Title: Inconsistent relationship between depth of sedation and intensive care outcome: systematic review and meta-analysis

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ABSTRACT

Purpose: To determine the effect of depth of sedation on intensive care mortality, duration of mechanical ventilation, and other clinically important outcomes.

Methods: We searched MEDLINE, Embase, CENTRAL, CINAHL, PsycINFO from 2000 - 2020. Randomised controlled trials and cohort studies that examined the effect of sedation depth were included. Two reviewers independently screened, selected articles, extracted data and appraised quality. Data on study design, population, setting, patient characteristics, study interventions, depth of sedation and relevant outcomes were extracted. Quality was assessed using Critical Appraisal Skills Programme tools.

Results: We included data from 26 studies (n=7865 patients): 8 RCTs and 18 cohort studies. Heterogeneity of studies was substantial. There was no significant effect of lighter sedation on intensive care mortality. Lighter sedation did not affect duration of mechanical ventilation in RCTs (mean difference [MD]: -1.44 days [95% CI -3.79 to 0.91]) but did in cohort studies (MD: -1.52 days [95% CI -2.71 to -0.34]). No statistically significant benefit of lighter sedation was identified in RCTs. In cohort studies lighter sedation improved time to extubation, intensive care and hospital length of stay and Ventilator Associated Pneumonia. We found no significant effects for hospital mortality, delirium or adverse events.

Conclusion: Evidence of benefit from lighter sedation is limited, with inconsistency between observational and randomised studies. Positive effects were mainly limited to low quality evidence from observational studies, which could be attributable to bias and confounding factors.

KEY MESSAGES

What is the key question?

Does depth of sedation effect intensive care mortality and duration of mechanical ventilation, as well as secondary physiological, hospital mortality, resource use, adverse event and life impact outcomes?

What is the bottom line?

Evidence of the effect of sedation depth is limited, with inconsistency between observational and randomised studies. Positive effects from lighter sedation were mainly limited to low to very low quality evidence from observational studies.

Why read on?

Depth of sedation appears to have differential effect on various outcomes. We need to build on the current evidence to determine how to optimise patient outcomes, both within and beyond intensive care.

INTRODUCTION

Mechanically ventilated patients in intensive care receive sedation and analgesia to manage their discomfort. Although these medications are considered important for many patients, there is recognition that both the amount and type of sedation that patients receive are potentially related to patient outcomes (1). Various proposals and guidelines recommend alternative ways of administering sedation or using different sedative agents to improve outcomes from critical illness (1-3). Although interpretation of this literature is challenging due to inconsistent and problematic definitions, evidence suggests lighter sedation is probably beneficial (1). Despite this, recent reports show many ICU patients worldwide continue to be deeply sedated (4-6).

In a recent review of outcomes associated with sedation depth in the first 48 hours of mechanical ventilation across the Emergency Department (ED) and Intensive Care Unit (ICU) lighter sedation was associated with reduced mortality, mechanical ventilation and ICU stay days (7). Given many critically ill patients remain heavily sedated for longer than 48 hours, it would be useful to know if this relationship between sedation depth and patient outcomes extends across patients' entire ICU stay and relates to a range of patient outcomes or only the short term outcomes of mortality and duration of mechanical ventilation and ICU stay. The effect of lighter sedation on selected outcomes was also examined in the PADIS guidelines, however the included meta-analysis incorporated only studies where sedation depth was defined *a priori* (1), with inconsistent evidence identified. These reviews provide some insights into the evidence to guide sedation practice, but both reviews focused on specific subgroups of studies. We therefore considered a review of a wider range of relevant studies appropriate and important.

Objective

To systematically examine the effect of depth of sedation in ICU patients on patient outcomes that extend across the ICU stay and beyond. ICU mortality and duration of mechanical ventilation were co-primary outcomes selected because ICU mortality is patient-focused and duration of mechanical ventilation reflects sedation practice. Secondary outcomes from the five domains of the outcome taxonomy proposed by Dodd and colleagues (8) were selected and included hospital mortality, physiological outcomes (time to extubation, ventilator free days (Vfd) to day 28), resource use (ICU

and hospital length of stay), adverse events (incidence of delirium, self-extubation, reintubation and tracheostomy, ventilator associated pneumonia (VAP)) and life impact outcomes (memories, anxiety, depression and symptoms or diagnosis of PTSD); these latter outcomes mirror those identified as important to patients and family members in a research priority setting exercise (9).

METHODS

The protocol for this systematic review was registered on PROSPERO (CRD42018092554; www.crd.york.ac.uk/prospero/display_record.php?RecordID=92554). Additional detail is available in supplementary materials.

Search strategy

MEDLINE, Embase, Cochrane Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and PsycINFO were searched with the following strategy: (intensive care OR critical care OR critically ill) AND (sedat* OR midazolam OR propofol) AND (length of stay OR mortality OR outcome assessment OR physical function OR psychological OR cognitive OR memories).

We searched for publications reporting randomized controlled, quasi-experimental and before-after trials, and cohort studies (prospective and retrospective) published in English between January 2000 and February 2020.

Types of participants

We included studies in adult patients receiving invasive mechanical ventilation in ICU, including patients who commenced their ventilation in another location, e.g. ED, operating room. We excluded studies: (i) in patients receiving non-invasive ventilation and mechanically ventilated patients not admitted to ICU; (ii) where the intervention included different sedative agents. Studies testing the effect of different sedative agents were excluded because it is not possible to determine if any difference in outcome was due to effect of the different agent or different depth of sedation. We defined our exposure as deeper sedation at any time throughout the period of mechanical ventilation in the ICU. Our classification of depth of sedation as either ‘lighter’ or ‘deeper’ did not need to be (but could be) predefined by study authors, but was based on published information incorporating any objective measures of sedation depth including assessment using a validated sedation assessment

instrument, hourly or daily doses of sedatives. To clarify, studies that tested any intervention (e.g. goal or protocol directed sedation, no sedation), other than different sedative agents, were eligible for inclusion if one group of patients received lighter sedation than another group of patients in the study. Studies were not excluded on the basis of which sedative agent they used, and no attempt was made to control analgesic use, although it is recognised that many have a secondary sedative effect. Only the RASS and Riker Sedation-Agitation Scale (SAS) were accepted as validated instruments (10).

Study selection

Titles and abstracts were screened independently by two researchers, with full text of included studies reviewed by two authors to assess eligibility. Studies where separation of depth into 'lighter' and 'deeper' sedation could not be identified were excluded. Studies including >2 groups based on sedation depth were not included in the meta-analysis but were retained in the additional analyses. Sedation was defined as the use of pharmacological agents that have the primary purpose of calming or inducing sleep, and alternative agents such as analgesics were not included despite acknowledging that secondary effects of sedation are often present. We did not include different outcomes from the same patient cohort, reported in multiple papers, twice in any analysis but this relationship was noted.

Data Extraction

Two authors extracted data on study design, population and setting, patient characteristics, study interventions, measure of depth of sedation (methodology and results) and relevant outcomes.

Assessment of bias

The domains of bias for RCTs and cohort studies were assessed consistent with current guidance (11,12). Relevant confounding factors were not identified *a priori*, but were based on the study method and cohort and included demographic, clinical, and treatment variables with the potential to influence relevant outcomes. No studies were excluded on the basis of quality assessment.

Data Analysis

Two authors extracted data on study design, population and setting, patient characteristics, study interventions, measure of depth of sedation (methodology and results) and relevant outcomes. All studies that contained data suitable for inclusion in at least one meta-analysis were included in the

quantitative analysis. Continuous data were analysed as means and standard deviations. Where the median and inter-quartile range was reported, these were converted to mean and standard deviation using a standard method (13). Dichotomous data were analysed as risks and relative risks. Random effects meta-analyses were undertaken with the meta package (14) in R (15). This allowed for both within and between studies variance to be calculated, the latter being reflected in a statistical test of heterogeneity. Cohort studies and RCTs were analysed separately based on an *a priori* decision. The quality of evidence was rated using Grades of Recommendation, Assessment, Development and Evaluation (GRADE) (16). For outcomes where significant methodological differences occurred (e.g. different instruments or time points) results were combined descriptively.

Sensitivity analysis

Categorisation of patients into 'lighter' and 'deeper' sedation groups could be based on either a difference in RASS or SAS scores, a difference in average dose of sedation over time (hourly/daily) or a combination of both. Due to the potential differential effect of sedation amounts on patients' sedation levels, a *post hoc* decision was made to repeat meta-analyses incorporating only those studies where categorisation was based on RASS or SAS scores alone or in combination with sedation dose, i.e. to exclude studies where categorisation was based solely on sedation dose. Similarly, a post hoc analysis of cohort studies to examine the influence of the temporal nature of the design (i.e. prospective or retrospective) was conducted.

RESULTS

After removal of duplicates, 3390 articles were identified (Figure 1), with full text of 116 articles assessed. Ninety were excluded: 69 met exclusion criteria; and 21 because, although patients were in groups, levels of sedation did not differ between the groups.

Twenty-six articles reporting the results of 23 studies incorporating 8575 patients remained for descriptive synthesis with 17 articles (7027 patients) included in a meta-analysis for at least one outcome (17-33). The included papers reported results prospective (n=16; n=5534) and retrospective (n=2; n=2028) cohort studies and randomised controlled trials (n=8; n=1534) published between 2001 and 2020 conducted across Asia (n=2), Australia and New Zealand (n=3), Europe (n=10), Middle-east (n=1) and North (n=7) and South America (n=4) (Table S1). Depth of sedation was measured either

using sedation assessment instruments or average doses of sedatives or a combination of both (Table 1, Table S2). The level of sedation that constituted 'lighter' or 'deeper' sedation was inconsistent across studies.

Risk of bias was highly variable in the cohort studies. In the RCTs risk of bias was more consistent, with lack of blinding being the main source of bias. Blinding of participants and personnel was not possible and blinding of outcome assessors was rare (Figure S1, Table S3). There was infrequent incorporation of relevant confounding factors into analysis in cohort studies (Figure S2, Table S4). Included studies addressed both our primary outcomes, and secondary outcomes within the five domains of mortality, physiological outcomes, resource use, adverse events and life impact outcomes (8) (Table S5), with most outcomes assessed in meta-analyses (Table 2). Outcomes within the life impact domain could not be pooled, but a descriptive synthesis of results related to memory and psychological function is provided (Table 3). Studies not included in the meta-analyses are synthesised under Additional Analyses.

Primary Outcomes

ICU Mortality: When comparing lighter versus deeper sedation we found no difference in ICU mortality in either RCTs or cohort studies (Table 2, Figure 2).

Duration of mechanical ventilation: We found no difference in duration of mechanical ventilation in the RCTs comparing lighter versus deeper sedation, but identified reduced duration of mechanical ventilation with lighter sedation in cohort studies (MD -1.52 days [95% CI:-2.71 to -0.34], I^2=87%, 8 studies, 3304 participants) (Table 2, Figure 2).

Secondary Outcomes

***Hospital Mortality*:** Pooled data from 5 RCTs and 5 cohort studies showed no difference between lighter and deeper sedation on hospital mortality (Table 2, Figure S3).

Physiological outcomes: Pooled data from 4 RCTs and 2 cohort studies showed no difference between lighter and deeper sedation on 28-day Vfd (Table 2, Figure S4). There was no difference in time to extubation in a single RCT, but cohort studies reported reduced duration with lighter sedation (MD -3.77 days [95% CI:-5.49 to -2.06], I^2=98%, 2 studies, 2132 participants). Pooled data from 4

RCTs and 4 cohort studies showed no difference between lighter and deeper sedation on incidence of delirium (Table 2, Figure S4).

Resource Use: Pooled data from 6 RCTs showed no difference between lighter and deeper sedation on ICU LOS or hospital LOS, but a significant reduction favouring lighter sedation was identified in ICU and hospital LOS in cohort studies (8 and 6 studies respectively Table 2, Figure S5). Lighter sedation had no effect on frequency of tracheostomy (4 RCTs, 2 cohort studies; Table 2).

Adverse Events: We found no difference between lighter and deeper sedation on self-extubation (2 RCTs, 3 cohort studies) or reintubation (5 RCTs, 2 cohort studies) (Table 2, Figure S6). Lighter sedation had no effect on risk of VAP in 1 RCT, although data from 2 cohort studies showed a reduced risk with lighter sedation (RR 0.56 [95% CI:0.33 to 0.96], I^2=51%, 1906 participants) (Table 2, Figure S6).

Sensitivity analyses

Meta-analyses, incorporating only those studies where RASS or SAS data were available to categorise patients as lighter or deeper sedation, were repeated on outcomes where studies existed. Results were largely similar, although fewer significant differences were identified (Table S6).

Meta-analyses examining the influence of the temporal nature of the design in cohort studies, i.e. prospective or retrospective, were conducted. Results were largely similar to the overall results, although analysis of only the prospective studies substantially reduced the heterogeneity when examining ICU and hospital mortality and hospital length of stay but had no effect on heterogeneity in relation to other outcomes (Table S7).

Additional analyses

Nine studies met the inclusion criteria, but were excluded from all meta-analyses for reasons detailed in the Methods (34-42). The main reasons were single group cohort studies with multivariable regression analysis (35,39) or more than 2 groups of patients not able to be combined based on sedation depth (34,40), as well as variable time points and methods for outcome measurement. In addition, some studies (where the primary outcome has been incorporated in meta-analyses above) incorporated life impact outcomes as secondary measures, however differences in methods of

outcome assessment precluded a meta-analysis of life impact outcomes. A descriptive synthesis is provided here.

Mortality, physiological outcomes and adverse events: A positive relationship between deep sedation and increased mortality (35,39) and increased duration of MV (39,40) was reported in cohort studies, but depth of sedation was not associated with MV duration across different stages of implementation of a sedation protocol and education intervention (34). A relationship between deeper sedation and both delirium (39) and VAP (34) was identified.

Life Impact: Outcomes reflecting the impact of sedation depth on a person's life focused only on memories and psychological health measured in 10 studies using a variety of instruments at different times (Table 3). There was some evidence of a relationship between sedation depth and presence or type of memories that patients reported. In a cohort study of 128 Brazilian patients, those who received any sedation reported less real memories (21[24%] vs 29 [69%]), more illusionary memories (7[8%] vs 0) and more amnesia (16[19%] vs 4[10%]) than patients who received no sedation (40). In a cohort study of 313 Swedish patients increased time deeply sedated was associated with having no recall of ICU (odds ratio [OR]:1.60, 95% CI:1.35–1.91) (37). In further analysis of the same cohort, patients who spent more time awake were more likely to remember the endotracheal tube (OR:1.45, 95% CI:1.29–1.62) and be bothered by memories of stressful ICU experiences (OR:1.37, 95% CI:1.13–1.67), but sedation depth was not associated with nightmares during recovery (38). In contrast, in 289 patients in Canada and USA, patients with no recall of ICU received lower daily doses of midazolam (26.9 [SD 63.7] vs 82.5 [SD 314] mg), but delusional memories were not associated with higher sedative doses (OR:1.18, 95% CI:0.37–3.81) (41). No difference in frequency or type of memories was reported in 2 studies (27,36) or in studies exploring the relationship between psychological distress and sedation depth (18,24,30,40,42).

DISCUSSION

In this systematic review of data from 26 studies incorporating just under 8000 adult patients there was inconsistent and inadequate evidence of the relationship between sedation depth and patient outcomes. Moderate level evidence from RCTs was identified in relation to the primary outcomes of

ICU mortality and duration of mechanical ventilation, as well as secondary outcomes including hospital mortality, time to extubation, ventilator free days, ICU LOS, incidence of delirium and tracheostomies, however no benefit of lighter sedation was identified in any of these outcomes. Outcomes where benefit of lighter sedation was shown in cohort studies included duration of mechanical ventilation, time to extubation, ICU and hospital length of stay and VAP; the evidence was assessed as very low level for all these outcomes. Reasons for low levels of evidence were multi-factorial but included inconsistency and imprecision, frequently with very high levels of heterogeneity, likely occurring as a result of differences in the primary aim and design of included studies as well as variation in interventions used to achieve lighter sedation. The multi-dimensional nature of factors that influence each of the outcomes also likely influences the inconsistency in results. High levels of heterogeneity potentially occurred as a result of the different designs (RCTs as well as prospective and retrospective cohort studies), the intent of the project (e.g. primarily as a quality improvement project) and the level of sedation and intervention fidelity achieved. The heterogeneity shown in this review highlights the issue of sedation being a complex healthcare invention influenced by multiple factors including agent chose, patient characteristics, protocols and practices, contextual issues within ICUs and individual clinician values and beliefs. These issues increase the relevance of the possible uncertainty highlighted in our review.

There was little evidence of effect of sedation depth on life impact outcomes. There was no evidence that anxiety, depression or symptoms of post-traumatic stress were related to sedation depth (18,24,30,40,42). There was, however, inconsistent evidence of whether, and how, sedation depth might influence the presence and type of memories (18,27,36-38,40,41). The role of memories after critical illness, and the relationship with psychological health, is inconsistent, with some suggestion that intrusive, persecutory or delusional memories may be more harmful than real memories (43), with the possibility that more frightening memories might be associated with greater psychological trauma (44). No evidence of a relationship between sedation depth and delirium was identified in this review, however any potential relationship between sedation, delirium and memories requires further investigation (43).

Few of the included studies identified an *a priori* aim related to sedation depth. Instead, many studies examined the effect of interventions to improve sedation practice, or explored the relationship between sedation and outcomes. Labelling of groups as 'deeper' and 'lighter' sedation in this review may not be appropriate given that 'deeper' sedation in one study could be similar to 'lighter' sedation in another study or setting. For example, RASS -3 indicated moderate sedation in one study (40) and deep sedation in others (17,20), while one pre-post study achieved 'lighter' sedation with a median first RASS score of -4 post-intervention (17). No studies targeted RASS 0 to -1 (alert and calm to drowsy), with the exception of work from Scandinavia examining 'no sedation' (25,29,42). The diversity of clinical practice strategies to achieve lighter sedation also presented challenges. We aimed to summarise whether strategies, whatever their design or content, that targeted deeper sedation avoidance were effective in changing outcomes relative to the comparator.

Recently, a Peruvian multi-centre observational cohort study examining the relationship between benzodiazepine dose and mortality was published (45). In this study benzodiazepine dose was associated with a higher risk of mortality and a significant decrease in Vfd, although it should be noted that 98% of participants were deeply sedated at some point during the study and depth of sedation was assessed using either the Glasgow Coma Scale, Ramsay Sedation Scale or RASS. The primary results of the SPICE-III study comparing dexmedetomidine to usual sedation are also published (6). SPICE-III compared different sedatives and was therefore ineligible for this review. However, it is worth noting that although the dexmedetomidine group had a slightly higher proportion of patients with lighter RASS scores (56.6% vs 51.8%), no difference in outcomes was observed. In two French studies also not meeting our inclusion criteria, one multicentre study found no difference in Vfd or mortality with the introduction of an oversedation prevention strategy (46), while a single centre study found reduced duration of mechanical ventilation by stopping sedation immediately after ICU admission (47). The most recent relevant study published was the Danish NONSEDA study where a strategy of no sedation was compared to light sedation (25). In this high quality RCT with clear separation in sedation levels, a non-significant trend towards higher mortality in the non-sedated

group was identified, emphasising the need for a strong body of evidence to illuminate the effect of sedation depth on a range of patient outcomes.

The reasons for reporting the effects of sedation depth on clinical outcomes from cohort studies alongside those from RCTs deserves attention. Changing sedation practice frequently requires an integrated or bundled approach to sedation assessment and management to achieve cultural change of clinician behaviour (2,48). Cohort (before and after) studies are more amenable to achieve practice change than randomised studies. Once a shift in clinicians' sedation management behaviour has been learned, it can be difficult to apply earlier (usual care) practices when patients are randomised. The RCTs in this review all randomised at the patient level. So, although cohort studies provide lower quality evidence than RCTs, in the area of sedation practice they have provided a pragmatic method for studies designed to modify sedation depth. To improve the quality of evidence, we recommend cluster randomised trials to address the weakness of intervention contamination in patient level randomisation and improve the quality of evidence. We have also provided ratings of evidence using the GRADE criteria (16), although we note the limitations of this system in that it is based on subjective judgements and does not take into account the benefits of various study methodologies as outlined above.

There have been multiple calls in clinical guidelines and opinion papers for lighter sedation in ICU patients (1,2); these calls have been based on sub-sets of the available evidence (7) or individual studies (e.g. (28,49). In response to these calls, multiple strategies have been proposed to achieve lighter sedation including protocols (50), expert staffing patterns (51) and daily interruption of sedation (52). To date, systematic reviews have not identified consistently useful strategies (53,54), although reviews are ongoing (55).

This review represents the most comprehensive description of the current evidence related to sedation depth and patient outcomes. Despite the use of liberal inclusion criteria, and a wide range of outcomes examined, the certainty of evidence remains low and inconsistent. Additionally, the findings are limited by the variable nature of how 'lighter' and 'deeper' sedation were determined in the studies, the lack of control of analgesic agents and the frequent lack of determining this differentiation *a priori*

or indeed stating it as an aim. In some studies, the only measure of sedation depth was average dose of sedation, which may not reflect sedative effect on the individual patient. Ideally validated sedation scores such as RASS or SAS should be used to indicate the actual depth to which a patient is sedated. Yet, despite a sensitivity analysis of studies where the difference in sedation depth was based on RASS or SAS, the lack of consistency in effect on patient outcomes remained. The review only included studies that used sedation assessment scales validated for use in the ICU environment in international practice guidelines (10), and thus may have had the effect of biasing the meta-analysis. The review was also limited by including English language publications and published data only. The preponderance of cohort studies including those using two groups of patients before and after a behaviour change intervention, and the implicit limitations of them, represents a limitation of this body of evidence. There was also no examination of the effect of sedation depth on related activities such as early mobilisation or on infrequently measured adverse events such as thromboembolic events.

Based on the low certainty of evidence, there is an urgent need for systematic evaluation of the effect of sedation depth on patient-centred outcomes to provide direction for sedation management. Studies addressing this question should use a randomised controlled trial design, ideally with randomisation at cluster level to achieve cultural change in clinician behaviour. Studies should incorporate *a priori* identification of target 'light' sedation levels, based on individual patient need, and the effect on a range of patient-centred outcomes (56,57) should be assessed.

Despite inconsistency in results, all clinical benefits identified in this review were related to lighter sedation, and importantly this review did not identify any harm related to lighter sedation. In this context, strategies to embed lighter levels of patient sedation in critical care are warranted. The challenging and multi-dimensional nature of sedation practice has been identified (58), and additional evidence-based strategies are urgently needed to optimise sedation and related areas of care such as early mobilisation.

CONCLUSION

Despite a considerable body of evidence discussing the relationship between sedation depth and various outcomes, we identified low to very low quality evidence suggesting that lighter sedation may be beneficial in some patient outcomes. The inconsistency of this evidence is exacerbated by the variable risk of bias in included studies, the different evidence of impact between RCTs and cohort studies, the inconsistent evidence of benefit across different outcomes and the inconsistent methods used, preventing combining data in meta-analyses. Future studies using rigorous controlled trial designs measuring patient centred outcomes, with randomisation occurring at the cluster level, are needed to understand the benefits associated with lighter patient sedation across a range of patient outcomes.

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Table 1 Criteria used in studies to separate 'deeper' vs 'lighter' sedation[1]

Study	Control / 'deeper' sedation	Intervention / 'lighter' sedation
Balzer 2015	Patients had >85% RASS scores ≤-3 First RASS -5[-5 to -4] Time to reach first RASS>-3:79[52-141]hrs	First RASS: -4[-5 to -1], p< 0.001 Time to reach first RASS >-3: 11 [5-20] hrs, p= 0.001
Bugedo 2013	Midazolam: 0.03[0.01-0.06] mg/kg/hr Fentanyl: 0.6[0.1-1.4] mcg/kg/hr Proportion: SAS 1–2:55%; SAS 3–4:37%	Midazolam: 0.01[0-0.03] mg/kg/hr, p<0.001 Fentanyl: 1.5[0.8-2.4] mcg/kg/hr, p<0.001 Proportion: SAS 1–2:44%; SAS 3–4:49%, p=0.001
Burry 2015	Midazolam: 97.0±200.8 mg/patient/day Fentanyl: 1.9±3.5 mg/patient/day	Midazolam: 64.7±245.8 mg/patient/day, p<0.0001 Fentanyl: 1.1±2.0 mg/patient/day, p<0.0001
Dale 2014	Hrly benzodiazepine dose: 0.23±0.018 mg Total benzodiazepine dose: 49.2±156.5 mg 24 hr weighted av. RASS: -1.30±0.026	Hrly benzodiazepine dose: 0.15±0.011 mg, p<0.01 Total benzodiazepine dose: 17.2±53.6, p<0.01 24 hr weighted av. RASS: -0.99±0.023, p <0.01
Faust 2016	RASS (median): -2.57[-3.23 to -1.40] % RASS scores -3 to -5 in first 24 hrs: 46.8±46.9%	RASS (median): -1.25[-2.3 to -0.40], p=0.001 % RASS scores -3 to -5 in first 24 hrs: 27.3±37.3%, p=0.006
Guttormson 2011	Classed as 'minimally arousable' based on Sedation Intensity Score	Classed as 'easily arousable' based on Sedation Intensity Score
Khan 2014	RASS scores – weekdays: median -4 RASS scores – weekends: median – 5	RASS – weekdays: increased by 0.88, p <0.0001 RASS – weekends: increased by 1.20, p <0.0001
Mehta 2012[2]	Midazolam: 102±326 mg/pt/day Fentanyl: 1780±4135 µg/pt/day	Midazolam: 102±326 mg/pt/day, p=0.04 Fentanyl: 1070±2066 µg/pt/day, p<0.001
Nassar Junior 2014	SAS scores: 3.2(2.6-3.7) Midazolam: 45(0,201) mg, Fentanyl: 1500(520-4215) mg	SAS scores: 3.6(3.4-4.0), p=0.035 Midazolam: 0(0.0-0.05) mg, p<0.001 Fentanyl: 300(100-1520) mg, p=0.004
Olsen 2020	Midazolam mg/kg/hr (day 2-28):0.000187 (0-0.003410) Propofol mg/kg/hr (day 1-2):0.84 (0.29-1.2); (day 3-28):0.0064 (0-0.034) Mean RASS: Day 1: -2.3; Day 7: -1.8	Midazolam mg/kg/hr (day 2-28):0(0-0.000005); NS Propofol mg/kg/hr (day 1-2): 0.22(0-0.054); Diff: -0.62 (-0.72; -0.53); (day 3-28): 0(0-0.013); Diff: -0.0063(-0.874; -0.0037) Mean RASS: Day 1: -1.3; Day 7: -0.8
Quenot 2007	Midazolam: 92±59 mg/pt/day Propofol: 2900±1400 mg /pt/day	Midazolam: 44±31 mg/pt/day, p=0.001 Propofol: 1840±750 mg/pt/day, p=0.01
Ren 2017	Sufentanil: 0.030±0.007 mg/kg/hr Midazolam: 0.029±0.007 mg/kg/hr	Sufentanil: 0.018±0.009 mg/kg/hr, p<0.0001 Midazolam: 0.017±0.009 mg/kg/hr, p<0.0001
Samuelson 2008	Target MAAS: 1 – 2 Actual MAAS: median 1.25(1.0)	Target MAAS: 3 – 4 Actual MAAS: median 3.0(0.0)
Sen 2017	Total benzodiazepine dose: 450±701 mg	Total benzodiazepine dose: 74±159 mg, p<0.01
Shehabi 2013	Dexmedetomidine: 20.58(20.58-20.58) µg Midazolam: 0.3(0.23-0.76) mg Propofol: 33.55(13.54-77.07) mg RASS assessments -2 to +1: 38%	Dexmedetomidine:36.55(16.38-13.23)µg, p<0.0001 Midazolam: 0.06(0.02-1) mg, p=0.036 Propofol: 9.89(2.41-22.51) mg, p=0.046 RASS assessments -2 to +1: 66%, p=0.01
Shehabi 2012	RASS -3 to -5 at 48 hours	RASS lighter than -3 to -5 at 48 hours
Strøm 2011	Propofol: 1.40(0.52-2.04) mg/kg/hr Midazolam: 0.01(0-0.04) mg/kg/hr	Propofol: 0(0-1.26) mg/kg/hr, p=0.013 Midazolam: 0(0-0) mg/kg/hr, p=0.003
Strøm 2010	Propofol: 0.77(0.15-1.65) mg/kg/hr Midazolam: 0.003(0-0.024) mg/kg/hr	Propofol: 0(0-0.52) mg/kg/hr, p=0.0001 Midazolam: 0(0-0) mg/kg/hr, p<0.0001
Treggiari 2009	Target Ramsay sedation score 3 – 4 Daily median Ramsay range: 3(2-4.5) to 4(3-5) Daily Midazolam range: 24.2±45.1 to 95.3±124.5 mg	Target Ramsay sedation score 1 – 2 Daily median Ramsay range: 1(1-2) to 3(1-3) Daily Midazolam range: 3.0±5.0 to 11.7±23.2 mg

1. It was not possible to create 2 categories of 'deeper' or 'lighter' sedation in 7 studies (34-39)
2. 'deeper' sedation group was the intervention (Daily Interruption of Sedation) group

Abbreviations: MAAS: Motor Activity Assessment Scale, RASS: Richmond Agitation Sedation Scale, SAS: Riker Sedation Agitation Scale.

Table 2: Summary of findings

Outcomes	Study Type	Number of studies (participants)	Values for clinical parameters in deep sedation groups for included studies [mean (range) of mean value reported in each study][1]	Effect Estimate & 95% CI (Risk ratio for events[2]; Mean Difference for duration[3])	I^2	Grade rating
Primary Outcomes						
Mortality						
ICU mortality (%)	RCT	4 (725)	28.8 (14.1 – 40.0)	0.82 [0.58 to 1.17][2]	30%	Moderate
	Cohort	3 (2474)	22.6 (2.2 – 38.9)	0.50 [0.13 to 1.86][2]	97%	Very low
Physiological outcomes						
Duration of mechanical ventilation (days)	RCT	2 (165)	6.6 (5.5 – 7.7)	-1.44 [-3.79 to 0.91][3]	20%	Moderate
	Cohort	8 (3304)	7.1 (1.2 – 10.7)	-1.52[-2.71 to -0.34][3]	87%	Very low
Secondary outcomes						
Mortality						
Hospital mortality (%)	RCT	5 (762)	29.8 (12.5 – 46.6)	0.93 [0.75 to 1.15][2]	0%	Moderate
	Cohort	5 (4636)	29.2 (13.7 – 44.7)	0.73 [0.41 to 1.30][2]	96%	Very low
Physiological outcomes						
Time to extubation (days)	RCT	1 (423)	8.0 (8.0 – 8.0)	-0.67 [-1.95 to 0.61][3]	0%	Moderate
	Cohort	2 (2132)	5.6 (3.7 – 7.4)	-3.77[-5.49 to -2.06][3]	98%	Very low
Ventilator free days to day 28 (days)	RCT	4 (910)	15.3 (9.6 – 20.1)	2.62 [-0.09 to 5.34][3]	31%	Moderate
	Cohort	2 (431)	17.0 (10.3 – 23.6)	0.65 [-0.65 to 1.95][3]	0%	Low
Delirium (%)	RCT	4 (556)	30.1 (0 – 52.8)	1.04 [0.88 to 1.23][2]	0%	Moderate
	Cohort	4 (3953)	37.2 (10.7 – 55.3)	1.01 [0.63 to 1.62][2]	95%	Very low
Resource Use						
ICU length of stay (days)	RCT	6 (1462)	14.8 (6.3 – 28.0)	0.28 [-1.46 to 2.02][3]	32%	Moderate
	Cohort	8 (4537)	11.9 (3.7 – 23.7)	-4.30[-7.39 to -1.21][3]	97%	Very low
Hospital length of stay (days)	RCT	5 (762)	27.5 (16.6 – 58.6)	-0.69 [-6.96 to 5.58][3]	80%	Very low
	Cohort	6 (4917)	19.9 (12.3 – 30.7)	-4.21[-7.22 to -1.19][3]	88%	Very low
Tracheostomy (%)	RCT	4 (725)	15.4 (3.3 – 29.3)	1.07 [0.81 to 1.43][2]	0%	Moderate
	Cohort	2 (431)	12.3 (7.7 – 16.9)	0.59 [0.31 to 1.12][2]	0%	Very low
Adverse Events						
Self-extubation (%)	RCT	2 (189)	3.2 (3.1 – 3.3)	1.31 [0.30 to 5.82][2]	0%	Moderate
	Cohort	3 (854)	6.4 (3.1 – 9.0)	1.32 [0.84 to 2.09][2]	0%	Low

Re-intubation (%)	RCT	5 (1348)	7.2 (1.6 – 13.3)	1.45 [0.78 to 2.71][2]	30%	Low
	Cohort	2 (362)	4.2 (1.5 – 6.9)	1.07 [0.43 to 2.65][2]	0%	Very low
VAP (%)	RCT	1 (113)	12.1 (12.1 – 12.1)	0.90 [0.32 to 2.52][2]	0%	Low
	Cohort	2 (1906)	10.8 (6.5 – 15.0)	0.56 [0.33 to 0.96][2]	51%	Very low

Abbreviations: ICU: Intensive Care Unit, RCT: Randomized Control Trial, VAP: Ventilator-Associated Pneumonia

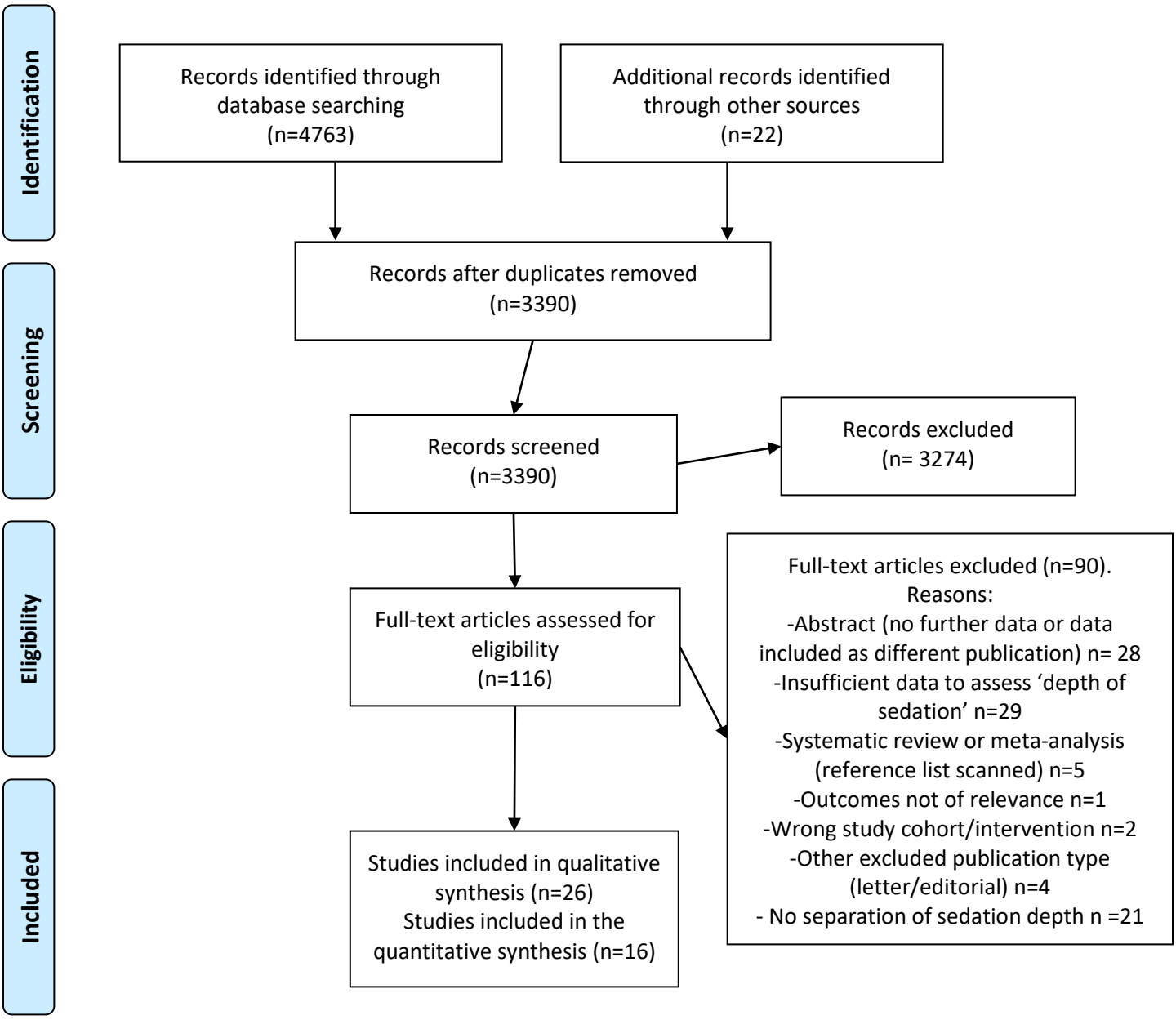
Grade Assessment: RCTs started at high quality; Cohort studies started at low quality (due to risk of bias); Reasons for downgrade included risk of bias (RCTs), imprecision, inconsistency, indirectness.

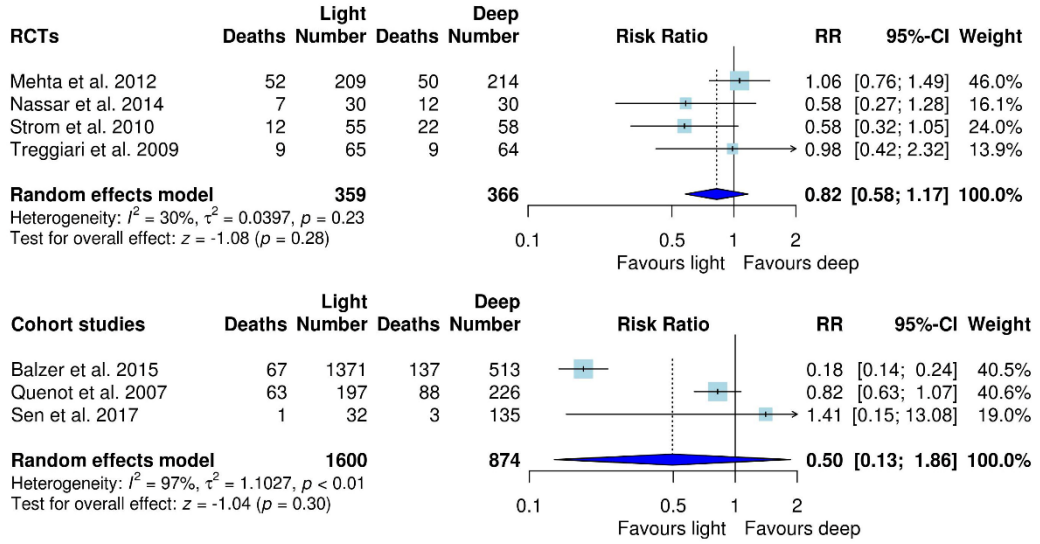
Notes: 1 – Values for clinical parameters in study populations in deep sedation groups for included studies [mean (range) of mean deep sedation group value reported in each study]; 2 – Risk ratio for events; 3 – Mean Difference for duration.

Table 3. Life impact outcomes

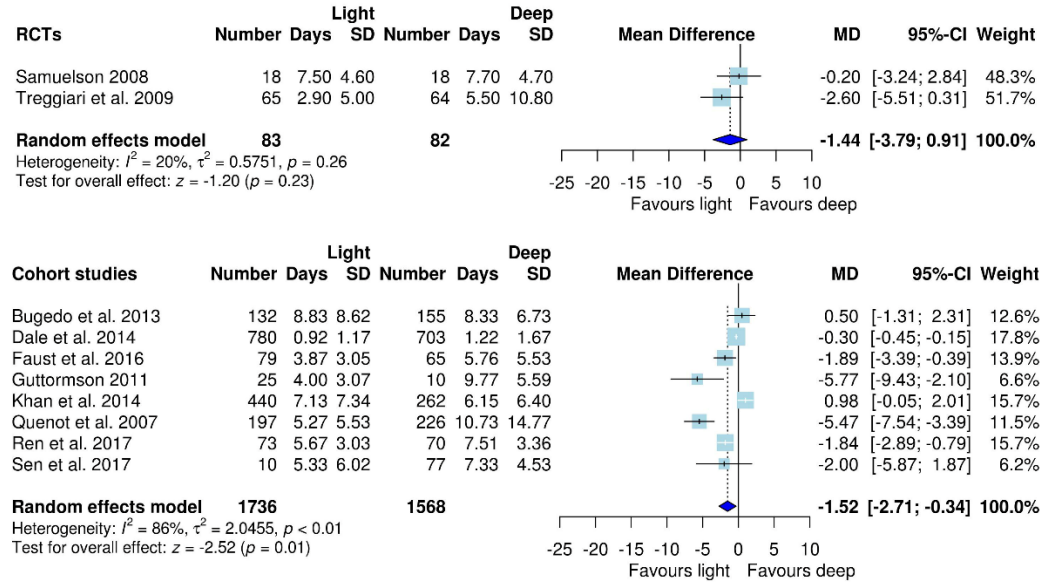
Study	Time point	Outcome measured	Results
Bugedo 2013	1 year post discharge	Screening for memories via telephone interview. Post-Traumatic Stress Syndrome – 10 (PTSS-10) Scale	No difference in incidence of nightmares (n= 22[55%] vs 15[43%], p=0.294), severe anxiety or panic (n= 16[40%] vs 12[34%], p=0.610) or pain (n= 12[30%] vs 13[37%], p=0.513, feelings of suffocation or PTSS-10 (28[19-3(sic)] vs 26[17-38], p=0.840) questionnaire scores between the deep and light sedation groups.
Burry 2015 (sub-study of Mehta 2012)	28 days post ICU discharge	ICU Memory Tool	Patients who reported 'not remembering the ICU' had less sedation (average daily midazolam dose 26.9 [SD 63.7] vs 82.5 [SD 314] mg), but no difference in SAS scores (3.34 [SD 0.70] vs 3.27 [0.65]). In a multivariate model, total midazolam (OR 1.182, 95% CI 0.37 – 3.81) and fentanyl (OR 2.27, 95% CI 0.64 – 8.14) exposure above the mean (deeper sedation) were not associated with increased risk of delusional memories.
Capuzzo 2001	6 months post hospital discharge	Memories explored through semi-structured interviewed, then retrospectively categorised.	No significant difference in recall of factual (A (No morphine/minimal sedatives): n=16[36%]; B (Morphine only): 29[34%]; C (Morphine and sedatives): 4[18%]), sensation (A: n=4[9%]; B: 13[15%]; C: 3[14%]) or emotional (A: n=4[9%]; B: 6[7%]; C: 4[18%]) memories of ICU between the groups.
Costa 2014	Approximately 3 days post ICU discharge	Locally adapted ICU Memory Tool Not specified how anxiety, depression or PTSD were measured	No difference in the incidence of anxiety, depression or PTSD across mild-moderate, deep or not sedation groups. Patients who received any level of sedation reported less real memories (21[24%] vs 29 [69%]), more real and illusory memories (42[49%] vs 9[21%]), more illusory memories (7[8%] vs 0) and more amnesia (16[19%] vs 4[10%]) than patients who received no sedated (p<0.001).
Nassar Junior 2014	6 months post ICU discharge	Impact of Events Scale (IES)	No difference in the level of psychological stress on the IES (22[8-31] vs 16[4-34], p=0.750) between intermittent sedation or daily interruption of sedation groups.
Samuelson 2006	3 – 5 days post ICU discharge	ICU Memory Tool	Deep sedation was associated with amnesia (OR 1.60, 95% CI 1.35 – 1.91) and delusional memories (OR 1.76, 95% CI 1.14 – 2.72) on multivariate analysis.
Samuelson 2007	3 – 5 days post ICU discharge	ICU Memory Tool Locally adapted ICU Stressful Experiences Questionnaire	Patients with memory of ETT had higher proportion of MAAS 3 (awake) than those with no memory (0.56[0.42] vs 0.18[0.42], p<0.0001) - this relationship was confirmed on multivariate analysis (OR 1.45, 95% CI 1.29 – 1.62). Similarly, patients with a higher proportion of MAAS 3 were more likely to be bothered by memories of stressful experiences of ICU (OR 1.37, 95% CI 1.13 – 1.67).
Samuelson 2008	3 – 5 days post ICU	ICU Memory Tool Locally adapted ICU	No difference in memories of ICU (n=15[88%] vs 17[94%], p=0.60), presence of delusional

	discharge & 2 months	Stressful Experiences Questionnaire Impact of Events Scale - Revised	memories in ICU (n=1[6%] vs 6[33%], p=0.09), or memories of pain (n=4[23%] vs 9[50%], p=0.20) between the groups.
Strom 2011	2 years post randomisation	ICU Memory Tool SF-36, Beck Depression Index (BDI), Impact of Events Scale (IES), State Anxiety Inventory, PTSD Symptoms (PTSS) - 10	No difference in psychological problems post-discharge (n=2[15%] vs 6[46%], p=0.20), PTSS-10 score >35 (n=1[8%] vs 0[0%], p=0.14) or any of the other psychological health outcomes between the no sedation and sedation groups.
Treggiari 2009	At discharge and 4 weeks post ICU discharge	PTSD Checklist (PCL) Impact of Events Scale – Revised (IES-R) Hospital Anxiety and Depression Scale (HADS)	No difference in PTSD questionnaire score (discharge: 57±30 vs 52±33, p=0.39; 4 wk follow-up: 56±29 vs 46±29, p=0.07), PTSD symptom clusters, anxiety or depression (discharge: 6.5±4.7 vs 5.3±3.4, p=0.13; 4 wk follow-up: 3.1±3.7 vs 3.4±3.7, p=0.72) scores or cases at either discharge or 4 week follow-up between the groups.


Identification
Screening
Eligibility
Included
Records identified through database searching (n=4763)
Additional records identified through other sources (n=22)
Records after duplicates removed (n=3390)
Records screened (n=3390)
Records excluded (n= 3274)
Full-text articles assessed for eligibility (n=116)
Full-text articles excluded (n=90). Reasons:
-Abstract (no further data or data included as different publication) n= 28
-Insufficient data to assess 'depth of sedation' n=29
-Systematic review or meta-analysis (reference list scanned) n=5
-Outcomes not of relevance n=1
-Wrong study cohort/intervention n=2
-Other excluded publication type (letter/editorial) n=4
- No separation of sedation depth n =21
Studies included in qualitative synthesis (n=26)
Studies included in the quantitative synthesis (n=16)



a)



b)

Figure 2: Forest plots for primary outcome: a) ICU mortality; b) Duration of mechanical ventilation

Note: data converted from median/IRQ to mean/SD[12] for duration of MV in the following studies: Bugedo et al 2013; Dale et al 2014; Guttormson et al 2011; Quenot et al 2007; Sen et al 2017.