# The effectiveness of non-pharmacological interventions in reducing the incidence and duration of delirium in critically ill patients: a systematic review and meta-analysis

Bannon, L., McGaughey, J., Verghis, R., Clarke, M., McAuley, D. F., & Blackwood, B. (2018). The effectiveness of non-pharmacological interventions in reducing the incidence and duration of delirium in critically ill patients: a systematic review and meta-analysis. *Intensive Care Medicine*. Advance online publication. https://doi.org/10.1007/s00134-018-5452-x

**Published in:**
Intensive Care Medicine

**Document Version:**
Peer reviewed version

**Queen's University Belfast - Research Portal:**
Link to publication record in Queen's University Belfast Research Portal

# Title

The effectiveness of non-pharmacological interventions in reducing the incidence and duration of delirium in critically ill patients: a systematic review and meta-analysis

# Short running title

Non-pharmacological interventions for delirium

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# Conflicts of interest

The lead author (LB) has been paid an honorarium for a presentation on non-pharmacological interventions for delirium management in critically ill patients by Orion pharmaceuticals. Other authors report no conflict of interest.

Word count 3821

# Abstract

**Purpose**: To evaluate the effect of non-pharmacological interventions versus standard care on incidence and duration of delirium in critically ill patients.

**Methods**: We searched electronic and grey literature for randomised clinical trials up to March 2018. Two reviewers independently screened, selected and extracted data. Meta-analysis was undertaken using random effects modelling.

**Results**: We identified 15 trials (2812 participants). Eleven trials reported incidence of delirium. Pooled data from four trials of bright light therapy showed no significant effect between groups (n = 829 participants, RR 0.45, 99% CI 0.10-2.13, P = 0.19, very low quality evidence). Seven trials of various individual interventions also failed to report any significant effects. A total of eight trials reported duration of delirium. Pooled data from two trials of multicomponent physical therapy showed no significant effect (n = 404 participants, MD (days) -0.65, 99% CI – 2.73-1.44, P = 0.42, low quality of evidence). Four trials of various individual interventions also reported no significant effects. A trial of family voice reorientation showed a beneficial effect (n = 30, MD (days) -1.30, 99% CI -2.41- -0.19, P = 0.003, very low quality evidence).

**Conclusions**: Current evidence does not support the use of non-pharmacological interventions in reducing incidence and duration of delirium in critically ill patients. Future research should consider well designed and described multicomponent interventions and include adequately defined outcome measures.



**Keywords:** critical care, delirium, meta-analysis, non-pharmacological interventions, systematic review.

# Introduction

Although delirium is not specific to intensive care units (ICU), Page and colleagues reported an incidence of 45% in a general ICU population including ventilated and non-ventilated patients however incidence is reportedly much higher (up to 80%) in mechanically ventilated critically ill patients [1, 2]. Delirium is also associated with an increased mortality and patients with delirium in ICU are three times more likely to die in the first six months after critical illness [2]. Studies of ICU survivors report up to 60% will have deterioration in their cognitive processes comparable to mild dementia or moderate traumatic brain injury [3, 4]. A recent study reported that these levels of cognitive impairment reduce over time with 40% impaired at 3 months and 24% impaired at 6 months [5]. Additionally, delirium is associated with significantly increased healthcare costs, longer duration of mechanical ventilation, longer ICU stay and long-term psychological problems [6-9].

Findings from surveys conducted in the United Kingdom (UK) and the United States of America (USA), in addition to a large 13 country cohort study report that delirium is often managed with haloperidol as a first choice treatment despite a lack of evidence for its efficacy [10-15]. Guidelines from the Society of Critical Care Medicine found moderate evidence to support non-pharmacological interventions such as early mobility, however there is still confusion about whether or not non-pharmacological interventions are effective in improving delirium outcomes [16]. As opposed to implementing single interventions, multicomponent strategies have been purported to target several risk factors for delirium simultaneously. A systematic review of 21 studies reported that using six or more interventions simultaneously has greater potential to improve clinical outcomes [17]. Furthermore, multicomponent interventions may have efficacious effects even without full compliance. In implementing a multicomponent bundle, Barnes-Daly and colleagues reported that a 10% increase in total bundle compliance translated to a 2% increase in delirium coma free days; and a 10% increase with partial compliance translated to a 15% increase in delirium and coma free days (18).

Studies in non-ICU populations have shown associations between use of non-pharmacological interventions and reductions in delirium incidence [19-21]. Currently there is no clear indication to guide practice on use of non-pharmacological interventions for critically ill patients who have greater risk factors for delirium.

The aim of this review was to evaluate the effectiveness of non-pharmacological interventions compared to standard care or other non-pharmacological or pharmacological interventions on the incidence and duration of delirium and other clinical outcomes in critically ill patients.

# Methods

The protocol was prospectively registered with PROSPERO (CRD42015016625) and published [22]. This paper focuses on findings from the randomised clinical trials (RCTs). We used Cochrane review methodology in protocol development and review conduct. The review is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [23].

## Search strategy

Using synonyms for delirium non-pharmacological interventions and critical care, we searched MEDLINE, EMBASE, CINAHL, all seven databases of the Web of Science, PsycINFO, AMED and the Cochrane library up to March 2018 for potentially eligible studies with no restrictions on language or year of publication. We searched Opengrey (http://www.opengrey.eu/), NHS evidence (https://www.evidence.nhs.uk/) and reference lists of included studies. Ongoing and unpublished trials were identified from metaRegister of Controlled Trials (http://www.controlled-trials.com/mrct/), ClinicalTrials.gov (http://clinicaltrials.gov) and the World Health Organisation International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/). The search strategies for each database are detailed in supplementary appendix A.

## Inclusion and exclusion criteria

We included RCTs of critically ill patients that evaluated the effectiveness of non-pharmacological interventions targeted at prevention or treatment or both compared to usual care (no intervention), different non-pharmacological interventions or pharmacological interventions for reducing the incidence and duration of delirium. Critically ill patients were defined as patients being nursed in an intensive care or high dependence unit of any specialty including cardiac, medical, surgical, neurosurgical, mixed or cancer units following elective or emergency admission. Trials focusing on post-ICU care, requiring specialist staff or equipment and non-randomised studies were excluded.

## Selection of studies, data extraction and quality assessment

Two authors (LB, JMcG) independently searched titles and abstracts for eligibility. The same authors reviewed full texts, performed data extraction, and assessed trial risk of bias using the Cochrane Risk of bias tool [24]. Data extracted included study characteristics, participant's characteristics, intervention and settings, adverse events, risk of bias and outcome data/results. Where necessary, we made attempts to contact study authors for missing data. The data extraction form is presented in supplementary Appendix B.

## Outcome measures

Primary outcomes were (a) incidence of delirium; and (b) duration of delirium. Secondary outcomes were ICU and hospital mortality, sleep quality, cognitive function, adverse events and quality of life measured by a validated tool. We included all outcome measures reported by the authors.

## Analysis

Data were analysed in Review Manager Version 5.3 software [25]. We calculated the difference in means, standard deviation and 95% confidence intervals (CIs) for continuous outcomes. Where necessary, we estimated mean and standard deviation from median and interquartile ranges using a standard approach [26]. For dichotomous data, we described treatment effects using risk ratios (RR) and 95% CIs. Meta-analyses were performed if outcomes from two or more studies with similar interventions were available. We used random-effects models to calculate pooled estimates.

We evaluated clinical heterogeneity by qualitative assessment of study and intervention differences. Statistical heterogeneity was evaluated using the Chi square test ($P < 0.1$, significant heterogeneity) and I2 statistic ($I2 > 50\%$, significant heterogeneity).

We planned to undertake subgroup analyses on paediatric patients, patients receiving mechanical ventilation versus no mechanical ventilation and studies of interventions aimed at prevention or treatment of delirium, but there were insufficient subgroups to do this. We undertook sensitivity analyses on (a) studies judged as having high risk of bias for sequence generation and allocation concealment, and (b) random versus fixed effects models.

Outcome data not suitable for meta-analysis are presented in the Summary of Findings Table 1, or the text. The quality of the evidence was rated using Grades of Recommendation, Assessment,

Development and Evaluation (GRADE) for incidence and duration of delirium, intensive care and hospital mortality, health related quality of life and adverse events [27].

## Results

Of the retrieved 7230 citations, 15 trials including 2812 adult participants were included (Figure 1) [28-42]. No paediatric trials were found.

Trials were conducted in ICU patient populations including: medical [33, 35-37, 42]; surgical [28, 29, 31, 41]; and mixed medical and surgical [30, 32, 34, 38-40]. There were five multi-centred [33, 37, 38, 40, 42] and ten single-centred trials [28-32, 34-36, 39, 41]. Sample sizes ranged from 15 to 734 participants. Trials were conducted in the USA [33, 35, 37, 40]; Japan [28, 29]; Italy [36]; Canada [38]; Belgium [32]; Netherlands [30]; Chile [34]; UK [41]; Turkey [42]; Thailand [31]; and Korea [39]. Interventions included: physical [35] and physical with occupational [33] therapy; bright light therapy [28-31]; range of motion exercises [42]; earplugs [32]; multicomponent orientation and cognitive stimulation protocol [36]; multicomponent occupational therapy including positioning, cognitive training, relative involvement [34]; a mirrors intervention [41]; multicomponent targeting risk factors for delirium [39]; protocolised weaning and daily sedation interruption [38]; re-orientation using family voice [40]; and paired awakening and breathing [37]. We found no trials comparing one intervention against another or a non-pharmacological against a pharmacological intervention. Usual care was either unreported or reported variably among ICUs and generally determined by the medical team in charge. Usual care groups did not mandate any pharmacological treatments for delirium however these were administered as directed by the medical team.

All 15 trials evaluated delirium: 11 reported incidence of delirium [28-32, 34, 36, 38, 39, 41, 42] and seven reported duration of delirium in days [30, 33, 35, 37, 40-42]; nine reported delirium as a primary outcome [29-32, 34, 36, 39-41], three as a secondary outcome [33, 37, 38] and three did not specify [28, 35, 42]. Trials screened for delirium using the CAM tool [34], CAM-ICU tool [30, 31, 33, 35-37, 39-42]; ICDSC [38]; or Neecham tool [28, 29, 32]. Five studies clearly specified that interventions were targeted at prevention of delirium in the title or abstract of the paper [28, 32, 39, 40, 42], 10 studies did not clearly specify if interventions were targeted at prevention or treatment of delirium. Follow-up periods were either not reported [31, 36, 40] or reported at five days [28, 29, 32], 12 weeks [41], ICU discharge [42], hospital discharge [34, 38], 28-day follow up [30, 33, 39], 6 months [35] and 1 year follow up [37].

A table of included study characteristics are in supplementary Appendix C and excluded and unclassified studies are presented in supplementary Appendices D and E.

## Methodological quality and risk of bias

The risk of bias within studies is presented in supplementary Appendix F. Blinding of participants and personnel was not possible in all trials due to the nature of the interventions being tested. In eight trials, blinding of outcome assessors was not undertaken [29, 38] or was unclear [28, 36, 37, 39, 40, 42]. Furthermore, there was unclear random sequence generation and allocation concealment [29, 42], incomplete outcome data and selective reporting [36], and potential for other bias due to limited information in the paper [29] and in translation [36].

## Primary outcome: incidence of delirium

Eleven trials [28-32, 34, 36, 38, 39, 41, 42] including 2016 participants reported incidence of delirium as an outcome for seven different interventions, but the relatively small number of participants available for each intervention provide little statistical power to detect either beneficial or harmful effects. There was significant clinical heterogeneity due to the variety of interventions. Incidence of delirium ranged from 20% to 62% in the included studies.

Pooled data from four trials of bright light therapy versus no bright light therapy [28-31] did not show any significant effect on incidence of delirium with substantial heterogeneity (n = 829, pooled RR 0.45, 99% CI 0.10-2.13, P=0.19; $I^2$ 69%, P=0.02) (Figure 2). Using GRADE summary of evidence the quality of evidence was very low, downgraded for indirectness, high risk of bias and imprecision.

Sensitivity analyses showed no significant change in the effect (RR 0.44, 99% CI 0.07-2.96, P=0.27) when one trial with unclear risk of bias was removed [29], and with using a fixed effects model (RR 1.03. 99% CI 0.80-1.33, P=0.74).

Seven trials of earplugs [32], occupational therapy [34], multicomponent orientation and cognitive stimulation [36], protocolised sedation with daily sedation interruption [38], multicomponent targeting risk factors [39], structured mirrors [41], and range of motion exercises [42] reported no significant effects (Table 1).

## Primary outcome: duration of delirium

Eight trials [30, 33-35, 37, 40-42] including 1961 participants evaluated seven different interventions and reported duration of delirium. Five trials reported more than one measure for this outcome. Duration of delirium ranged from 1 hour to 4 days in the included studies.

Six trials reported number of days with delirium [33-35, 37, 40, 41] and two reported number of hours [30, 42]. We pooled data from two trials of similar interventions (physical therapy) [33, 35] that showed no significant effect on number of days with delirium (n = 404, Pooled MD (days) -0.65, 99% CI – 2.73 to -1.44, P=0.42; $I^2$ 77 %, P=0.04). Using GRADE the quality of evidence was low, downgraded for indirectness and imprecision. We did not pool data from the remaining trials as the interventions were all different. One trial evaluating family voice re-orientation showed a favourable effect (n=20, MD (days) -1.30, 99% CI -2.41 to -0.19, P=0.003) [40], and the remaining five trials reported no significant effects on number of days with delirium [34, 37, 41] or number of hours with delirium [30, 42] (Table 1 Summary of Findings).

Three trials reported the percentage of time spent delirious. A trial of physical and occupational therapy reported a significantly reduced proportion of delirium days/100 patient days (control 57% versus intervention 33%, P = 0.02) [33]. A trial of intensive occupational therapy reported significantly reduced proportion of delirium days/100 patient days (control 8.2% versus intervention 1 %, P < 0.001) [33]. A trial of standardised rehabilitation therapy reported no significant difference in delirium days/100 patient days (control median 0, IQR 0-9.1) versus intervention (median 0, IQR 0 – 12.5, P = 0.71) [35].

Two trials reported delirium free days. A trial of bright light therapy reported no significant effect (median 27, IQR 16-28) versus control (median 26, IQR, 17-28), P = 0.29 [30]. A trial of family voice reorientation reported a significant difference (P = 0.04) between groups of family voice (mean 1.9, SD 0.99), unknown voice (mean 1.6, SD 1.07) and control (mean 1.6, SD 1.13) [40].

## Secondary outcomes

### Hospital mortality

Hospital mortality was reported in four trials [30, 33, 38, 39]. A trial of a multicomponent intervention targeting risk factors reported a significantly reduced risk of mortality compared to usual care [n = 123, RR 0.32, 99% CI 0.08-1.31, P = 0.04). [39]. There were no significant differences

in mortality reported by the other three trials: protocolised sedation with daily interruption [n = 423, RR 0.98, 99% CI 0.66-1.43, P = 0.87) [38]; physical rehabilitation during sedation interruption [n = 104, RR 0.72, 95% CI 0.27-1.92, P = 0.39) [33]; and bright light therapy [n = 714, RR 0.96, 99% CI 0.64-1.44, P = 0.78] [30].

### Sleep quality

A trial of earplugs used a self-report sleep questionnaire reported a significant improvement in sleep quality after the first night in the intervention group (data not reported, P = 0.04) (32). A trial of bright light therapy used a night-time movement count measured by accelerometer as a surrogate measurement of sleep quality [28]. The researchers reported no significant differences in hourly movement counts to day three and a significantly lower count in the intervention group on day four (1750 vs 400 at 2am; 1500 vs 600 at 4am; 2100 vs 1100 at 6am;and 2600 vs 1600 at 7am; $P < 0.05$ [28].

### Cognitive function

Two trials measured cognitive function with the Mini Mental Scale Assessment (MMSE, range 0 – 30, greater than 24 = normal) [34, 35]. One trial evaluated an occupational therapy protocol and reported a significantly higher MMSE at discharge in the intervention group (median [IQR], intervention 28 [25, 29] versus control 26 [24, 28], P = 0.04) [34] whereas a study of rehabilitation therapy reported no significant effect at hospital discharge and 2, 4 and 6-months with all means and 95% CI above score 24 [35].

### Quality of life

Two trials measured quality of life as a study outcome [35, 41]. A trial of standardised rehabilitation reported no significant differences in the mean (95% CI) for SF-36 physical functioning at 2 months (1.2, -1.8 – 4.3), 4 months (2.3, -0.9 – 5.5) and 6 months (3.4, -0.02 – 7.0); or mental health summary scores at 2 months (0.1, -3.5 – 3.7), 4 months (0.2, -3.2 – 3.6) and 6 months (2.4, -1.2 - 6.0) [35]. A trial of a mirrors intervention found no significant differences in the EQ-5D visual analogue scale at 12 weeks (mean [SD], 73 [19] versus 77 [15] P = 0.127) and EQ-5D index scores (0.87 [0.13] versus 0.87 [0.13], P = 0.95) [41].

### Adverse events

Three trials evaluated adverse events [33, 35, 37]. A spontaneous awakening and breathing versus standard care trial reported a significantly increased percentage of self-extubation in the

intervention group (n=16 versus 6, 6% difference, 95% CI 0.6-11.8, P = 0.03) [37]. However, there were no significant differences in numbers requiring re-intubation after self-extubation. In a study of early physical and occupational therapy there was one event in 498 therapy sessions of desaturation to 80%, one episode of radial arterial line removal, and therapy was discontinued in 4% of all cases due to perceived ventilator asynchrony in the intervention group [33]. In a study of standardised rehabilitation adverse events were similar in both groups [35].

### Additional analyses

We used our findings to calculate the required information size to test a hypothesis that non-pharmacological treatment compared to usual care reduces the incidence of delirium. Based on a 20% relative risk reduction, a baseline risk of delirium in the control group of 45%, two-tailed alpha of 0.05 and power of 90%, we calculated this to be 645 patients per arm.

## Discussion

We included 15 studies that evaluated the effectiveness of non-pharmacological interventions compared to usual care or other non-pharmacological or pharmacological interventions on the incidence and duration of delirium, hospital mortality, sleep quality, cognitive function, quality of life or adverse events in critically ill adult patients. No paediatric studies were included. Study interventions and outcomes were highly variable and as a result data from many studies could not be pooled. Pooling of data from a small number of studies showed that the implementation of single interventions, such as bright light therapy, or multicomponent physical therapy has no significant effect on the incidence (very low certainty of evidence; four studies) or duration of delirium (low certainty of evidence; two studies) in critically ill adult patients.

From twelve non-pharmacological intervention studies measuring incidence or duration of delirium, nine interventions showed no effect. Comparisons across studies were limited due to heterogeneity in terms of interventions delivered (type, number of components, duration, intensity); outcomes reported (specific measurement variable; analysis metric; aggregation method; time-points); and patient populations. Only three trials of three different interventions reported a positive effect on delirium primary outcomes, but due to heterogeneity limitations they provide low quality evidence. A pilot study of a multicomponent intensive occupational therapy intervention delivered twice per day for 40 minutes each session reported a significantly reduced incidence of delirium in addition to

a lower proportion of time delirious and a beneficial effect on cognitive functioning [34]. An incremental physical therapy intervention delivered daily during sedation holds reported a beneficial effect on duration of delirium in days; however the effect disappeared when the findings were pooled in a meta-analysis [33]. Consistent with other systematic reviews [43, 44], the beneficial effect of one bright light therapy trial on incidence of delirium also disappeared when study outcomes were pooled. A discovery was the lack of a positive effect on delirium outcomes for multicomponent risk factor interventions targeting orientation and cognitive stimulation [36, 39] as these strategies have been effective in other patient populations [19, 20]. Interventions may need to be more personalised to their respective population i.e. medical, surgical or cardiac. Some studies recruited small numbers without appropriate sample size calculation, which may have influenced the power to detect an effect on delirium outcomes. There is insufficient evidence to support single or multicomponent non pharmacological interventions. However as delirium has multiple causes, interventions with multicomponent interventions may present a more credible opportunity to target several risk factors simultaneously and further work in this field is ongoing. Indeed, a new multifaceted approach targeting factors to minimise delirium was proposed (eCASH: Early implementation of Comfort and Analgesia using minimum Sedation and Human care), but it has yet to be evaluated in a randomised clinical trial [45].

Additional beneficial patient outcomes were reported for four non-pharmacological interventions including improved sleep quality (earplugs [32] and bright light therapy [28]); physical health at 6-months (standard rehabilitation [40]); and hospital mortality (multicomponent intervention [39]). However, these were small studies and the quality of evidence to support these benefits is very low. The majority of outcomes were measured within the ICU stay except for cognitive function (range discharge to 6-months) and quality of life (range 2 – 6-months).

The strengths of our review were the high quality systematic review Cochrane methodology used to screen, extract data and assess quality independently by two reviewers and the comprehensive search strategy developed with two independent medical librarians.

We acknowledge that there were important limitations in the studies included in this systematic review. There was considerable heterogeneity in the types of interventions studied, how they were delivered, and the outcome measures. Duration of delirium was reported in a variety of ways and this presented difficulties for presentation of data and grading findings in a meaningful way. This underscores the important need for a core outcome measurement set for future trials, which is

currently in development [46]. Many included trials were single centred, included a range of patient populations such as postoperative and cardiac surgery patients or patients with lower severity of illness and where standard care was reported it was variable, limiting generalisability of findings. There was large variation in the interventions studied, including duration of time and intensity of delivery, generating further challenges to drawing strong conclusions from the data.

Inter-professional research into prevention, treatment and management of patients with ICU-acquired delirium has grown considerably over the last 10 years, and a recent review has outlined a proposed research agenda for the next 10 years [47]. Adding to this following our review, we recommend that future clinical trials into non-pharmacological interventions should focus on defined patient populations that would most benefit from patient-centred interventions. The sample size calculation which our systematic review has informed should help trial design. Investigators should clearly and fully describe their interventions, methods and required resources using the template for intervention description and replication (TIDieR) checklist and guide [48]. To overcome the considerable outcome variation that we found, outcomes and their measures should be clearly defined and investigators should use the delirium core outcome set when this becomes available [46]. Additionally, investigators should consider incorporating a process evaluation alongside multicomponent complex trials to identify the barriers and facilitators to successful implementation and sustainability of non-pharmacological interventions [49].

Although pharmacological management of delirium was not the focus of this systematic review, atypical antipsychotics could be considered for short-term use for agitated patients with hyperactive delirium and alpha 2 agonists such as dexmedetomidine may be effective for delirium management but should be used with caution for patients at risk of hypotension or bradycardia [50, 51]. Results of pending trials may provide better evidence to support the use of some of these agents [52].

## Conclusion

There is low to very low quality evidence to suggest that single or multi-component non-pharmacological interventions are effective in reducing the incidence and duration of delirium in critically ill patients. As delirium has multiple causes, multicomponent interventions may be useful in targeting several of these simultaneously. Further robust research may likely change our confidence in the findings. Future research should focus on patient populations with high risk factors for delirium; the feasibility of multicomponent interventions; and should clearly describe interventions and outcome measures.

## Differences between the protocol and the review

We amended the search strategy to identify more relevant information related to non-pharmacological interventions. As we had two primary outcomes and five secondary outcomes, we applied a more conservative 99% confidence interval instead of 95%. We were unable to conduct sub-group analyses as studies did not always report if the intervention was targeting prevention or treatment, or if the sample received mechanical ventilation. Additionally we found no paediatric trials.

## Acknowledgements

The authors acknowledge Mrs Patricia Watt, Mrs Brenda Allen and Mr Richard Fallis from Queen's University Belfast medical library for their invaluable help in developing a search strategy and locating full text of manuscripts. The authors also thank E Alvarez, R Simons, L Denehy, P Black, and C Smith for providing additional information on their studies. This work was funded by a Doctoral Fellowship Award to LB by the Northern Ireland Health and Social Care research and development division.

## Captions for Tables and Figures

Table 1: Summary of findings: non-pharmacological interventions for reducing delirium versus usual care/no intervention

**Fig. 1** PRISMA flowchart

**Fig. 2** Forest plot for incidence of delirium in bright light therapy versus standard care trials

**Fig. 3** Forest plot for duration of delirium (days) in physical rehabilitation versus standard care trials

## E-Supplementary Material

Appendix A: Search strategy.

Appendix B: Data extraction form.

Appendix C: Summary table of characteristics of included studies

Appendix D: List of excluded studies

Appendix E: List of unclassified studies

Appendix F: Risk of bias within studies

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