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Randomized ICU Trials Do Not Demonstrate an Association Between Interventions That Reduce Delirium Duration and Short-Term Mortality: A Systematic Review and Meta-Analysis

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Abstract

Background—Interventions that reduce delirium duration may also lower short-term mortality. We reviewed randomized trials of adult ICU patients of interventions hypothesized to reduce delirium burden to determine whether interventions that are more effective at reducing delirium duration are associated with a reduction in short-term mortality.

Search Methods—We searched CINHAHL, EMBASE, MEDLINE and the Cochrane databases from 2001 through 2012. Citations were screened for randomized trials that enrolled critically ill adults, evaluated delirium at least daily, compared a drug or non-drug intervention hypothesized to reduce delirium burden with standard care (or control), and reported delirium duration and/or short-term mortality (< 45 days). In duplicate, we abstracted trial characteristics and results and evaluated quality using the Cochrane risk of bias tool. We performed random effects model meta-analyses and meta-regressions.

Results—We included 17 trials enrolling 2,849 patients which evaluated a pharmacologic intervention (n=13) [dexmedetomidine (n=6); an antipsychotic (n=4); rivastigmine (n=2); and clonidine (n=1)], a multimodal intervention (n=2) [spontaneous-awakening (n=2)]; or a non-pharmacologic intervention (n=2) [early mobilization (n=1); increased perfusion (n=1)]. Overall, average delirium duration was lower in the intervention groups [difference = −0.64 days; 95% CI, −1.15 to −0.13; P = 0.01] being reduced by < 3 days in 3 studies, 0.1 to < 3 days in 6 studies, 0

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days in 7 studies and < 0 days in 1. Across interventions, for 13 studies where short-term mortality was reported, short-term mortality was not reduced (risk ratio = 0.90; 95% CI, 0.76 to 1.06; P = 0.19). Across 13 studies that reported mortality, meta-regression revealed that delirium duration was not associated with reduced short-term mortality (P = 0.11).

Conclusions—A review of current evidence fails to support that ICU interventions that reduce delirium duration reduce short-term mortality. Larger controlled studies are needed to establish this relationship.

Keywords

critical illness; delirium; mortality; meta-analysis; systematic review; randomized controlled study; antipsychotic; dexmedetomidine

Delirium is common in the intensive care unit (ICU), is associated with a prolonged mechanical ventilation and hospital stay, and may be linked to cognitive and/or functional impairment (1–4). The ‘burden of delirium’ in the critically ill can be quantified by its duration, severity or intensity, or as various delirium-associated complications. Among markers of delirium burden, delirium duration is the simplest and most reliable measure. Delirium severity scales require patients to communicate verbally (5). Delirium screening tools are limited in their ability to evaluate delirium severity, assessment results may be confounded by concomitant conditions (e.g. level of sedation), and the longer-term complications of delirium of greatest clinical relevance remain unclear. Delirium assessment tools are limited by the paucity of data as well as confounders for delirium detection and longitudinal outcomes preclude using this association as a measure (6–10).

Mortality in the first month after ICU admission has been commonly used as an outcome to evaluate the efficacy and safety of interventions in the critically ill (11, 12). A number of pharmacological (e.g., antipsychotics, dexmedetomidine) and non-pharmacological (e.g., early mobilization) interventions have been shown to reduce delirium burden in the critically ill (5, 13–15). However, when evaluated in prospective, randomized studies, none of these interventions have been shown to reduce short-term mortality. Many studies were too small to detect a difference in short-term mortality or evaluated an ICU population with a low mortality rate (e.g. cardiac surgery) (14).

While duration of CAM-ICU screened delirium has been associated independently with higher mortality in the critically ill (16–18), it remains unclear if interventions that decrease delirium duration in the critically ill will also reduce short-term mortality (19). Using the increased power of meta-analytic techniques, we sought to review published randomized trials to test the hypothesis that interventions that reduce the duration of delirium are associated with a reduction in short-term mortality.

METHODS

Trial Identification

An experienced medical librarian assisted our search for eligible studies using the following key words: “delirium” OR “brain dysfunction” AND “intensive care” OR “critical care” OR “ICU” AND “random*”. We searched six databases (EMBASE, MEDLINE, CINAHL, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and www.ClinicalTrials.gov) for relevant trials from 2001 to December 2012. We reviewed personal files, reference lists of review articles, and reference lists in eligible studies for additional trials. In addition, we requested advice from experts in the field, searched abstract books from major critical care, surgical and geriatric scientific meetings, and contacted investigators conducting randomized controlled trials in this area. We chose 2001 as the initial search year since two ICU delirium screening instruments with good psychometric strength, and frequently used in clinical practice, were published that year [i.e., CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC)](5, 10, 20). Non-English language and grey literature (unpublished, non-peer reviewed studies) were excluded. The IRB at Northeastern University waived the need for IRB approval.

Eligibility Criteria

We included randomized controlled parallel group or factorial trials of adults (≥ 19 years or older) admitted to an ICU at the time of study randomization. We included any pharmacological, non-pharmacological or mixed pharmacological/non-pharmacological strategy hypothesized to decrease delirium burden (i.e., delirium duration, delirium severity or delirium-associated complications) with any other strategy. To be included, trials had to measure delirium at least once daily with a validated technique such as the CAM-ICU or ICDSC or have delirium assessed by a psychiatrist or neurologist using Diagnostic and Statistical Methods (DSM –IV) criteria (10, 20, 21). Ideally, trials reported both delirium duration and short-term mortality (i.e., either at hospital discharge or 21, 28, 30, or 45 days after the time of study randomization).

Trial Selection

We screened abstracts and titles in duplicate for potentially relevant studies. These were re-screened in duplicate in full-text form. For articles that did not report either delirium duration or short-term mortality we contacted the corresponding author to provide the missing outcome(s) or to confirm that these data were not collected during the study. Corresponding authors who failed to respond after the first contact were contacted two additional times over a 6-week period.

Data Abstraction and Risk of Bias Assessment

Using a custom-made data collection form, two reviewers independently abstracted data regarding the design, patient population, intervention and comparison, clinical outcomes, and methodological quality using the “risk of bias tool” recommended by the Cochrane Collaboration (22). For each trial, risk of bias was evaluated for six domains [i.e., reporting, attrition, detection, performance, selection and other (ie. potential sources of bias not

accounted for in the prior 6 domains)] and an ‘overall’ risk of bias was estimated. For each domain risk of bias was categorized as “low”, “unclear”, or “high”. Disagreement for all methodological steps was resolved by discussion and consensus.

Data Synthesis

We separately analyzed differences in delirium duration (in days) and risk ratios (RR) of short-term mortality across all studies with adequate data using random effects model meta-analyses. For the calculation of the mean difference delirium duration, data on the means and standard errors were required; these were estimated for studies reporting median and interquartile or full ranges if investigators did not report these values or respond to queries (23). To assess the association between effect of intervention on delirium duration and the short-term mortality, we attempted to run a multivariate random effects meta-analysis with the “mvmeta” function in Stata 11.2 (StataCorp, College Station, TX). However, since the algorithm failed to converge, except under infeasible assumptions about the within-study correlation between delirium duration and mortality ($r > 0.95$), we proceeded with a random effects model meta-regression of all studies where both duration of delirium and short-term mortality were reported. Meta-analyses and the meta-regression were conducted using the “metan” and “metareg” function in Stata 11.2. For each meta-analysis, we report the statistical significance of the chi-squared test for heterogeneity and the I^2 statistic, which estimates the variation in the outcome attributable to heterogeneity rather than chance (24, 25).

Sensitivity Analyses

To explore the clinical and statistical heterogeneity across the studies, we conducted six post hoc sensitivity analyses for delirium duration, short term mortality, and the association between these two outcomes, to account for potential factors that we hypothesized could influence one or more of these outcomes/relationships: 1) the method of delirium assessment (i.e., CAM-ICU vs. ICDSC) given evidence suggesting that the sensitivity and specificity of these two instruments may differ (5, 26, 27); 2) the predominate ICU service that the patient was admitted to (i.e., medical versus surgical); 3) the presence of delirium at the time of enrollment in some or all patients versus the presence of delirium in none; 4) patients at low risk for mortality (5%) versus those at high risk for mortality (10%); 5) patients administered a pharmacological intervention versus those administered a non-pharmacological intervention; and 6) among patients administered a pharmacological intervention, those administered antipsychotic versus an alpha-2 receptor agonist (e.g., clonidine or dexmedetomidine) or an acetylcholinesterase inhibitor (e.g., rivastigmine). For each meta-analysis, we conducted meta-regressions including each of the sensitivity analysis factors as covariates evaluating the statistical significance of the interaction between each factor and the outcome; e.g., we tested the interaction between the method of delirium assessment and delirium duration. We also conducted a sensitivity analysis of the meta-regression between delirium duration and death excluding any study where the duration of delirium was longer in the intervention than the control group.

RESULTS

Trial Identification

Our search yielded 145 publications (136 from the electronic database search; 9 from hand searching). (Figure 1) We excluded 122 articles based on a review of the title and abstract; of 23 remaining studies, 6 were excluded during full review: neither delirium or short-term mortality was evaluated or reported (n=4)(28–31); delirium was evaluated only once at the end of the study (n=1)(32) and agitation, rather than delirium, was evaluated (n=1)(33).

We included 17 randomized trials enrolling 2,849 patients in this systematic review (34–50). Of these, four evaluated antipsychotic therapy (34–37); one evaluated IV clonidine (38); six evaluated dexmedetomidine (39–44); two evaluated rivastigmine (45, 46); two evaluated daily sedative interruption (47, 50); one evaluated early mobilization after daily sedation interruption (48); and one evaluated the maintenance of a high peri-operative perfusion pressure (49).

Trial Characteristics

Table 1 describes the characteristics of the 17 studies (34–50). Eleven of the 17 studies were blinded (34–39, 42–46). Among the six unblinded studies (40, 41, 47–50), four evaluated a non-pharmacological intervention that would be challenging to apply in a blinded fashion (47–50).

Delirium was evaluated either by a member of the study's research team using the CAM-ICU (35, 37, 39, 43, 46–48); by bedside clinicians using either the CAM-ICU (42, 44, 45) or the ICDSC (34, 41, 50); by a psychiatrist using DSM-IV criteria (38, 40, 47) or the bedside clinician using the ICDSC with confirmation by a psychiatrist using DSM-IV criteria (36). Duration of delirium was either not collected during the study or was not retrievable from two studies (43, 49). Mortality was reported at hospital discharge for six studies (34, 36, 40, 44, 45, 50), and at post-study randomization day 21 in two studies (35, 47), day 28 in three studies (37, 39, 48), day 30 in three studies (42, 46, 49) or day 45 in one study (43). Short-term mortality was not able to be determined from authors for two studies (38, 40). Most of the studies (n=14) had a low Cochrane risk of bias (34–39, 42, 44–50). (Supplemental Figure)

Table 2 highlights the patient characteristics (34–50). The studies enrolled either a mixed-medical-surgical population (n=8) (34, 35, 39, 41–43, 46, 50); a surgical population (n=7) (36–38, 40, 45, 49); or a medical population (n=2) (47, 48). Most (n=13) of the studies enrolled only patients who were intubated (35, 38–45, 47–50). The average patient age was older than 50 years across all intervention and control groups in all 17 studies. Where reported, the average Acute Physiology and Chronic Health Evaluation (APACHE) II score varied widely across the studies. In eight of the studies, all patients were delirium-free at the time of study randomization (36–38, 40, 44–5, 48, 49), and in two of the studies all patients had delirium at the time of randomization (34, 46).

Duration of Delirium

All 17 trials reported duration of delirium (Figure 2). The average delirium duration (vs. control) was reduced in the intervention groups (difference = -0.64 days; 95% confidence interval [CI], -1.15 to -0.13 ; $P = 0.014$) and was reduced on average 3 days for 3 studies, 0.1 to < 3 days for 6 studies, 0 days for 7 studies and < 0 days for one study. Across studies, there was a wide range of net effects on delirium duration, from a significant reduction by 3.4 days to a nonsignificant increase by 2.0 days. Consistent with the range of effects, the studies were significantly heterogeneous ($P < 0.001$); 71% of the differences are attributable to heterogeneity.

Short-Term Mortality

Thirteen trials reported short-term mortality (Figure 3). Across the studies the short-term mortality rate was similar between the intervention (15.6%) and control (16.5%) groups ($p = 0.54$). Compared with control, the interventions had no significant effect on death ($RR = 0.90$; 95% CI 0.76 to 1.06 ; $P = 0.19$). The studies were statistically homogeneous ($P = 0.63$, $I^2 = 0\%$).

Across 13 studies where both duration of delirium and mortality was reported (Figure 4), meta-regression revealed that delirium duration was not associated with a statistically significant reduced short-term mortality; the slope of the $\ln(RR \text{ mortality}) = -0.17$ (95% CI -0.39 , 0.04 ; $P = 0.11$). There was no residual heterogeneity for this association ($I^2 = 0\%$). Because the study by van Eijk et al. found a relatively large increase in delirium duration with an intervention meant to decrease delirium duration, we ran a sensitivity analysis of the meta-regression without this study (46). The relationship between delirium duration and short-term mortality was not substantially changed and remained non-significant; the slope of the $\ln(RR \text{ mortality}) = -0.10$ (95% CI -0.34 , 0.15 ; $P = 0.40$).

Sensitivity Analyses

The results of the six sensitivity analyses are presented in Table 3. There was no evidence that either the outcomes duration of delirium or short-term mortality, nor the association between the two, were different for any of the tested subgroups.

DISCUSSION

This systematic review and meta-analysis is the first to summarize published randomized trials evaluating an intervention in critically ill adults hypothesized to reduce delirium burden. Our analyses confirm that pharmacological and non-pharmacological interventions in the ICU can reduce delirium duration. However, current randomized controlled trial data fail to support that a treatment that reduces delirium duration is associated with a reduction in short-term mortality. Analyses within large trials or patient-level meta-analysis across studies are needed to establish this association.

Our findings appear to differ with the results of a recently published meta-analysis and three published cohort studies (16–18, 51). The meta-analysis of 14 ICU observational studies involving 5891 patients, found that patients who developed delirium had a higher mortality

rate than patients who did not (odds ratio: 3.22; 95% confidence interval: 2.30–4.52) (51). However, this meta-analysis did not consider delirium duration and thus conclusions about the association between delirium duration and mortality cannot be made. The three cohort analyses used regression techniques to demonstrate that a significant relationship between delirium duration and mortality exists at 28-days (18), 6 months (16) and 1 year (17). The first analysis of 275 mechanically ventilated ICU patients, found that each additional day spent in delirium was associated with a 10% increased risk of death at six months [hazard ratio (HR), 1.1; 95% confidence interval (CI), 1.0–1.3; $p=0.03$] (16). The second analysis of 304 medical ICU patients aged ≥ 60 years revealed that the number of days spent in delirium was significantly associated with greater 1-year mortality [HR, 1.10; 95% CI, 1.02–1.18] (17). A third analysis of 354 patients enrolled in the SEDCOM study found that delirium duration was the strongest predictor of 30-day mortality ($p < 0.001$) among eight different covariates that were modeled and that a dose-response increase in mortality was seen with increasing durations of delirium (18).

Our results, and their contrast with the above meta-analysis and cohort analyses, raise a number of important questions. Delirium duration may not be a direct cause of death in the ICU; other factors such as severity of illness may influence delirium incidence, delirium duration and short-term mortality (52, 53). The relationship between delirium duration and mortality may vary by the specific delirium-reducing intervention evaluated. Current clinical trials may be too small to identify a relationship between delirium duration and short-term mortality.

Delirium may not always have been accurately recognized in the studies included (54). Only one screening method, the CAM-ICU, has been used in studies showing an association between delirium duration and mortality (16–18). Recent data have suggested that sedation may confound CAM-ICU assessments, and delirium screening with CAM-ICU or ICDSC may not be similar (55–58). This is important given that the method of delirium assessment was found to account for the heterogeneity between studies in the meta-analysis by Zhang et al that associated delirium presence with great mortality (51).

Sedation-induced coma is an independent predictor of ICU and hospital mortality in several studies (59–61). It is possible that confounding factors within and between studies, including the wide variability in the baseline incidence of delirium and the nature of different interventions that also influence coma incidence may have influenced our results (62). Future studies evaluating the association between delirium duration and mortality, should incorporate coma as an independent outcome.

There are important limitations to the data included in the review. We restricted our search to English language studies, did not search the gray literature, and were not able to obtain duration of delirium data from two authors. Although 13 published randomized trials have evaluated the effect of interventions to reduce delirium in the ICU on duration of delirium and death, these studies were highly clinically heterogeneous. Specific statistical techniques (e.g., sensitivity analysis) were thus required. This heterogeneity among the included studies we included may have masked different effects of specific interventions on the duration of delirium and its relationship with mortality. Furthermore, since each intervention was

evaluated only within one or two trials, we could not assess whether differences across studies were due to chance or real differences. Thus, our main analyses evaluated the effect of the category of “delirium-reducing interventions” rather than any specific intervention.

Since our primary question of interest was whether interventions that are more effective at reducing delirium duration are also more effective at reducing mortality, not the effect on delirium duration per se on mortality, we believe the meta-regression of the association is informative in its suggestion of a lack of association between reduction in delirium duration and short-term mortality. Multivariate meta-analysis would have been a preferable analysis to explore the simultaneous treatment effects on the two outcomes. Since this algorithm failed to converge, the meta-regression constituted a reasonable alternative analysis. The individual studies included in our systematic review were generally underpowered to assess short-term mortality, resulting in rare events in many studies and wide confidence intervals for the RR of death. This lack of heterogeneity in treatment effect on mortality may also largely explain the lack of heterogeneity in the meta-regression of delirium duration and death and thus reduced the likelihood of our finding a relationship between these two outcomes.

Another concern is the possibility of publication or reporting bias, wherein unpublished studies (or results) are systematically different than available evidence. We aimed to minimize the reporting bias by contacting authors of studies with missing data. We successfully retrieved both delirium duration and mortality data for 13 of 17 trials (2 missing duration data, 2 missing mortality data). We found no reason to suspect that data were omitted in a biased manner. We also found no reason to suspect that unpublished studies would indicate a different association between delirium duration and mortality.

While our analysis suggests that treatments effective at reducing delirium duration may also not reduce short-term mortality, appropriate analyses within (existing or new) RCTs that are adequately powered to test for mortality are needed to further evaluate this relationship. The meta-regression across studies can only be hypothesis-generating and speak only to an association, not causation, between the outcomes. While multivariate meta-analysis would have been a preferable meta-analysis tool, results from such an analysis would still be only hypothesis-generating. Within-study (or patient-level meta-analyses) are needed for more definitive conclusions.

Duration of delirium may be related to other factors such as changing severity of illness, the use (or avoidance) of ICU interventions that may influence mortality or practice misalignment between intervention and controls groups (1)(63–4). If an intervention reduces delirium but not the underlying severity of illness, that intervention may not improve mortality. Moreover, while the APACHE II score was used to define severity of illness in each study, it is a poor predictor of mortality in current ICU practice (65). Severity of illness may influence both delirium incidence and mortality; once delirium has occurred, use of interventions to decrease delirium duration may not influence short-term mortality. Lastly, given that a number of recent studies have demonstrated that an association exists between delirium duration and longer-term brain dysfunction, and generated substantial debate and

discussion, future studies evaluating an intervention that may reduce delirium duration should incorporate an assessment of longer-term cognitive outcomes (2–4, 10, 66–70).

CONCLUSION

Among RCTs evaluating interventions hypothesized to reduce delirium burden in the ICU, delirium duration is reduced, but our analysis suggests that these treatments may not be associated with reduced short-term mortality. To better answer this question, adequately powered randomized trials testing individual delirium-reducing interventions are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Literature flow

Abbreviations: ICU, intensive care unit.

Figure 2. Meta-analysis of difference in duration of delirium

The data markers indicate the difference in duration of delirium in days. The size of the grey boxes indicates the weight of each study in the meta-analysis.

Abbreviations: DI, daily interruption; N, number analyzed; OT, occupational therapy; PS, protocolized sedation; PT, physiotherapy; SAT; spontaneous awakening trial; SBT; spontaneous breathing trial.

* These studies reported on second control groups that were not included in this meta-analysis.

Figure 3. Meta-analysis of risk ratio for short-term mortality

The data markers indicate the risk ratio for mortality. The size of the grey boxes indicates the weight of each study in the meta-analysis.

Abbreviations: DI, daily interruption; n/N, number of deaths/number analyzed; OT, occupational therapy; PS, protocolized sedation; PT, physiotherapy; RR, risk ratio; SAT, spontaneous awakening trial; SBT, spontaneous breathing trial.

* This study reported on a second control group that was not included in this meta-analysis.

Figure 4. Scatter plot of difference in duration of delirium versus risk ratio for death

Each circle represents a unique study that reported both the difference between treatments in duration of delirium and the risk ratio (RR) for death. The size of the circles indicates the weight of each study in the random effects model meta-regression. The solid line describes the random effects model meta-regression association across all studies of difference in duration of delirium versus RR death ($P=0.11$). The dashed line describes the association excluding the study where the intervention resulted in a longer duration of delirium than the control (46) ($P=0.40$). The equation for each meta-regression line is provided for the logarithm of RR against delirium duration.

Table 1

Description of Study Characteristics

Author (year)	Double-blind design? (Y/N)	Description of study intervention		Method by which delirium evaluated	Duration of study follow-up	Short-term mortality reporting period	Overall Cochrane risk of bias score
		Intervention group	Control group				
PHARMACOLOGICAL INTERVENTION							
Antipsychotic therapy							
Devlin (2010)	Y	Quetiapine 50mg PO q12h; ↑ by 50 mg q24h to 200mg q12h + PRN IV haloperidol (n=18)	Placebo 50mg PO q12h; ↑ by 50 mg q24h to 200mg q12h + PRN IV haloperidol (n=18)	ICDSC by the bedside nurse twice daily	14 days	Hospital admission	L
Girard (2010)	Y	Ziprasidone PO q6h + PRN haloperidol (n=30)	C1: Haloperidol 5mg PO q6h + PRN haloperidol (n=35); C2: Placebo PO q6h + PRN haloperidol (n=36)	CAM-ICU by research team member twice daily	21 days	21 days	L
Hakim (2012)	Y	Postoperative 0.5 mg PO risperidone q12h until either ICDSC=0 or ICDSC 4 (n = 51)	Postoperative placebo q12h until either ICDSC=0 or ICDSC 4 (n=50)	ICDSCby bedside MD q shift; psych. confirmation	Hospital discharge	Hospital admission	L
Wang (2012)	Y	Postoperative haloperidol (0.5 mg IV x 1 then 0.1mg/hr IV x 12 hr) (n=229)	Postoperative placebo (0.5 mg IV x 1 then 0.1mg/hr IV x 12 hr) (n=229)	CAM-ICU by research team member daily	28 days	28 days	L
Clonidine							
Rubino (2010)	Y	Postoperative clonidine (0.5 mg/kg IV x 1 then 1–2 mg/kg/hr) (n=15)	Postoperative placebo (0.5 mg/kg IV x 1 then 1–2 mg/kg/hr) (n=15)	DSM-IV by research team member daily	Extubation	NR	L
Dexmedetomidine							
Pandharipande (2007)	Y	Dexmedetomidine IV 0.15–1.5 mcg/kg/hr +PRN propofol (n=52)	Lorazepam IV 1–10 mg/hr + PRN propofol (n=51)	CAM-ICU by a research nurse twice daily	28 days	28 days	L
Maldonado (2009)	N	Postoperative dexmedetomidine IV (load then 0.2–0.7 mcg/kg/hr) (n=40)	C1: Postoperative propofol IV 25– 50 mcg/kg/min (n=38) C2:Postoperative midazolam IV 0.5–2 mg/hr (n=40)	DSM-IV by a neuropsychiatrist daily	Hospital discharge	NR	H
Reade (2009)	N	Dexmedetomidine IV (load then 0.2–0.7 mcg/kg/hr) (n=10)	Haloperidol IV (2.5mg load then 0.5–2mg/hr (n=10)	ICDSC by the bedside nurse every 4 hours	Hospital discharge	Hospital admission	H

Author (year)	Double-blind design? (Y/N)	Description of study intervention		Method by which delirium evaluated	Duration of study follow-up	Short-term mortality reporting period	Overall Cochrane risk of bias score
		Intervention group	Control group				
Riker (2009)	Y	Dexmedetomidine IV (load then 0.2–1.4 mcg/kg/hr + PRN IV midazolam (n=244)	Midazolam IV (0.02–0.1mg/kg/hr) + PRN IV midazolam (n=122)	CAM-ICU by the bedside nurse daily	30 days	30 days	L
Ruokonen (2009)	Y	Dexmedetomidine IV 0.8–1.4 mcg/kg/hr (n=41)	Standard sedation (midazolam or propofol) protocol (n=44)	CAM-ICU by trained research personnel	45 days	45 days	U
Shehab (2009)	Y	Postoperative dexmedetomidine IV 0.1–0.7 mcg/kg/hr (n=152)	Postoperative morphine IV 10–70 mcg/kg/hr (n=147)	CAM-ICU by the bedside nurse daily	Hospital discharge	Hospital admission	L
Rivastigmine							
Gamberini (2009)	Y	Rivastigmine 1.5mg PO 3x daily (n=56)	Placebo 3x daily (n=57)	CAM-ICU by the bedside nurse daily	Hospital discharge	Hospital admission	L
Van Eijk (2010)	Y	Rivastigmine PO 2.5mg daily up to 6mg twice daily (n=54)	Placebo PO 2.5mg daily up to 6mg twice daily (n=50)	CAM-ICU by the research nurse daily	30 days	30 days	L
NON-PHARMACOLOGICAL INTERVENTION							
Girard (2008)	N	Daily awakening trial - spontaneous breathing trial (n=168)	Usual sedation care-spontaneous breathing trial (n=168)	CAM-ICU by trained study personnel daily	21 days	21 days	L
Schweickert (2009)	N	Early mobilization after daily sedative interruption (n=49)	Usual physiotherapy after daily sedative interruption (n=55)	CAM-ICU by a research team member daily	28 days	28 days	L
Siepe (2011)	N	Maintenance of high intraoperative perfusion pressure (n=44)	Maintenance of low intraoperative perfusion pressure (n=44)	Psychiatric evaluation	30 days	30 days	U
Mehta (2012)	N	Protocolized sedation + daily sedative interruption (n=214)	Protocolized sedation alone (n=209)	ICDSC by a bedside nurse daily	Hospital discharge	Hospital admission	L

Y=yes; N=no; PRN=as needed; PO=by mouth or feeding tube; IV=intravenous; ICDSC=Intensive Care Delirium Screening Checklist; CAM-ICU=Confusion Assessment for the Intensive Care Unit; DSM=Diagnostic and Statistical Manual; NR=not reported; L=low; H= high; U=unclear

Table 2

Description of Patient Characteristics and Pertinent Study Outcomes

Author (year)	Medical (M) or Surgical (S) (%)	Age (years)	Male (%)	Intubated at study entry (%)	Severity of illness at study entry ^C	Prevalence of delirium at time of study entry (%)	Duration of delirium (days)	Method by which duration of delirium reported
PHARMACOLOGICAL INTERVENTION								
Antipsychotic								
Devlin (2010) ^A	M=75	62	56	72	17	100	1.5	Days of delirium
Girard (2010) ^B	M=62	51	57	100	26	50	4	Days of delirium
		C1:54 C2:56	C1:70 C2:61		C1:26 C2:26	C1:46 C2:47		
Hakim (2012) ^B	S=100 (all cardiac)	67	65	0	61 ^D	0	3	Days of delirium
Wang (2012) ^A	S=100 (91% abd.)	75	63	79	9	0	0	Days of delirium
Clonidine								
Rubino (2010) ^A	S=100 (all aortic)	64	67	100	NR	0	0.84	Days of delirium
Dexmedetomidine								
Pandharipande (2007) ^B	M=70	60	58	100	29	61.5	2.5	Days of delirium
Maldonado (2009) ^A	S=100 (all cardiac)	55	65	100	3.3 ^E	0	2	Days of delirium
		C1:58 C2:60	C1:58 C2:68	C1:100 C2:100	C1:3.5 ^E C2:3.5 ^E			
Reade (2009) ^B	M=50	52	90	100	13	30	0	Time to delirium resolution
Riker (2009) ^A	M=86	62	51	100	19	60	1.4	Days of delirium
Ruokonen (2009) ^B	M=53	64	78	100	100 ^F	NR	NR	NR
Shehabi (2009) ^B	S=100 (all cardiac)	72	71	100	NR	0	2	Days of delirium

Author (year)	Medical (M) or Surgical (S) (%)	Age (years)		Male (%)		Intubated at study entry (%)		Severity of illness at study entry ^C		Prevalence of delirium at time of study entry (%)		Duration of delirium (days)		Method by which duration of delirium reported
		I	C	I	C	I	C	I	C	I	C	I	C	
Rivastigmine														
Gamberini (2009) ^B	S=100 (all cardiac)	74	74	70	66	100	100	35 ^G	40 ^G	0	0	2.5	3	Days of delirium
Van Eijk (2010) ^A	S=69	68	70	70	58	NR	NR	20	20	100	100	5	3	Days of delirium
NON-PHARMACOLOGICAL INTERVENTION														
Girard (2008) ^B	M=100	60	64	54	51	100	100	26	27	NR	NR	2	2	Days of delirium
Schweickert (2009) ^B	M=100	58	54	41	58	100	100	20	19	0	0	2	4	Days of delirium
Siepe (2011) ^A	S=100 (all cardiac)	69	65	83	77	100	100	5.2 ^H	5.4 ^H	0	0	NR	NR	NR
Mehta (2012) ^B	M=84	57	60	56	56	100	100	24	23	30 ^I	23	1	1	Days of delirium

^A Reported as mean

^B Reported as median

^C Acute Physiology and Chronic Health Evaluation (APACHE)-II score unless otherwise indicated

^D Percent of patients with New York Heart Association (NYHA) Class III or IV heart failure

^E American Society of Anesthesiologists (ASA) Physical Status Classification System score

^F Patients having a Sequential Organ Failure Assessment (SOFA) score 2

^G Simplified Acute Physiology (SAPS)-II score

^H The European System for Cardiac Operative Risk Evaluation (EuroSCORE)

I=intervention; C=control; abd. = abdominal; NR=not reported

Table 3

Results of Sensitivity Analyses

	Decrease in duration of delirium [net difference (days), 95% confidence interval; P value for comparison]	Short term mortality [risk ratio (RR), 95% confidence interval; P value for comparison]	Change in short-term mortality by delirium duration (P –value from meta-regression)
Overall	0.64 (0.13, 1.15)	0.90 (0.76, 1.06)	P=0.11
Method of delirium assessment			
CAM-ICU	0.11 (–0.34, 0.57)	0.97 (0.73, 1.29)	P=0.80
ICDSC	0.74 (–0.08, 1.57) P=0.46	0.87 (0.70, 1.08) P=0.51	
Predominate ICU admitting service			
Medical	1.06 (0.09, 2.04)	0.89 (0.75, 1.05)	P=0.24
Surgical	0.40 (–0.32, 1.12) P=0.34	0.97 (0.40, 2.34) P=0.51	
Presence of delirium in some or all patients at baseline			
Yes	0.36 (–0.27, 0.98)	0.92 (0.77, 1.09)	P=0.61
No	1.02 (0.25, 1.79) P=0.30	0.67 (0.37, 1.21) P=0.34	
Mortality risk			
Low (5%)	0.13 (–0.26, 0.51)	0.90 (0.77, 1.06)	P=0.43
High (10%)	0.88 (–0.008, 1.76) P=0.48	0.91 (0.77, 1.08) P=0.34	
Use of a pharmacological intervention			
Yes	0.71 (0.02, 1.41)	0.92 (0.70, 1.20)	P=0.50
No	0.59 (–0.75, 1.94) P=0.87	0.67 (0.37, 1.21) P=0.83	
Class of pharmacological intervention			
Antipsychotic	0.82 (–0.86, 2.50)	0.79 (0.35, 1.76)	P=0.75
Alpha-2 agonist	0.59 (–0.75, 1.94)	0.86 (0.64, 1.16)	

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	Decrease in duration of delirium [net difference (days), 95% confidence interval; P value for comparison]	Short term mortality [risk ratio (RR), 95% confidence interval; P value for comparison]	Change in short-term mortality by delirium duration (P-value from meta-regression)
Cholinesterase inhibitor	-0.57 (-3.00, 1.85) P=0.54	2.44 (0.91, 6.59) P=0.31	