing liver resection surgery<br>Exclusion: Parkinso''s disease | Mean (SD) age: 61<br>Female %: 58<br>Race %: NR<br>Delirium %: 0<br>ASA II-III %: 92<br>Median MMSE: 29 (29 to 30)<br>Postop %: 100<br>Cancer %: 83 | Main outcomes: The incidence of POD did not differ significantly between the physostigmine and placebo groups (20% vs. 15, p=0.334). Lower mortality rates were found in the physostigmine group compared with placebo at 3 months (2% [95% CI 0 to 4] vs. 11% [95% CI 6 to 16], p=0.002) and at 6 months (7% [95% CI 3 to 12] vs. 16% [95% CI 10 to 23], p=0.012) after surgery.<br>Attrition: 2% vs. 8% | Low |
| Xin et al. (2017) | Design: RCT<br>Setting: Postop, orthopedic<br>Country: China<br>Funding: Government | Randomized N: 120<br>Analyzed N: 120<br>Intervention (N=60): 7.5% hypertonic saline; right before anesthesia<br>Control (N=60): Normal | Inclusion: >65 years who underwent hip arthroplasty for femoral neck fracture surgery<br>Exclusion: Those with dementia or MMSE <24, preop delirium, history of neurologic | Mean (SD) age: 76.1 (5.7)<br>Female %: 48.3<br>Race %: NR<br>Delirium %: 0 (excluded)<br>ASA score of 2 %: 60.8<br>Dementia %: 0 (excluded)<br>Mean (SD) MMSE: 25.6 (1.3) | Main outcomes: Hypertonic saline had a lower risk of POD vs. normal saline (OR 0.13, 95% CI 0.04 to 0.41, p=0.001).<br>Attrition: NR | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | saline; right before anesthesia<br>Intervention mean (SD) duration of anesthesia: 98.5 (12.3) minutes<br>Control mean (SD) duration of anesthesia: 102.2 (13.3) minutes<br>Follow-up (days): 3 | or mental illness, current use of tranquilizers or antidepressants, history of an endocrine or metabolic disorder, recent use of glucocorticoids or other hormones, suffering from infections or chronic inflammatory conditions, or intake of anti-inflammatory drugs | Postop %: 100<br>Cancer %: NR<br>Mean (SD) duration of anesthesia, minutes: 100.3 (12.8) | | |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; ASA=American Society of Anesthesiologists; CI=confidence interval; CPB=cardiopulmonary bypass; df=degree of freedom; ECOG-PS= Eastern Cooperative Oncology Group Performance Status; GI=gastrointestinal; ICU=intensive care unit; IQR=interquartile range; IV=intravenous; MMSE=Mini-Mental State Examination; N=number; NR=not reported; OR=odds ratio; POCD=post-operative cognitive dysfunction; POD=post-operative delirium; postop=post-operative; preop=pre-operative; RCT=randomized controlled trial; RR=relative risk; SD=standard deviation; TUG=timed up and go.

## Additional Pharmacological Interventions for Treatment of Delirium

### *Cholinesterase Inhibitors*

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Overshott et al. (2010) | Design: RCT<br>Setting: Inpatient<br>Country: U.K.<br>Funding: Government, university | Randomized N: 15<br>Analyzed N: Unclear<br>Intervention 1 (N=8): Rivastigmine 1.5 mg once a day increasing to 1.5 mg twice a day; higher dose after 7 days<br>Intervention 2 (N=7): Placebo tablets identical to drug, increasing to 2 | Inclusion: >65 years with delirium by CAM<br>Exclusion: Patients who "were too ill" taking a cholinesterase inhibitor, or had blood test abnormalities (urea, creatinine, transaminases, bilirubin); myocardial infarction, unstable cardiac arrhythmia, or severe respiratory disease | Mean (SD) age: 82.5 (9.9)<br>Female %: 47<br>Race %: NR<br>Delirium %: 100<br>Baseline scale of function: NR<br>Dementia %: 47<br>Postop %: 0 (medical wards)<br>Cancer %: NR | Main outcomes: All of the rivastigmine group, but only 3 of the placebo group, were negative for delirium on the CAM when they left the study. There was no significant difference in the duration of delirium between the 2 groups (rivastigmine group 6.3 days vs. placebo group 9.9 days, 95% CI -15.6 to 8.4, p=0.5). | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | tablets; higher dose after 7 days<br>Duration: Treated until delirium resolved or for maximum 28 days<br>Follow-up (days): 28 | | | Attrition: 13% vs. 14% | |
| van Eijk et al. (2010) | Design: RCT<br>Setting: ICU<br>Country: The Netherlands<br>Funding: Industry and nonprofit | Randomized N: 109<br>Analyzed N: 104<br>Intervention 1 (N=55): Rivastigmine oral solution, increasing dose starting at 0.75 mL (1.5 mg) twice daily and increasing in increments to 3 mL (6 mg) twice daily as tolerated, as an adjunct to usual care with haloperidol<br>Intervention 2 (N=54): Placebo oral solution, increasing dose starting at 0.75 mL twice daily and increasing in increments to 3 mL twice daily as tolerated, as an adjunct to usual care with haloperidol<br>Duration: Dose increased between days 4 and 9, stable from day 10 onwards<br>Follow-up (days): 90 | Inclusion: ≥18 years; ICU patients with delirium according to CAM-ICU or clinical diagnosis by a psychiatrist, geriatrician, or neurologist; expected to remain in the ICU for ≥48 hours<br>Exclusion: Unable to receive enteric drugs, receiving renal replacement therapy, liver failure with hepatic encephalopathy, second- or third-degree atrioventricular block or bradycardia with hemodynamic consequences, or without a functioning pacemaker | Mean (SD) age: 69.0 (11.8)<br>Female %: 36<br>Race %: NR<br>Delirium %: 100<br>Baseline scale of function, APACHE II score: mean (SD) 20.0 (8.4)<br>Dementia %: NR<br>Postop %: 69<br>Cancer %: NR | Main outcomes: Median duration of delirium was longer in the rivastigmine group than in the placebo group, but the difference between the groups was not significant (5.0 days [IQR 2.7–14.2] vs. 3.0 days [IQR 1.0–9.3], p=0.06). Delirium was significantly higher severity in the rivastigmine group than in the placebo group. Mortality in the rivastigmine group (n=12, 22%) was higher than in the placebo group (n=4, 8%) (p=0.07).<br>Attrition at follow-up: 35% vs. 28% | Moderate |

*Abbreviations.* APACHE II=Acute Physiology and Chronic Health Evaluation II; CAM=Confusion Assessment Method; CAM-ICU=Confusion Assessment Method for the ICU; CI=confidence interval; ICU=intensive care unit; IQR=interquartile range; N=number; NR=not reported; OR=odds ratio; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

### *Benzodiazepine Antagonist*

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Schomer et al. (2020) | Design: RCT<br>Setting: ICU<br>Country: U.S.<br>Funding: University | Randomized N: 22<br>Analyzed N: 20<br>Intervention 1 (N=11): Flumazenil 0.1 mg IV, titrated up every 5 minutes by 0.1 mg increments to a maximum dose of 2 mg<br>Intervention 2 (N=11): Placebo<br>Duration: During ICU stay<br>Follow-up (days): Until discharge | Inclusion: ≥18 years; critically ill who previously received benzodiazepines while in the ICU and had hypoactive delirium associated with benzodiazepine exposure<br>Exclusion: Those with an alternate explanation for altered mental status, acute brain injury, and/or history of seizures | Mean (SD) age: 58.1 (7.31)<br>Female %: 31.8<br>Race %: NR<br>Delirium %: 100<br>Mean (SD) Charlson Comorbidity Index: 5 (3)<br>Dementia %: NR<br>Postop %: 4.5 (1/22)<br>Cancer %: NR<br>Mean (SD) time since last benzodiazepine, hours: 49 (30.8)<br>Benzodiazepine indication<br>-Ventilator asynchrony %: 50<br>-Alcohol withdrawal syndrome %: 50 | Main outcomes: The median number of delirium-free days alive without coma within 14 days of enrollment was similar between the 2 groups (12.7 vs 9.2, p=0.19). There was no difference in the probability of delirium resolution within the first 14 days with 90% vs. 70% in the flumazenil and placebo groups, respectively (p=0.2). There was no statistical difference (OR 0.17, 95% CI 0.022 to 1.23, p=0.079) in delirium- and coma-free days at the end of the study drug infusion.<br>Attrition: 9% vs. 9% | Moderate |

*Abbreviations.* CI=confidence interval; ICU=intensive care unit; IV=intravenous; N=number; NR=not reported; OR=odds ratio; postop=post-operative; RCT=randomized controlled trial; SD=standard deviation.

### *Additional Medications*

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| Atalan et al. (2013) | Design: RCT<br>Setting: Postop, cardiac<br>Country: Turkey<br>Funding: Unclear | Randomized N: 53<br>Analyzed N: 53<br>Intervention 1 (N=27): Morphine sulfate 5 mg intramuscularly<br>Intervention 2 (N=26): | Inclusion: Cardiac surgery patients with hyperactive-type delirium<br>Exclusion: Patients with dementia, abnormal level of consciousness, Parkinso''s | Mean (SD) age: 65.87 (9.03)<br>Female %: 26<br>Race %: NR<br>Delirium %: 3.0 vs. 2.9 (RASS score)<br>APACHE II score: 6.33 vs. 5.69 | Main outcomes: Target Richmond Agitation and Sedation Scale scores percentages in the morphine group were statistically higher than the haloperidol group | High |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | Haloperidol 5 mg intramuscularly<br>Patients still agitated after administration of 20 mg/day of morphine/haloperidol also received 2.5 mg of lorazepam perorally, twice a day.<br>Duration: Postop, up to 10 days<br>Follow-up (days): 10, every 12 hours until discharge or 10 days | disease, recent seizures, or hypoactive-type delirium patients | Dementia %: 0<br>Postop %: 100 cardiac surgeries<br>Cancer %: NR<br>Hepatic or renal impairment: NR<br>Alcohol use %: 19 vs. 4<br>Drug use %: 4 vs. 12<br>Medications taken at baseline %: psychotropic drugs 4 vs. 12 | (p=0.042 and p=0.028, respectively). The number of patients requiring additive sedatives was significantly more in the haloperidol group when compared with the morphine group (p=0.011).<br>Attrition: NR | |
| Bakri et al. (2015) | Design: RCT<br>Setting: Postop, mixed<br>Country: Saudi Arabia<br>Funding: None | Randomized N: 96<br>Analyzed N: 96<br>Intervention 1 (N=32): Dexmedetomidine continuous IV infusion of 1 µg/kg<br>Intervention 2 (N=32): Ondansetron continuous IV infusion 4 mg<br>Intervention 3 (N=32): Haloperidol continuous IV infusion 5 mg<br>Duration: Twice a day for 3 consecutive days<br>Follow-up (days): POD 3 | Inclusion: Patients who screened positive for delirium within the first 3 days of ICU admission<br>Exclusion: Severely injured, deeply comatose, moribund patients, underlying neurological diseases, significant hearing loss, intracranial injury, or ischemic/hemorrhagic stroke | Mean (SD) age: 31 (5.5)<br>Female %: 9<br>Race %: NR<br>Delirium %: 100 (required)<br>Functioning scale: NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR<br>Mean (SD) duration of surgery, minutes: 211 (34)<br>Mean (SEM) Injury Severity Score: 25.4 (2.9)<br>Patients on MV on ICU admission %: 27 | Main outcomes: At the end of the study, the number of remaining delirious patients was 3, 6, and 2 in dexmedetomidine, ondansetron, and haloperidol groups, respectively, without statistical significance. During the study period, no significant difference was found in the number of patients who needed “rescue haloperidol” between dexmedetomidine and haloperidol groups (5 vs. 3, p=0.7), but the difference was significantly higher in ondansetron and haloperidol groups (11 vs. 3, p=0.03). The mean total “rescue haloperidol” | Moderate |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | | | | dose was significantly higher in ondansetron group than haloperidol group (p<0.001), but there was no difference between dexmedetomidine and haloperidol groups (p=0.07).<br>Attrition: NR | |
| Furuya et al. (2015) | Design: Retrospective cohort<br>Setting: Inpatient<br>Country: Japan<br>Funding: NR | Analyzed N: 32<br>Intervention 1* (N=19 analyzed): No ramelteon<br>Intervention 2* (N=13 analyzed): Ramelteon<br>*Both groups received antipsychotics (risperidone, quetiapine, perospirone [not available in U.S.], haloperidol, or chlorpromazine)<br>Duration: NR<br>Follow-up (days): NR | Inclusion: patients diagnosed with delirium using the DSM-IV-TR by psychiatric specialists<br>Exclusion: Severe liver dysfunction or use of fluvoxamine | Mean age: 80 vs. 78<br>Female %: 63 vs. 46<br>Race: NR<br>Delirium %: 100<br>Baseline scale of function: NR<br>Dementia %: NR<br>Postop %: 68 vs. 69<br>Cancer %: NR | Main outcomes: Duration of delirium in the ramelteon group was significantly less than that in the no ramelteon group: mean (SEM) 6.6 days (1.0) vs 9.9 days (1.3) (p=0.048). Dose of antipsychotics in the ramelteon group was significantly smaller than that in the no ramelteon group: mean (SEM) 444.5 mg (95.7) vs. 833.4 mg (137.9) (p=0.044).<br>Attrition: NR | High |
| Hov et al. (2019); LUCID | Design: RCT<br>Setting: Inpatient<br>Country: Norway<br>Funding: Mixed | Randomized N: 20<br>Analyzed N: 20<br>Intervention 1 (N=10): Clonidine 75 µg loading dose of 1 capsule every third hour up to 4 doses then twice daily until delirium-free for 2 days, discharge, or a maximum of 7 days of treatment<br>Intervention 2 (N=10): Placebo; loading placebo | Inclusion: ≥65 years who were acutely admitted with delirium or subsyndromal delirium<br>Exclusion: Bradycardia, bradycardia due to sick-sinus-syndrome, second- or third-degree atrioventricular block (if not treated with pacemaker), or any other reason causing heart rate <50 bpm; hypotension or | Mean (SD) age: 86.5<br>Female %: 65<br>Race %: NR<br>Delirium or subsyndromal Delirium %: 100<br>ADL independent %: 25<br>Cognitive Impairment %: 58 (IQCODE≥3.82)<br>Postop %: NR<br>Cancer %: NR | Main outcomes: There was no difference in time to first day without delirium (3 days vs. 3 days, p=0.59) or in final delirium resolution (5 days vs. 8 days, p=0.40); this study was underpowered.<br>Overall attrition: 0% | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | dose given but other details of dosing unclear<br>Duration: Until delirium-free for 2 days, discharge, or a maximum of 7 days<br>Follow-up (days): Until 7 days or discharge | orthostatic hypotension or a systolic blood pressure <120 mmHg; ischemic stroke or critical peripheral ischemia; acute coronary syndrome, unstable or severe coronary heart disease, and moderate to severe heart failure; polyneuropathy, phaeochromocytoma, or renal insufficiency; body weight <45 kg; considered as moribund on admission; unstable to take oral medications; use of tricyclic antidepressants, monoamine reuptake inhibitors, or ciclosporin; previously included in the study; adverse reactions to clonidine or excipients (lactose, saccharose); no speaking or reading Norwegian; other conditions; admission to ICU | | | |
| Liu et al. (2018) | Design: RCT<br>Setting: Postop, mixed<br>Country: China<br>Funding: Nonprofit | Randomized N: 100<br>Analyzed N: 100<br>Intervention 1 (N=25): Dexmedetomidine IV 0.2 µg/kg bolus followed by 0.6 µg/kg/hour<br>Intervention 2 (N=25): Sufentanil IV 0.2 µg/kg | Inclusion: Age 20-40 years scheduled for general anesthesia<br>Exclusion: Delirium preop | Mean (SD) age: 30.95 (4.87)<br>Female %: 46<br>Race %: NR<br>Delirium %: 100<br>ASA I, II %: 100<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: Dexmedetomidine and sufentanil decreased the duration of POD through 8 hours postop, but more individuals had delirium in the dexmedetomidine group at 8 | Low |

| Author (year); trial name | Study characteristics | Study protocol including numbers of participants, interventions, duration, and follow-up | Study population including main inclusion and exclusion criteria | Sample demographics | Results including main outcomes and attrition rates | Risk of Bias |
|---|---|---|---|---|---|---|
| | | bolus followed by 0.2 µg/kg/hour<br>Intervention 3 (N=25): Sufentanil IV 0.2 µg/kg bolus followed by combined dexmedetomidine 0.6 µg/kg/hour and sufentanil 0.2 µg/kg/hour<br>Intervention 4 (N=25): Sufentanil IV 0.2 µg/kg bolus followed by combined dexmedetomidine 0.3 µg/kg/hour and sufentanil 0.1 µg/kg/hour<br>Duration: Postop<br>Follow-up (days): Through 8 hours | | | hours than the other 3 groups (36% vs. 8% to 16%, p<0.05).<br>Overall attrition: 0% | |
| Tagarakis et al. (2012) | Design: RCT<br>Setting: Postop, cardiac<br>Country: Greece<br>Funding: NR | Randomized N: 80<br>Analyzed N: 80<br>Intervention 1 (N=40): Ondansetron 8 mg IV<br>Intervention 2 (N=40): Haloperidol 5 mg IV<br>Duration: Once for 10 minutes<br>Follow-up (days): 1 | Inclusion: Developed delirium post on-pump heart surgery, using a 4-point scale (threshold for delirium NR)<br>Exclusion: History of severe psychiatric disease | Mean (SD) age: 71<br>Female %: 34<br>Race %: NR<br>Delirium %: NR<br>Baseline scale of function: NR<br>Dementia %: NR<br>Postop %: 100<br>Cancer %: NR | Main outcomes: A statistically significant improvement was shown after the administration of both ondansetron (percentage improvement 61.29%, p<0.01) and haloperidol (percentage improvement 58.06%, p<0.01), but no between group differences were found.<br>Attrition: NR | High |

*Abbreviations.* ADL=activities of daily living; APACHE II=Acute Physiology and Chronic Health Evaluation II; ASA=American Society of Anesthesiologists; DSM-IV-TR= Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision; ICU=intensive care unit; IQCODE=Informant Questionnaire on Cognitive Decline in the Elderly; IV=intravenous; MV=medical ventilation; N=number;

NR=not reported; OR=odds ratio; POD=post-operative delirium; postop=post-operative; RASS=Richmond Agitation Sedation Scale; RCT=randomized controlled trial; SD=standard deviation; SEM=standard error of the mean.

# Appendix I. Considerations in Use of Guidelines to Enhance the Quality of Care

Clinical practice guidelines can help enhance quality of care by synthesizing available research evidence and delineating recommendations for care on the basis of the available evidence. In some circumstances, practice guideline recommendations will be appropriate to use in developing quality measures. Guideline statements can also be used in other ways, such as educational activities or electronic decision support, to enhance the quality of care that patients receive. Furthermore, when availability of services is a major barrier to implementing guideline recommendations, improved tracking of service availability and program development initiatives may need to be implemented by health organizations, health insurance plans, federal or state agencies, or other regulatory programs.

Typically, guideline recommendations that are chosen for development into quality measures will advance one or more aims of the Institute of Medicine's report on "Crossing the Quality Chasm" (Institute of Medicine 2001) by facilitating care that is safe, effective, patient-centered, timely, efficient, and equitable. To achieve these aims, quality measures (Watkins et al. 2015) are needed that span the continuum of care (e.g., prevention, screening, assessment, treatment, continuing care), address the different levels of the health system hierarchy (e.g., system-wide, organization, program/department, individual clinicians), and include measures of different types (e.g., process, outcome, patient-centered experience). Emphasis is also needed on factors that influence the dissemination and adoption of evidence-based practices (Drake et al. 2008; Greenhalgh et al. 2004; Horvitz-Lennon et al. 2009).

Often, quality measures will focus on gaps in care or on care processes and outcomes that have significant variability across specialties, health care settings, geographic areas, or patients' demographic characteristics. Administrative databases, registries, and data from electronic health record (EHR) systems can help to identify gaps in care and key domains that would benefit from performance improvements (Acevedo et al. 2015; Patel et al. 2015; Watkins et al. 2016). Nevertheless, for some guideline statements, evidence of practice gaps or variability will be based on anecdotal observations if the typical practices of psychiatrists and other health professionals are unknown. Variability in the use of guideline-recommended approaches may reflect appropriate differences that are tailored to the patient's preferences, treatment of co-occurring illnesses, or other clinical circumstances that may not have been studied in the available research. On the other hand, variability may indicate a need to strengthen clinician knowledge or address other barriers to adoption of best practices (Drake et al. 2008; Greenhalgh et al. 2004; Horvitz-Lennon et al. 2009). When performance is compared among organizations, variability may reflect a need for quality improvement initiatives to improve overall outcomes but could also reflect case-mix differences such as socioeconomic factors or the prevalence of co-occurring illnesses.

Conceptually, quality measures can be developed for purposes of accountability, for internal or health system–based quality improvement, or both. Accountability measures require clinicians to report their rate of performance of a specified process, intermediate outcome, or outcome in a specified group of patients. Because these data are used to determine financial incentives or penalties based on performance, accountability measures must be scientifically validated, have a strong evidence base, fill gaps in care, and be broadly relevant and meaningful to patients, clinicians, and policy makers.

Development of such measures is complex and requires detailed development of specification and pilot testing (Center for Health Policy/Center for Primary Care and Outcomes Research and Battelle Memorial Institute 2011; Fernandes-Taylor and Harris 2012; Iyer et al. 2016; Pincus et al. 2016; Watkins et al. 2011). In contrast, internal or health system–based quality improvement measures are typically designed by and for individual providers, health systems, or payers. They typically focus on measurements that can suggest ways for clinicians or administrators to improve efficiency and delivery of services within a particular setting. Internal or health system–based quality improvement programs may or may not link performance with payment, and, in general, these measures are not subject to strict testing and validation requirements.

Regardless of the purpose of the quality measure, it must be possible to define the applicable patient group (i.e., the denominator) and the clinical action or outcome of interest that is measured (i.e., the numerator) in validated, clear, and quantifiable terms. The measure also needs to be feasible. More specifically, the health system's or clinician's performance on the measure must be readily ascertained from chart review, patient-reported outcome measures, registries, or administrative data. In addition, use of the measure should yield improvements in quality of care to justify any clinician burden (e.g., documentation burden) or related administrative costs (e.g., for manual extraction of data from charts, for modifications of EHRs to capture required data elements).

Documentation of quality measures can be challenging, and, depending on the practice setting, can pose practical barriers to meaningful interpretation of quality measures based on guideline recommendations. For example, when recommendations relate to patient assessment or treatment selection, clinical judgment may need to be used to determine whether the clinician has addressed the factors that merit emphasis for an individual patient. In other circumstances, standardized instruments can facilitate quality measurement reporting, but it is difficult to assess the appropriateness of clinical judgment in a validated, standardized manner. Furthermore, utilization of standardized assessments remains low (Fortney et al. 2017), and clinical findings are not routinely documented in a standardized format. Many clinicians appropriately use free text prose to describe symptoms, response to treatment, discussions with family, plans of treatment, and other aspects of care and clinical decision-making. Reviewing these free text records for measurement purposes would be impractical, and it would be difficult to hold clinicians accountable to such measures without advances in natural language processing technology and further increases in EHR use among mental health professionals.

Possible unintended consequences of any derived measures would also need to be addressed in testing of a fully specified measure in a variety of practice settings. For example, in many health care systems, multiple clinicians are involved in the care of a patient and attributing measure performance to one clinician, or one group of clinicians, can be misleading. As another challenge, fully specified measures may lead to overuse of standardized language that does not accurately reflect what has occurred in practice. If multiple discrete fields are used to capture information, data will be easily retrievable and reportable, but oversimplification is a possible unintended consequence of measurement and documentation burden is likely to be high (Johnson et al. 2021). Just as guideline developers must balance the benefits and harms of a particular guideline recommendation, developers of performance

measures must weigh the potential benefits, burdens, and unintended consequences in optimizing quality measure design and testing.

## Assessment and Treatment Planning

### *Statement 1 – Structured Assessments for Delirium*

APA recommends **(1C)** that patients with delirium or who are at risk for delirium undergo regular structured assessments for the presence or persistence of delirium using valid and reliable measures.

Use of structured assessments for delirium could be incorporated into performance-based measures or quality improvement activities as well as being incorporated into EHR decision support. Such measures would not need to specify use of a particular structured assessment because there are many available options (see Statement 1, Implementation). However, most organizations choose one or two assessments for incorporation into their documentation. Performance-based measures or quality improvement activities could determine the proportion of high-risk patients who had been assessed for delirium. Categories of individuals at high-risk could be based on a number of factors including situational context (e.g., post-operative patients, ICU patients), demographic factors (e.g., age), and co-occurring diagnoses (e.g., dementia). For performance-based measures, assessment could be specified at easily defined transitions or time points (e.g., admission, discharge, admission to or discharge from intensive care, specified number of post-operative days). If more frequent assessments are being done, such as for patients in intensive care, quality improvement activities could also examine the proportion of days with a delirium assessment. EHR decision support could prompt clinicians to determine the patient's neurocognitive status (Statement 2) or conduct a thorough assessment for delirium risk factors (Statement 3) based on a structured assessment finding that suggests the presence of delirium. EHR decision support could include passive alerts, suggestions to use delirium-specific order sets, documentation templates that are specific to delirium, or easy access to detailed reference information on delirium.

### *Statement 2 – Determination of Baseline Neurocognitive Status*

APA recommends **(1C)** that a patient's baseline neurocognitive status be determined to permit accurate interpretation of delirium assessments.

This statement would be difficult to incorporate into a performance-based measure or quality improvement activity because determining and documenting the patient's baseline neurocognitive status may include administration of a structured cognitive assessment that could be identified electronically, but could also involve obtaining historical and collateral information, which would be documented in free text. However, as natural language processing evolves, neurocognitive status may be more readily identified through analysis of free-text format. In addition, reminders to obtain and document the patient's baseline neurocognitive status could be incorporated into EHR decision support such as passive alerts, linked reference materials, or documentation templates that are specific to delirium.

*Statement 3 – Review for Predisposing or Contributing Factors*

APA recommends **(1C)** that patients with delirium or who are at risk for delirium undergo a detailed review of possible predisposing or contributing factors.

Although a detailed review of possible predisposing or contributing factors is important to the evaluation of patients with delirium or who are at risk for delirium, it would be challenging to incorporate this recommendation into a performance-based measure. Given the breadth of possible predisposing or contributing factors and the various ways in which they are documented, it would be difficult to ascertain details on specific factors from chart or administrative data. However, with advances in natural language processing and predictive algorithms, such information may be able to be ascertained more easily and used in quality improvement. In addition, quality-related efforts at the local level could assess whether EHR templates include prompts for documenting co-occurring conditions and whether such aspects of the evaluation are typically completed, while still allowing flexibility in the documentation of findings. Use of delirium-specific order sets could also suggest laboratory tests, imaging studies, or other evaluations aimed at identifying predisposing or contributing factors for delirium. Passive alerts or easily accessed links to reference materials can also be used to provide decision support to clinicians within the EHR workflow.

*Statement 4 – Review of Medications*

APA recommends **(1C)** that a detailed medication review be conducted in patients with delirium or who are at risk for delirium, especially those with pre-existing cognitive impairment.

Key elements of this guideline recommendation are already incorporated into a number of performance-based measures, quality improvement activities, and aspects of EHR decision support. For example, obtaining an accurate medication list and reviewing medications as part of medication reconciliation are part of The Joint Commission's requirements at the time of hospital admission (The Joint Commission 2023). A measure for "Documentation of Current Medications in the Medical Record" is also part of the Merit-Based Incentive Payment System Program, among other programs (Centers for Medicare and Medicaid Services 2022). Other available measures include a process measure for "Use of High-Risk Medications in Older Adults" (Centers for Medicare and Medicaid Services 2021b). Many EHRs also incorporate decision support alerts related to prescriptions that confer increased risk in older individuals (e.g., using the Beers criteria; American Geriatrics Society Beers Criteria® Update Expert Panel 2023). In addition to these performance-based measures, quality improvement activities, and EHR decision support tools, organizations could also assess whether gaps are occurring with medication review and reconciliation in patients with a diagnosis of delirium, pre-existing cognitive impairment, or significant risk factors for delirium (see Appendix I, Statement 1). In addition to EHR alerts, decision support could also include easily accessed links to reference materials on medications that may predispose someone to or exacerbate delirium.

*Statement 5 – Use of Restraints*

APA recommends **(1C)** that physical restraints not be used in patients with delirium, except in situations where injury to self or others is imminent and only:

- after review of factors that can contribute to racial/ethnic and other biases in decisions about restraint;
- with frequent monitoring; and
- with repeated reassessment of the continued risks and benefits of restraint use as compared to less restrictive interventions.

Regulatory policy and hospital conditions of participation already include requirements for monitoring and reporting related to use of physical restraints (Code of Federal Regulations 2019). Additional performance-based measures, quality improvement activities, or EHR decision support are not likely to be indicated.

### *Statement 6 – Person-Centered Treatment Planning*

APA recommends **(1C)** that patients with delirium have a documented, comprehensive, and person-centered treatment plan.

An overarching performance-based measure derived from this recommendation is not recommended because of the associated burdens and practical challenges. Clinical judgment would be needed to determine whether a documented treatment plan was comprehensive and person-centered. If a performance measure assessed for the presence or absence of specific text related to treatment planning in the medical record, increased documentation burden could result. Such an approach could also foster overuse of standardized language that would not accurately reflect what has occurred in practice. Use of this statement as part of a quality improvement activity would face many of the same challenges as a performance-based measure, given the individualized focus of this recommendation. However, with advances in natural language processing and predictive algorithms, information on treatment planning and health-related needs, including social determinants of health, may be able to be identified more easily from electronic records and used in quality improvement and decision support. EHR decision support could also be provided through easily accessed links to reference materials or delirium-specific documentation templates or order sets.

## Non-Pharmacological Interventions

### *Statement 7 – Multi-Component Non-Pharmacological Interventions*

APA recommends **(1B)** that patients with delirium or who are at risk for delirium receive multi-component non-pharmacological interventions to manage and prevent delirium.

Multi-component non-pharmacological interventions are key elements in the care of patients with delirium yet are challenging to measure as part of quality measurement initiatives due to many elements in typical multi-component bundles and variations in fidelity and consistency in providing individual bundle components. However, performance improvement activities within organizations could implement rounding checklists, EHR orders sets, EHR documentation templates to assess bundle adherence, and easily accessed EHR links to reference materials on non-pharmacological interventions (King et al. 2023a, 2023b; Stollings et al. 2020). Quality improvement activities could also be developed to assess adherence with individual aspects of the multi-component bundle such as early mobility and use of both spontaneous awakening and spontaneous breathing trials.

## Pharmacological Interventions

### *Statement 8 – Principles of Medication Use*

APA recommends **(1C)** that antipsychotic agents and other medications to address neuropsychiatric disturbances of delirium be used only when all the following criteria are met:

- verbal and non-verbal de-escalation strategies have been ineffective;
- contributing factors have been assessed and, insofar as possible, addressed; and
- the disturbances cause the patient significant distress and/or present a risk of physical harm to the patient or others.

Although it is important to determine whether the criteria in this recommendation are met prior to using antipsychotic agents and other medications to address neuropsychiatric disturbances of delirium, it would be challenging to incorporate this recommendation into a performance-based measure or quality improvement activity because this information is typically documented in free text. In addition, some of the information such as assessment of contributing factors may be based on multiple prior assessments rather than being documented in a single location. However, as natural language processing evolves, this information may be able to be extracted from the EHR more readily. In addition, delirium-specific documentation templates and links to reference materials might be incorporated into EHRs to prompt clinicians to consider these criteria prior to the ordering of medication to address neuropsychiatric disturbances of delirium.

### *Statement 9 – Antipsychotic Agents*

APA recommends **(1C)** that antipsychotic agents not be used to prevent delirium or hasten its resolution.

Because antipsychotic agents could be used for reasons other than prevention or treatment of delirium, incorporation into performance-based measures, quality improvement activities, or EHR decision support would be challenging. However, many EHRs already incorporate decision support alerts related to prescriptions, such as antipsychotic medications, that confer increased risk in older individuals (e.g., using the Beers criteria; American Geriatrics Society Beers Criteria® Update Expert Panel 2023).

### *Statement 10 – Benzodiazepines*

APA recommends **(1C)** that benzodiazepines not be used in patients with delirium or who are at risk for delirium, including those with pre-existing cognitive impairment, unless there is a specific indication for their use.

Because benzodiazepines could be used for reasons other than prevention or treatment of delirium, incorporation into performance-based measures, quality improvement activities, or EHR decision support would be challenging. However, many EHRs already incorporate decision support alerts related to prescriptions, such as benzodiazepines, that confer increased risk in older individuals (e.g., using the Beers criteria; American Geriatrics Society Beers Criteria® Update Expert Panel 2023).

*Statement 11 – Dexmedetomidine to Prevent Delirium*

APA suggests **(2B)** that dexmedetomidine be used rather than other sedating agents to prevent delirium in patients who are undergoing major surgery or receiving mechanical ventilation in a critical care setting.

As a suggestion, this guideline statement is not appropriate for use as a performance-based measure or quality improvement activity or incorporation into EHR decision support.

*Statement 12 – Dexmedetomidine in Patients with Delirium*

APA suggests **(2C)** that when patients with delirium are sedated for mechanical ventilation in a critical care setting, dexmedetomidine be used rather than other sedating agents.

As a suggestion, this guideline statement is not appropriate for use as a performance-based measure or quality improvement activity or incorporation into EHR decision support.

*Statement 13 – Melatonin and Ramelteon*

APA suggests **(2C)** that melatonin and ramelteon not be used to prevent or treat delirium.

As a suggestion, this guideline statement is not appropriate for use as a performance-based quality measure. Because melatonin and ramelteon could be used for reasons other than prevention or treatment of delirium, incorporation into quality improvement activities or EHR decision support would be challenging and not warranted.

*Statement 14 – Medication Review at Transitions of Care*

APA recommends **(1C)** that, in patients with delirium or who are at risk for delirium, a detailed medication review, medication reconciliation, and reassessment of the indications for medications, including psychotropic medications, be conducted at transitions of care within the hospital.

As described in Appendix I, Statement 4, key elements of this guideline recommendation are already incorporated into a number of performance-based measures, quality improvement activities, and aspects of EHR decision support. These include, but are not limited to, The Joint Commission's requirements for medication reconciliation (The Joint Commission 2023) and EHR decision support related to prescriptions that confer increased risk in older individuals (e.g., using the Beers criteria; American Geriatrics Society Beers Criteria® Update Expert Panel 2023). In addition, organizations could assess whether gaps are occurring with medication review and reconciliation in patients with a diagnosis of delirium, pre-existing cognitive impairment, or significant risk factors for delirium at transitions of care within the hospital.

*Statement 15 – Follow-up Planning at Transitions of Care*

APA recommends **(1C)** that, when patients with delirium are transferred to another setting of care, plans for follow-up include:

- continued assessments for persistence of delirium;
- detailed medication review, medication reconciliation, and reassessment of the indications for medications, including psychotropic medications;

- assessment of consequences of delirium (e.g., post-traumatic symptoms, cognitive impairment); and
- psychoeducation about delirium for patients and their care partners.

As described in Appendix I, Statement 4, key elements of this guideline recommendation related to medication review are already incorporated into a number of performance-based measures, quality improvement activities, and aspects of EHR decision support. These include, but are not limited to, The Joint Commission's requirements for medication reconciliation (The Joint Commission 2023) and EHR decision support related to prescriptions that confer increased risk in older individuals (e.g., using the Beers criteria; American Geriatrics Society Beers Criteria® Update Expert Panel 2023). A performance-based process measure also exists for "Medication Reconciliation Post-Discharge" (Centers for Medicare and Medicaid Services 2021a). Performance-based measures, quality improvement activities, and aspects of EHR decision support could also be developed to address post-transfer assessment for persistence of delirium. Information for patients and their care partners can be included in EHRs to assist with psychoeducation and can leverage existing EHR features that suggest patient education materials based on diagnosis. EHR related decision support could also be provided through easily accessed links to reference materials or rating scales for assessing persistence of delirium or consequences of delirium (e.g., post-traumatic symptoms, cognitive impairment).

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