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RESEARCH ARTICLE

Efficacy of Non-Pharmacological Interventions to Prevent and Treat Delirium in Older Patients: A Systematic Overview. The SENATOR project ONTOP Series

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Abstract

Non-pharmacological intervention (e.g. multidisciplinary interventions, music therapy, bright light therapy, educational interventions etc.) are alternative interventions that can be used in older subjects. There are plenty reviews of non-pharmacological interventions for the prevention and treatment of delirium in older patients and clinicians need a synthesized, methodologically sound document for their decision making.

Methods and Findings

We performed a systematic overview of systematic reviews (SRs) of comparative studies concerning non-pharmacological intervention to treat or prevent delirium in older patients. The PubMed, Cochrane Database of Systematic Reviews, EMBASE, CINHAL, and PsychINFO (April 28th, 2014) were searched for relevant articles. AMSTAR was used to assess the quality of the SRs. The GRADE approach was used to assess the quality of primary studies. The elements of the multicomponent interventions were identified and compared among different studies to explore the possibility of performing a meta-analysis. Risk ratios were estimated using a random-effects model. Twenty-four SRs with 31 primary studies satisfied the inclusion criteria. Based on the AMSTAR criteria twelve reviews resulted of moderate quality and three resulted of high quality. Overall, multicomponent non-pharmacological interventions significantly reduced the incidence of delirium in surgical wards [2 randomized trials (RCTs): relative risk (RR) 0.71, 95% Confidence Interval (CI) 0.59 to 0.86, I²=0%; (GRADE evidence: moderate)] and in medical wards [2 CCTs: RR 0.65, 95%CI 0.49

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Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

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to 0.86, I²=0%; (GRADE evidence: moderate)]. There is no evidence supporting the efficacy of non-pharmacological interventions to prevent delirium in low risk populations (i.e. low rate of delirium in the control group)[1 RCT: RR 1.75, 95%CI 0.50 to 6.10 (GRADE evidence: very low)]. For patients who have developed delirium, the available evidence does not support the efficacy of multicomponent non-pharmacological interventions to treat delirium. Among single component interventions only staff education, reorientation protocol (GRADE evidence: very low]) and Geriatric Risk Assessment MedGuide software [hazard ratio 0.42, 95%CI 0.35 to 0.52, (GRADE evidence: moderate)] resulted effective in preventing delirium.

Conclusions
In older patients multi-component non-pharmacological interventions as well as some single-components intervention were effective in preventing delirium but not to treat delirium.

Introduction
The healthcare system is increasingly demanding rapid access to current research to ensure evidence-based informed decision making and practice. Previously, guideline developers and decision makers were overwhelmed by the number of primary studies; they currently contend with an excess of reviews [1]. The number and variety of systematic reviews (SRs) is rapidly growing. Various sources report that for a single topic several systematic reviews can often be identified [2,3]. Furthermore, there is a tendency to perform systematic reviews of reviews in order to provide clinical decision makers with the evidence they need.

There are several reviews of non-pharmacological interventions for the prevention and treatment of delirium in older patients[4–7]. Delirium is the most common complication of hospital admission in older patients with an incidence rate that varies between 11% and 42% among patients in medical wards[8] and is as high as 80% in some surgical conditions in the post-operative phase[9]. Delirium is associated with increased morbidity, mortality and length of hospital stay as well as increased use of healthcare services and costs[10,11]. Since there is no evidence that pharmacological prevention or treatment of delirium is effective, a great deal of attention has been devoted to non-pharmacological interventions[12–19].

The non-pharmacological interventions to prevent or treat delirium are quite diverse, ranging from simple single component interventions (e.g., music therapy) to complex multicomponent interventions.

This paper describes the methods used to identify all published systematic reviews concerning non-pharmacological interventions for delirium; identifies and critically appraises the primary studies included in the SRs; lists the elements that compose the multicomponent interventions and, based on the components shared among the studies, presents the meta-analyses, critically summarizes the evidence, discusses the limitations and proposes research priorities for future studies.

Methods
This work is part of the ONTOP (Optimal Evidence-Based Non-drug Therapies in Older People) project, a workpackage of a European Union funded FP 7 research named SENATOR (SoftwareENGINE for the Assessment & Optimization of drug and non-drug Therapy in OlderpeRsons). The
ONTOP aim is to undertake a literature search of systematic reviews concerning evidence-based non pharmacological treatments of 15 prevalent medical conditions affecting older people, including delirium[20].

To gather the evidence about non-pharmacological intervention to prevent or treat delirium, the ONTOP Evidence Group was established and took responsibility for defining the clinical questions. To define appropriate clinical question the Group identified a list of outcomes and a list of non-pharmacological interventions deemed relevant independent from the evidence according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) [21]. After three rounds of consultations, important and critical outcomes were identified. For delirium prevention the outcome delirium incidence was considered critical whereas for delirium treatment the outcomes delirium improvement (intended as either a delirium resolution and a reduction in its severity) and functional status (intended as the degree of functional autonomy of the patient) were considered critical. In the present paper only the results of the critical outcomes will be presented. For details see S1 Box, S1 and S2 Tables. For results of secondary outcome see S1 File.

Search Strategy and Inclusion Criteria for Systematic Reviews

The search sources included Cochrane Database of Systematic Reviews, PubMed, PsychINFO, EMBASE and CINAHL (S2 Box).

Two criteria were considered for further evaluation of an abstract: a) a paper defined as a review or meta-analysis, b) the mention of any non-pharmacological intervention for delirium.

Subsequently, full-texts of relevant abstracts were obtained and screened to identify SRs of interest based on:

1. the use of at least one medical literature database;
2. the inclusion of at least one primary study; and
3. the use of at least one non-pharmacological intervention for delirium prevention or treatment for patients of 60+ years of age.

Only studies written in English, Italian or Spanish were considered.

We assessed the methodological quality of each systematic review using the AMSTAR (A Measurement Tool to Assess Reviews) instrument that contains 11-items to appraise the quality[22]. Two reviewers independently assessed the quality of the SRs and disagreement was resolved by consensus.

Inclusion Criteria for Primary Studies

From the included SRs we identified any experimental comparative study, either randomized or nonrandomized, that investigated any non-pharmacological intervention to prevent or treat delirium in older patients. Primary studies were excluded if they were observational studies or before-after studies with historical controls.

Data extraction and management

Extracted data were transferred onto data extraction forms. Information collected included trial characteristics, patients characteristics, intervention and comparator characteristics, and outcome measures.

Pairs of reviewers independently screened titles, abstracts and full-texts of articles. Disagreement was resolved by discussion.
Itemizing the elements of the multicomponent intervention

To better understand the characteristics of the multicomponent interventions, we itemized each element of the multicomponent intervention. This process helped to decide whether or not it was appropriate to perform a formal meta-analysis of different studies.

Risk of bias assessment

Assessment of risk of bias for the included primary studies was carried out using criteria from the Cochrane Collaboration[23]. The domains considered were random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other potential biases (e.g., balance in baseline characteristics). We assigned a risk of bias to one of three categories: low risk, high risk and unclear risk. Two reviewers independently assessed the risk of bias of individual studies and any differences in quality assessment results between raters was resolved through consensus.

Grading the quality of evidence

The quality of evidence was assessed with GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology by a panel of reviewers with experience in geriatrics, internal medicine and methodology.

GRADE assessment took into consideration the risk of bias[24], consistency of results across the available studies[25], precision of the results[26], directness[26], and likelihood of publication bias[27]. Randomized trials were privileged for the GRADE evaluation. Where evidence is without randomized trials the GRADE evaluation is performed for other study designs (e.g., controlled clinical trials). The quality of the evidence was categorized as high, moderate, low, or very low based on the judgments for the primary outcome (delirium incidence for prevention; delirium improvement and functional status for treatment). Summary tables were constructed using GRADEpro version 3.6.

Data Synthesis and Analysis

Where a meta-analysis was possible with at least two studies, DerSimonian and Laird random-effects models were used to pool risk ratios of delirium incidence (Review Manager software version 5.3). We used the Chi² test and I² statistic to assess heterogeneity[23]. We considered heterogeneity to be statistically significant if the P value is less than 0.1. Publication bias was assessed by visual judgment of a funnel plot and by Egger’s regression method.

Results

Systematic reviews

Our search identified 3329 abstracts after excluding 295 duplicates. Among the 80 potentially relevant publications, 26 were considered relevant for inclusion and 54 were excluded (see Fig 1 for study screening process and S3 Table for list of excluded reviews with reasons). The publication year ranged from 1996 to 2014 and 5 reviews were published in 2014.

While all articles used PubMed to search for primary studies, 13 papers also employed CINAHL[5–7,28–37], 11 articles also used the Cochrane Library[7,30,31,34,36,38–43], 10 studies also accessed Embase [7,32,34,36,38,41,43–46], and 3 studies also searched PsychINFO [5,32,36].

None of the SRs was sponsored by a company. Six studies were funded by a governmental institution[7,38,41] or a non-profit organization[5,43,47].
Fig 1. Flow diagram of literature search and study selection.

doi:10.1371/journal.pone.0123090.g001

Potentially relevant reviews identified: 3329 (single records)
Medline (Pubmed): 657
Embase: 2525
The Cochrane Library: 160
DARE: 73
PsycINFO (OVID): 67
CINAHL (EBSCO): 142

Reviews excluded based on title/abstract evaluation: 3249

Reviews identified for full-text evaluation: 80

Reviews excluded with reason:
- Delirium not considered: 54
- Non-pharmacological interventions not considered: 12
- Search strategy not reported: 11
- Review not in English: 3
- No primary studies included: 2
- Not found: 2
- Database searched unclear: 1
- Guideline: 1
- Delirium detection: 1
- No systematic search: 1
- Not a review: 1
- Overview of reviews: 1
- Review of guidelines: 1

Systematic review/meta-analysis included: 26

Primary studies evaluated for inclusion: 78

Primary studies excluded with reason:
- Non-pharmacological intervention not considered: 11
- Delirium incidence not considered: 8
- Historical control: 6
- Secondary publication: 4
- Economic analysis: 3
- Participants age less than 63 years: 3
- Study protocol: 2
- Diagnostic accuracy study: 1
- No control group: 1
- Other: 8

Primary studies identified from SR/meta-analysis: 31
The reviews were heterogeneous. Some reviews, in addition to examining interventions to treat or prevent delirium, also evaluated the pathogenesis of delirium[47], examined the role of sitsers[48], or studied approaches to diagnose delirium[28,39,49]. Only two reviews assessed single component interventions (music therapy[33] and earplugs[50]). The remaining SRs appraised multicomponent interventions.

Three SRs ranked as being of high quality (scoring 8–11), 12 of medium quality (scoring 4–7), and 11 of low quality (scoring 0–3) (S4 Table).

Table 1 summarizes the basic characteristics of the SRs.

Primary studies

Overall the 26 SRs yielded 78 primary studies of which 31 satisfied our inclusion criteria. (see Fig 1 and S5 Table for excluded primary studies).

The identified primary studies are described based on the type of the intervention (single or multicomponent), the aim of the intervention (prevention or treatment), the setting (e.g., surgical), and the study design [randomized controlled trial (RCTs), Controlled Clinical Trials (CCT), and Before After (BA) study].

**Evidence of multicomponent, non-pharmacological interventions to prevent delirium in surgical setting.** Nine studies evaluated the efficacy of multicomponent non-pharmacological interventions to prevent delirium in surgical wards. Two studies were randomized trials [62,63], one was a CCT[64] and six were BA studies[65–70]. Except for Chen et al.[66] all studies assessed patients with hip fractures. The study characteristics are described in Table 2. All studies considered the incidence of delirium as primary outcome except Chen et al.,[66] who investigated functional and cognitive function as the primary outcomes.

The components of the non-pharmacological intervention that were common among the studies are shown in Table 3.

**Methodological issues.** Given the nature of the intervention, all the comparative studies suffered from performance bias because blinding of patients and personnel could not be carried out. However, all the three trials were immune from detection bias[62–64]. Of the two RCTs, only Lundstrom et al.[62] explicitly reported the method of allocation concealment. The non-randomized studies (CCTs and BA studies) were, by their nature, at risk of selection bias. In two of the four BA studies, the outcome assessor could not be blinded, thus raising the possibility of detection bias. Fig 2 summarizes the risk of bias in each study.

**Efficacy**

**Incidence of delirium.** Two RCTs presented data that could be combined, given the similarity between the population samples and the items of the non-pharmacological interventions [62,63]. In fact these two trials had the following interventions in common: comprehensive geriatric assessment, management and rehabilitation, prevention, early detection and treatment of major postoperative complications, oxygen therapy, regulation of bowel/bladder function, nutrition and hydration (Table 3).

The study by Marcantonio et al.[63] reported the cumulative incidence of delirium during hospitalization and used the Delirium Symptom Interview (DSI), the Memorial Delirium Assessment Scale (MDAS), and the Confusion Assessment Method (CAM)[73] to assess delirium. Lundstrom et al.[62] measured delirium based on nurses’ interviews and the modified Organic Brain Syndrome Scale, which was applied at 3–5 days after hospital admission. The pooled results showed that the multicomponent intervention significantly reduced the incidence of delirium by 29% [RR 0.71 (95% CI, 0.59 to 0.86); I20%]. The overall GRADE quality of evidence was judged to be moderate (Table 4).
<table>
<thead>
<tr>
<th>Systematic review</th>
<th>Aim</th>
<th>Search strategy date</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Primary studies on non-pharmacological intervention included/total studies included in the review</th>
<th>Reviews also interested in pharmacological intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alway 2013 [51]</td>
<td>To summarize the evidence of earplugs and eye masks.</td>
<td>Unclear</td>
<td>Critically ill adults</td>
<td>Earplugs and eye masks</td>
<td>Sleep and delirium outcomes</td>
<td>2/7</td>
<td>No</td>
</tr>
<tr>
<td>Bitsch 2004 [47]</td>
<td>To summarize the pathogenesis of postoperative delirium and to identify strategies for prevention and management.</td>
<td>March 2003</td>
<td>Patients with hip fracture</td>
<td>Educational staff, multicomponent intervention, multidisciplinary team</td>
<td>Delirium prevention and treatment</td>
<td>2/12</td>
<td>Yes</td>
</tr>
<tr>
<td>Carr 2013 [52]</td>
<td>To describe the usage, training, clinical and cost effectiveness of sitters in delirium</td>
<td>October 2011</td>
<td>Heterogeneous population including patients at risk of delirium</td>
<td>Use of sitter</td>
<td>Unclear</td>
<td>4/37</td>
<td>No</td>
</tr>
<tr>
<td>Clegg 2014 [53]</td>
<td>To assess the effectiveness of interventions for preventing delirium</td>
<td>April 2013</td>
<td>People (aged 65 + years) in permanent long-term care residence</td>
<td>Multi- or single-component interventions</td>
<td>Delirium prevention</td>
<td>2/2</td>
<td>Yes</td>
</tr>
<tr>
<td>Cole 1999 [28]</td>
<td>To review evidence related to the effectiveness of systematic interventions in preventing or detecting and treating delirium.</td>
<td>March 1998</td>
<td>Any</td>
<td>Educational staff, multicomponent intervention, multidisciplinary team</td>
<td>Delirium prevention and treatment</td>
<td>2/17</td>
<td>No</td>
</tr>
<tr>
<td>Conn 2001 [49]</td>
<td>To outline current approaches to diagnosing and managing delirium in the elderly</td>
<td>1998</td>
<td>Unclear</td>
<td>Family support, multicomponent intervention</td>
<td>Delirium prevention and treatment</td>
<td>1/10</td>
<td>Yes</td>
</tr>
<tr>
<td>Fick 2002[4]</td>
<td>To assess prevalence, associated features, outcomes, and management of delirium superimposed on dementia.</td>
<td>February 2002</td>
<td>Patients with dementia</td>
<td>Multicomponent intervention</td>
<td>Delirium prevention and treatment</td>
<td>2/7</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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### Table 1. (Continued)

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<th>Search strategy date</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcomes</th>
<th>Primary studies on non-pharmacological intervention included/total studies included in the review</th>
<th>Reviews also interested in pharmacological intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fox 2012[7]</td>
<td>To compare the effectiveness of acute geriatric unit care in the acute phase of illness or injury</td>
<td>Unclear (2012?)</td>
<td>Acutely ill or injured adults</td>
<td>Multicomponent intervention</td>
<td>Falls, pressure ulcers, delirium, functional decline, hospital stay, discharge destination, mortality, costs, hospital readmissions</td>
<td>2/19</td>
<td>No</td>
</tr>
<tr>
<td>Gonzales 2003[54]</td>
<td>To assess prevalence, etiology, prognostic factors, diagnosis and management of delirium</td>
<td>Unclear</td>
<td>Any</td>
<td>Multicomponent intervention</td>
<td>Delirium treatment and prevention</td>
<td>1/unclear</td>
<td>Yes</td>
</tr>
<tr>
<td>Greer 2011[5]</td>
<td>To assess prevalence, diagnosis and treatment of delirium</td>
<td>November 2010</td>
<td>Adult inpatients</td>
<td>Educational staff, multicomponent intervention, Multidisciplinary team</td>
<td>Delirium incidence</td>
<td>11/40</td>
<td>Yes</td>
</tr>
<tr>
<td>Hempenius 2011[30]</td>
<td>To assess the efficacy of interventions to prevent delirium and to explore which factors increase the effectiveness of these interventions</td>
<td>July 2009</td>
<td>Patients at risk of delirium</td>
<td>Educational staff, multicomponent intervention, Multidisciplinary team</td>
<td>Delirium incidence</td>
<td>4/16</td>
<td>Yes</td>
</tr>
<tr>
<td>Holroyd-Leduc 2010[38]</td>
<td>To assess the effective interventions for prevention and treatment of delirium</td>
<td>October 2007</td>
<td>Patients aged 65 or older with delirium or at risk of developing delirium</td>
<td>Educational staff, multicomponent intervention</td>
<td>Delirium prevention and treatment</td>
<td>6/11</td>
<td>Yes</td>
</tr>
<tr>
<td>Inouye 2014[56]</td>
<td>To provide an overview of epidemiology, causes, and non-pharmacological and pharmacological management of delirium</td>
<td>August 2012</td>
<td>Any population</td>
<td>Pharmacological and non-pharmacological</td>
<td>Delirium prevention and treatment</td>
<td>13/29</td>
<td>Yes</td>
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<th>Population</th>
<th>Intervention</th>
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<th>Primary studies on non-pharmacological intervention included/total studies included in the review</th>
<th>Reviews also interested in pharmacological intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mak 2010 [34]</td>
<td>To update evidence-based guidelines for the treatment of proximal femoral fractures</td>
<td>June 2008</td>
<td>Patients with proximal femoral fractures</td>
<td>Time to surgery, thromboprophylaxis, anaesthesia, analgesia, prophylactic antibiotics, surgical fixation of fractures, nutritional status, mobilization, rehabilitation and daily proactive geriatrics consultation</td>
<td>Surgical wound closure, management of postoperative delirium, osteoporosis treatment and hip protectors</td>
<td>1/128</td>
<td>Yes</td>
</tr>
<tr>
<td>Marik 2006 [44]</td>
<td>To review the effect of an aging society on the utilization of critical care services and the physiology of aging as it applies to critical illness and prognosis and management issues in the intensive care unit</td>
<td>unclear</td>
<td>Older patients admitted in intensive care unit</td>
<td>Daily proactive geriatrics consultation, bright light therapy, music therapy</td>
<td>Several outcomes of elderly patients admitted to intensive care unit including prevention of delirium</td>
<td>2/5</td>
<td>Yes</td>
</tr>
<tr>
<td>Milisen 2005 [57]</td>
<td>To determine the characteristics and efficacy of multicomponent intervention strategies for delirium</td>
<td>August 2003</td>
<td>Hospitalized older people</td>
<td>Educational staff, multicomponent intervention</td>
<td>Incidence, duration and severity of delirium, change in cognitive functioning, functional rehabilitation, length of stay and mortality.</td>
<td>7/7</td>
<td>No</td>
</tr>
<tr>
<td>Morrison 1998 [58]</td>
<td>To review the evidence for clinical decisions that medical consultants make for patients with hip fracture and to develop recommendations for care</td>
<td>June 1997</td>
<td>Patients with hip fracture</td>
<td>Supportive reorientation and environmental manipulation</td>
<td>Prevention of delirium</td>
<td>1/9</td>
<td>No</td>
</tr>
<tr>
<td>Moyce 2014 [59]</td>
<td>To determine the efficacy of perioperative interventions in decreasing the incidence of postoperative delirium.</td>
<td>January, March, August 2012</td>
<td>Patients receiving non-cardiac surgery</td>
<td>Any</td>
<td>Incidence of delirium within seven days of surgery</td>
<td>5/29</td>
<td>Yes</td>
</tr>
</tbody>
</table>

(Continued)
Combining the former results with the single CCT[64], which had similar characteristics, yielded pooled results which remained statistically significant with no change in heterogeneity [RR 0.71 (95%CI, 0.60 to 0.84)] (Fig 3).

In three of the 5 BA studies the CAM was employed to assess delirium, while a clinical evaluation was used by Williams et al.[70] and SPMSQ and OBS scale was used by Bjorkelund[65]. Moreover, the assessment time points varied considerably; Wong et al.[69] measured the incidence of delirium every month, Williams et al.[70] measured it within 5 postoperative days, while the remaining studies did not provide the time frame. However, an attempt to pool the data across the studies with patients that received orthopedic surgery, in a meta-analysis, yielded a statistically significant result in favor of the multicomponent interventions [RR 0.57 (95% CI 0.39 to 0.85); I² 27%, P = 0.25][67–70].

Evidence of multicomponent, non-pharmacological interventions to prevent delirium in medical setting. Seven studies evaluated the efficacy of multicomponent interventions to prevent delirium in older patients hospitalized in medical departments. Two studies were RCTs [74,75], three were CCTs[76,77,82] and two were BA studies[83,84](Table 5).
### Table 2. Characteristics of Primary Studies. Non-Pharmacological Interventions for Delirium Prevention in Surgical Setting.

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Study period</th>
<th>Setting</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lundstrom 2007</td>
<td>Randomized trial</td>
<td>199 patients with femoral neck fracture aged 70 + (mean age 82), 74% women</td>
<td>Staff education (focusing on the assessment, prevention and treatment of delirium and associated complication): application of comprehensive geriatric assessment, management and rehabilitation</td>
<td>Primary: number of days of post-operative delirium. Secondary: complications during hospitalization, length of stay, and in-hospital and one-year mortality.</td>
<td>May 2000 and December 2002</td>
<td>A specialized geriatric ward or a conventional orthopedic ward</td>
<td>Government, not for-profit.</td>
</tr>
<tr>
<td>Marcantonio 2001</td>
<td>Randomized trial</td>
<td>86 patients 65 + admitted emergently for surgical repair of hip fracture (mean age 79), 79% women,</td>
<td>Proactive geriatrics consultation</td>
<td>Primary: delirium incidence (DSI, (MDAS) (CAM) MMSE) Secondary outcomes: delirium severity (MDAS, CAM), cognitive status (MMSE), length of stay, nursing home discharge</td>
<td>not reported</td>
<td>Orthopedic dept.</td>
<td>Private non-profit.</td>
</tr>
<tr>
<td>Deschodt 2012</td>
<td>Controlled clinical trial</td>
<td>171 people with hip fracture aged 65 and older; female 65%</td>
<td>inpatient geriatric consultation teams</td>
<td>Incidence and duration of delirium (CAM), severity of delirium (Delirium Index), and cognitive status (MMSE)</td>
<td>unclear</td>
<td>Two trauma wards</td>
<td>None</td>
</tr>
<tr>
<td>Björkelund 2010</td>
<td>Before/after study</td>
<td>263 patients with hip fracture, age ≥65 years; female 70%.</td>
<td>Multifactorial intervention (supplemental oxygen, hydration, nutrition, monitoring of vital physiological parameters, adequate pain relief, avoid delay in transfer logistics, daily delirium screening using OBS scale, avoid polypharmacy, and perioperative /anesthetic period protocol)</td>
<td>Delirium incidence (SPMSQ; OBS scale)</td>
<td>April 2003–April 2004</td>
<td>Orthopedic ward</td>
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<tr>
<td>Chen 2011</td>
<td>Before/after study</td>
<td>256 patients (mean age 71, female 46%) undergoing elective abdominal surgery (e.g. gastrectomy).</td>
<td>The intervention (modified Hospital Elder Life Program): daily hospital-based care protocol, which included 3 key protocols, i.e., early mobilization, nutritional assistance, and therapeutic (cognitive) activities 3 times daily.</td>
<td>Primary: functional and nutritional status, cognitive function. Secondary: depressive symptoms, cognitive function, and delirium (CAM)</td>
<td>August 2007–April 2009</td>
<td>Gastrointestinal ward</td>
<td>Government, not for-profit.</td>
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</table>

(Continued)
Yoo et al. evaluated, in a CCT, the efficacy of interdisciplinary intervention by non-geriatricians to prevent delirium. The components of the non-pharmacological intervention in the remaining studies are shown in Table 3. Delirium incidence was a primary outcome in every study except in Asplund et al. [75].

Methodological issues. Of the two RCTs, Asplund et al. [75] did not report the exact method of random sequence generation and the personnel could have been aware of the group

Table 2. (Continued)

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Study period</th>
<th>Setting</th>
<th>Funding</th>
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<tr>
<td>Milisen 2001 [68]</td>
<td>Before/after study</td>
<td>120 patients with a traumatic fracture of proximal femur, median age 81, 80% females.</td>
<td>Education of nursing staff, systematic cognitive screening, consultative services, use of a scheduled pain protocol</td>
<td>Delirium incidence (CAM); severity of delirium; cognitive and functional status (MMSE).</td>
<td>Unclear</td>
<td>Emergency room and 2 traumatological units</td>
<td>Private for profit/Government</td>
</tr>
<tr>
<td>Wong 2005 [69]</td>
<td>Before/after study</td>
<td>99 patients with hip fracture, average age 82 years, female 78%</td>
<td>Ten strategies protocol (oxygen delivery, nutrition and hydration, minimizing medications, regulation of bladder/bowel function, early mobilization, prevention and treatment of major peri- and post-operative complications.</td>
<td>Major outcomes: proportions of subjects with delirium (CAM), discharge destination and length of stay.</td>
<td>15 August and 24 December 2001</td>
<td>Surgical orthopedic setting</td>
<td>Not reported</td>
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<tr>
<td>Williams 1985 [72]</td>
<td>Before/after study</td>
<td>227 patients, mean age 79 years, female 82%</td>
<td>Preventing approaches related to: strange environment, altered sensory input, loss of control and independence, disruption in life pattern, immobility and pain, and disruption in elimination pattern. Ameliorative approaches related to: mild behaviors suggestive of confusion, sundowning, unsafe behavior, hallucinations or illusions, and fright.</td>
<td>Incidence of delirium or acute confusion identified using a score based on 4 types of behaviors.</td>
<td>unclear</td>
<td>Surgical orthopedic setting</td>
<td>Government, not for-profit.</td>
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</table>

DSI, Delirium Symptom Interview; CAM, Confusion Assessment Method; MDAS, the Memorial Delirium Assessment Scale; MMS, Mini-Mental State Examination; OBS, Organic Brain Syndrome

doi:10.1371/journal.pone.0123090.t002
<table>
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<tr>
<th>Study</th>
<th>Observation of Multi-sensory deprivation</th>
<th>Avoidance of Multi-disciplinary team</th>
<th>Sleep protocol</th>
<th>Early mobilization</th>
<th>Pain control</th>
<th>Drug list review</th>
<th>Oxygen delivery</th>
<th>Elimination of unnecessary medications</th>
<th>Study Regulation of bowel/bladder function</th>
<th>Environmental stimuli treatment of agitated delirium</th>
<th>Delirium treatment</th>
<th>Secondary prevention of falls and fractures</th>
<th>Osteoporosis prophylaxis</th>
<th>Family education</th>
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</table>

RCT, randomized controlled trial; CCT, controlled clinical trial; BAS, before-after study; (*) studies that evaluated non-pharmacological interventions to treat delirium

doi:10.1371/journal.pone.0123090.003
allocation with block randomization, therefore the study was judged to be at high risk of selection bias. In addition, Asplund et al.[75] was at high risk of attrition bias, because the data were analyzed per protocol.

In the remaining non-randomized studies despite selection bias is a threat to these studies, the baseline characteristics of the population were well balanced. Fig 2 describes the risk of bias table.

### Efficacy

**Randomized trials.** The two RCTs differed substantially in the patient population evaluated. In Asplund et al.[75] where delirium was not a primary outcome and patients were at low risk of developing delirium, non-pharmacological interventions were not able to prevent delirium [RR 1.75 (95% CI 0.50 to 6.10), GRADE quality of evidence was very low]. Conversely, in Martinez et al.[74] patients were at high risk of delirium (age >70 years, a documented cognitive impairment, alcoholism and metabolic imbalances) and the multicomponent intervention, which was performed by family members, was able to reduce the incidence of delirium (evaluated daily with the CAM) by 58% [RR 0.42 (95% CI 0.19 to 0.92)GRADE quality of evidence was low][74].

**Controlled clinical trials.** Two of CCTs investigated very similar patient populations (patients at intermediate/high risk of delirium), and type of multicomponent interventions...
Table 4. GRADE quality of evidence summary table for the comparisons of multicomponent non-pharmacological interventions with usual care for delirium prevention or treatment.

<table>
<thead>
<tr>
<th>Quality assessment for comparison</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delirium incidence in surgical setting</td>
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<tr>
<td>Non-pharmacological intervention</td>
<td>76/164 (46.3%)</td>
<td>0.71 (0.59 to 0.86)</td>
<td>+++</td>
<td>Moderate (a)</td>
</tr>
<tr>
<td>Usual care</td>
<td>105/161 (65.2%)</td>
<td>17 fewer per 100 (from 8 fewer to 24 fewer)</td>
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<tr>
<td>Relative risk (95% CI)</td>
<td>Absolute</td>
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<td>Delirium incidence in medical setting (Multicomponent intervention provided by family members)</td>
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<tr>
<td>Non-pharmacological intervention</td>
<td>8/144 (5.6%)</td>
<td>0.42 (0.19 to 0.92)</td>
<td>++</td>
<td>Low (b)</td>
</tr>
<tr>
<td>Usual care</td>
<td>19/143 (13.3%)</td>
<td>35 fewer per 100 (from 5 fewer to 48 fewer)</td>
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<td>Delirium incidence in medical setting</td>
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<tr>
<td>Non-pharmacological intervention</td>
<td>6/182 (3.3%)</td>
<td>1.75 (0.5 to 6.1)</td>
<td>+</td>
<td>Very low (c)</td>
</tr>
<tr>
<td>Usual care</td>
<td>4/212 (1.9%)</td>
<td>1 more per 100 (from 1 fewer to 10 more)</td>
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<tr>
<td>Relative risk (95% CI)</td>
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<tr>
<td>Non-pharmacological intervention</td>
<td>62/596 (10.4%)</td>
<td>0.65 (0.49 to 0.86)</td>
<td>+++</td>
<td>Moderate (d)</td>
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<td>Usual care</td>
<td>133/798 (16.7%)</td>
<td>21 fewer per 100 (from 12 fewer to 30 fewer)</td>
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<tr>
<td>Relative risk (95% CI)</td>
<td>Absolute</td>
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</table>

Quality assessment for the comparison of non-pharmacological interventions with usual care for the prevention of delirium:

- **Risk of bias:** Serious
- **Inconsistency:** No serious inconsistency
- **Indirectness:** No serious indirectness
- **Imprecision:** No serious imprecision
- **Other considerations:** None

- **No of patients:** 76/164 (46.3%)
- **Effect:** 0.71 (0.59 to 0.86)
- **Quality:** +++
- **Importance:** Moderate (a)

- **Delirium incidence in medical setting:**
  - **Risk of bias:** Serious
  - **Inconsistency:** No serious inconsistency
  - **Indirectness:** Serious
  - **Imprecision:** None
  - **Other considerations:** None

  - **No of patients:** 8/144 (5.6%)
  - **Effect:** 0.42 (0.19 to 0.92)
  - **Quality:** ++
  - **Importance:** Low (b)

- **Delirium incidence in medical setting:**
  - **Risk of bias:** Serious
  - **Inconsistency:** No serious inconsistency
  - **Indirectness:** Serious
  - **Imprecision:** None
  - **Other considerations:** None

  - **No of patients:** 6/182 (3.3%)
  - **Effect:** 1.75 (0.5 to 6.1)
  - **Quality:** +
  - **Importance:** Very low (c)

- **Delirium incidence in medical setting:**
  - **Risk of bias:** Serious
  - **Inconsistency:** No serious inconsistency
  - **Indirectness:** No serious indirectness
  - **Imprecision:** No serious imprecision
  - **Other considerations:** None

  - **No of patients:** 62/596 (10.4%)
  - **Effect:** 0.65 (0.49 to 0.86)
  - **Quality:** +++
  - **Importance:** Moderate (d)

Quality assessment for the comparison of non-pharmacological interventions with usual care for the treatment of delirium:

- **Risk of bias:** Serious
- **Inconsistency:** No serious inconsistency
- **Indirectness:** No serious indirectness
- **Imprecision:** No serious imprecision
- **Other considerations:** None

- **Delirium improvement:**
  - **No of patients:** -
  - **Effect:** Not pooled
  - **Quality:** +
  - **Importance:** Very low (e)

- **Functional status:**
  - **No of patients:** -
  - **Effect:** Not pooled
  - **Quality:** +
  - **Importance:** Very low (f)

- **Allocation concealment not clear in one study (Lundstrom 2007); both studies exposed to performance bias.**
- **Unclear blinding of outcome assessor and large confidence interval.**
- **Allocation concealment inadequate; unclear blinding of outcome assessor; per-protocol analysis; and large confidence interval.**
- **Not randomized, controlled clinical trials.**
- **Two studies with unclear/inadequate allocation concealment; 3 studies did not report data on delirium improvement, inconsistency of results (1 study in favor of the experimental treatment and 1 with non-significant results).**
- **Two studies with unclear/inadequate allocation concealment; 2 of the 4 studies did not report data on functional status.**

doi:10.1371/journal.pone.0123090.t004
In both studies, delirium was evaluated daily. The meta-analysis demonstrated a significant risk reduction of 35% of delirium incidence [RR 0.65 (95% CI 0.49 to 0.86); I² 0%] (Fig 4). The overall GRADE quality of evidence was judged to be moderate.

The third CCT evaluated an intervention carried out by non-geriatricians which was not effective in preventing delirium[82].

Before-after studies

The two BA studies were different in the patient populations, settings and interventions [84,85] (Table 5) and the interventions in the two studies were not effective in preventing delirium.

**Evidence of multiple-component, non-pharmacological interventions to treat delirium in hospitalized patients.** Four RCTs evaluated the efficacy of non-pharmacological interventions to treat delirium in older patients hospitalized with acute illness in a medical ward trials [78–81] and their characteristics are described in Table 6.

The components of the non-pharmacological interventions differed between the studies, with only the individual care planning being a common element to all four studies (Table 3). Three studies[79–81] measured the mortality rate as a primary outcome, while Cole et al.[78] assessed cognitive improvement as a single primary outcome. The length of hospital stay was evaluated as a primary outcome in two studies[79,81].

**Methodological issues.** Two of the RCTs had an adequate method of randomization [78,80]. In the study by Lundstrom et al.[81], the randomization method was unclear, in addition to having a high risk of bias in the allocation concealment (their allocation method depended on the availability of a free bed). The allocation concealment in the study by Cole et al.
Table 5. Characteristics of Primary Studies—Non-Pharmacological Interventions for Delirium Prevention in Medical Setting.

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Study period</th>
<th>Setting</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asplund</td>
<td>Randomized</td>
<td>413 patients; mean age 81 years; 39% men</td>
<td>Acute Geriatric Ward (multidisciplinary team, multicomponent intervention, staff education, early rehabilitation, planning discharge) vs Medical Wards</td>
<td>Primary outcome: delirium incidence (CAM, daily assessment). Secondary outcomes: duration, severity and recurrence of delirium; mortality.</td>
<td>March 18 to December 8, 1996</td>
<td>Acute geriatrics ward and general medical wards</td>
<td>Government, private not for profit</td>
</tr>
<tr>
<td>Martinez</td>
<td>Randomized</td>
<td>287 hospitalized patients at intermediate or high risk of delirium (MMSE &lt;24, prior hospitalization, alcoholism or metabolic imbalances on admission); mean age 78; 38% men</td>
<td>Family education, clock and calendar in the room, avoidance of sensory deprivation (glasses, denture and hearing aids), familiar objects in the room, reorientation of patient provided by family members, extended visitation (5 h daily).</td>
<td>Primary outcomes: incidence, severity and duration of delirium during hospitalization (CAM). Secondary outcomes: functional decline, length of stay, mortality, discharge location, need for new social support, number of prescribed drugs</td>
<td>15 September 2009 to 30 May 2010</td>
<td>Internal medicine ward of a Chilean Naval Hospital</td>
<td>Not reported</td>
</tr>
<tr>
<td>Inouye</td>
<td>Controlled</td>
<td>852 subjects at intermediate or high risk of delirium, with at least: visual impairment, severe illness, cognitive impairment, high ratio of blood urea to creatinine; mean age 80; 39% men</td>
<td>Elder Life Program: a trained interdisciplinary team targeted the following risk factors: cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration; daily monitoring of adherence.</td>
<td>Primary outcomes: delirium incidence (CAM, every two days) severity, duration, falls, length of stay, cognitive and functional status, cost effectiveness, residential care placement.</td>
<td>March 25, 1995 to March 18, 1998.</td>
<td>General-medicine units at a university-associated hospital</td>
<td>Government</td>
</tr>
<tr>
<td>Vidan</td>
<td>Controlled</td>
<td>542 patients 70 years or older at intermediate or high risk of delirium (at least: visual impairment, acute disease, cognitive impairment, dehydration); mean age 83; 44% men</td>
<td>In the geriatric unit: staff education and specific actions in seven risk areas: orientation, sensory impairment, sleep, mobilization, hydration, nutrition, drug use; daily monitoring of adherence.</td>
<td>Primary outcomes: Incidence of delirium (intensive care delirium screening checklist, assessed 24 h), ICU length of stay, hospital length of stay, antipsychotic use, mortality.</td>
<td>January 15 to December 15, 2007</td>
<td>Geriatric unit and internal medicine ward at University hospital in Madrid, Spain</td>
<td>Private non for profit</td>
</tr>
<tr>
<td>Yoo</td>
<td>Controlled</td>
<td>283 older patients allocated to each group; 43% older than 80 years; male 41%</td>
<td>Interdisciplinary intervention by non-geriatrics specialist physicians vs usual care</td>
<td>Primary outcomes: delirium and transition to a nursing home.</td>
<td>Unclear</td>
<td>Medical setting</td>
<td>Private non for profit</td>
</tr>
<tr>
<td>Caplan</td>
<td>Before/after</td>
<td>37 patients at intermediate/high risk of delirium, with at least: MMSE=24, sleep deprivation, any impairment of ADL, vision/hearing impairment, dehydration); mean age: 85; 21% men</td>
<td>The Recruitment of Volunteers to Improve Vitality in the Elderly program: re-orientation; cognitive stimulation; feeding and hydration assistance; vision and hearing protocols.</td>
<td>Primary outcome: delirium incidence (CAM, daily assessment). Secondary outcomes: duration, recurrence and severity of delirium; mortality.</td>
<td>March to August 2003</td>
<td>Geriatric wards at a tertiary referral hospital, Australia.</td>
<td>Government</td>
</tr>
</tbody>
</table>

(Continued)
[79] was unclear. In terms of detection bias three studies displayed low risk of bias and one study [80] had an unclear risk (Fig 2).

**Efficacy**

**Delirium Improvement.** The differences in the components of the interventions and the methods used to assess the outcomes precluded a meta-analysis. In the study by Lundstrom et al. [81], delirium was assessed at day 1, 3 and 7 of hospitalization. Complete remission rate at day 7 was significantly higher in patients that received the non-pharmacological intervention \( \text{RR 1.58 (95%CI 1.15 to 2.17)} \). Pitkala et al. [80] assessed delirium severity using the MDAS scale. Despite the significant statistical difference in favor of the experimental group, the number of incident cases of patients who improved was not reported. Cole et al. [79] used the CAM to assess delirium, but not to determine delirium improvement. In a subsequent publication in 2002 [78], the authors assessed the time and rate of improvement of Delirium Index Score, without finding a significant effect of the intervention. The overall GRADE quality of evidence was judged to be very low (Table 4).

<table>
<thead>
<tr>
<th>Author</th>
<th>Type of study</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Study period</th>
<th>Setting</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skrobik 2010[84]</td>
<td>Before/after study</td>
<td>1133 adult patients admitted &gt;24 hours; mean age 63.3 years; 59% men</td>
<td>Teaching staff protocol–based ICU patient assessments targeting non-pharmacological and pharmacological management of pain, sedation and delirium</td>
<td>Primary outcomes: incidence, severity and duration of delirium (CAM, daily assessment + interview of family and nurses and review of medical records of the afternoon/night). Secondary outcomes: functional decline, length of stay, mortality, discharge location, number of prescribed drugs</td>
<td>Before: August 2003 to February 2004; After: April 2005 to November 2005</td>
<td>A single tertiary care adult ICU (Canada)</td>
<td>Government</td>
</tr>
</tbody>
</table>

CAM, Confusion Assessment Method; ICU, Intensive care unit

doi:10.1371/journal.pone.0123090.t005

Fig 4. Forest plot of risk ratios comparing multicomponent non-pharmacological interventions vs usual care for delirium prevention in older patients in medical setting.

doi:10.1371/journal.pone.0123090.g004
Functional status. Only two studies evaluated the functional status using the Barthel Index score and results were not statistically significant [78,80].

Evidence of multicomponent, non-pharmacological interventions to treat delirium in post-acute care facilities. A cluster RCT evaluated the efficacy of a nurse-led delirium abatement program for post-acute care (PAC) in skilled nursing facilities[86]. The primary outcome was the delirium persistence at 2 weeks and 1 month after post-acute care unit admission. Methodological limitations of the trial are synthesized in Fig 2. The intervention allowed a better identification of delirium but was ineffective at reducing delirium[86].

Evidence of single-component, non-pharmacological interventions to prevent delirium. Nine studies evaluated the efficacy of single-component non-pharmacological interventions to prevent delirium in acute medical wards (Table 7). The risk of bias is summarized in Fig 5. Two RCTs evaluated the efficacy of Bright Light Therapy in an intensive care unit[87,88]. The intervention reduced the incidence of delirium but without statistically significance[RR 0.29 (95% CI, 0.07 to 1.25)]. Van Rompaey’s randomized trial studied the efficacy of using Ear Plugs to prevent delirium and found a hazard ratio of documenting any benefit for delirium prevention [RR 1.05 (95%CI 0.53 to 2.06)] [89].
<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Population</th>
<th>Intervention</th>
<th>Outcome</th>
<th>Study period</th>
<th>Setting</th>
<th>Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ono 2011 [87]</td>
<td>Randomized trial</td>
<td>22 patients undergoing esophageal cancer surgery, mean age 63 years, 100% men</td>
<td>Bright light therapy</td>
<td>Physical activity, incidence of post-operative arrhythmia and level of acute delirium (Japanese NEECHAM scale).</td>
<td>February 2006-October 2006</td>
<td>Intensive care unit, post-operative care</td>
<td>Not reported</td>
</tr>
<tr>
<td>Taguchi 2007 [88]</td>
<td>Randomized trial</td>
<td>11 patients undergoing esophageal cancer surgery, mean age 60 years, 100% men</td>
<td>Bright light therapy</td>
<td>Postoperative adjustment of the circadian rhythm, delirium incidence (Japanese NEECHAM scale).</td>
<td>July-December 2003</td>
<td>Intensive care unit, post-operative care</td>
<td>Not reported</td>
</tr>
<tr>
<td>Van Rompaey 2012 [89]</td>
<td>Randomized trial</td>
<td>136 patients in intensive care unit, mean age 59 years, 66% men</td>
<td>Sleep-wake rhythm (ear plugs)</td>
<td>Onset of delirium or confusion (NEECHAM scale), quality of sleep</td>
<td>November 2008-April 2009</td>
<td>Intensive care unit</td>
<td>Not reported</td>
</tr>
<tr>
<td>Lapane 2011 [90]</td>
<td>Cluster randomized trial</td>
<td>3203 residents living in nursing homes, median age 85, 28% men</td>
<td>Geriatric Risk Assessment MedGuide software used to identify resident-specific medications that may contribute to delirium and falls risk.</td>
<td>Incidence of potential delirium, falls, hospitalizations potentially due to adverse drug events, and mortality</td>
<td>2003–2004</td>
<td>Nursing homes</td>
<td>Government</td>
</tr>
<tr>
<td>McCaffrey 2004 [91]</td>
<td>Randomized trial</td>
<td>66 patients undergoing elective hip or knee surgery, mean age 73 years, 100% men</td>
<td>Music therapy</td>
<td>Number of patients with more than one episode of delirium, ambulation readiness profile</td>
<td>7 months</td>
<td>Surgical ward</td>
<td>Not reported</td>
</tr>
<tr>
<td>McCaffrey 2006 [92]</td>
<td>Randomized trial</td>
<td>124 patients undergoing elective hip or knee surgery, mean age 77 years, 18% men</td>
<td>Music therapy</td>
<td>Incidence of delirium, level of patient satisfaction</td>
<td>Not reported</td>
<td>Surgical ward</td>
<td>Not reported</td>
</tr>
<tr>
<td>McCaffrey 2009 [93]</td>
<td>Randomized trial</td>
<td>22 patients undergoing elective hip or knee surgery, mean age 75 years, 36% men</td>
<td>Music therapy</td>
<td>Acute confusion (NEECHAM scale), cognitive function post-surgery (MMSE)</td>
<td>Not reported</td>
<td>Surgical ward</td>
<td>Not reported</td>
</tr>
<tr>
<td>Tabet 2005 [94]</td>
<td>Controlled clinical trial</td>
<td>250 patients, mean age 80 years, 40% men</td>
<td>Staff education</td>
<td>Point prevalence of delirium (modified delirium rating scale). Secondary outcome: recognition and diagnosis of delirium.</td>
<td>December 2001-August 2002</td>
<td>Medical ward</td>
<td>Not reported</td>
</tr>
<tr>
<td>Culp 2003 [95]</td>
<td>Cluster-randomized trial</td>
<td>98 residents of 7 care homes, mean age 84, 48% men</td>
<td>Hydration management</td>
<td>Incidence of delirium (NEECHAM scale)</td>
<td>-</td>
<td>Nursing-home residence</td>
<td>Not for profit institution</td>
</tr>
</tbody>
</table>

DSI, the Delirium Symptom Interview; CAM, Confusion Assessment Method; NEECHAM, Neelon and Champagne Confusion Scale; MDAS, Memorial Delirium Assessment Scale; MMS, Mini-Mental State Examination

doi:10.1371/journal.pone.0123090.t007
In a large cluster-RCT Lapane et al.\[90\] a Geriatric Risk Assessment MedGuide software was used to identify resident-specific medications that may contribute to delirium. The intervention significantly reduced the incidence of delirium in newly admitted residents in the intervention homes than those in usual care homes (hazard ratio 0.42, 95%CI 0.35 to 0.52).

In a cluster RCT, Culp et al.\[95\] evaluated the efficacy of Hydration management in 98 residents of 7 care homes without documenting any efficacy (RR 0.85, 95% CI 0.18 to 4.00).

McCaffrey et al. studied Music Therapy in three RCTs but results of delirium incidence were not clearly reported\[91–93\].

In a CCT, Tabet et al.\[94\] evaluated the efficacy of Staff Education to prevent delirium in a medical ward. The incidence of delirium was significantly lower on the intervention ward despite a wide confidence interval [RR 0.50 (95%CI 0.26 to 0.96)]\[94\].

In a controlled BA study, Colombo et al.\[96\] evaluated the efficacy of a Reorientation protocol in 314 critically-ill patients admitted to an ICU. Delirium occurrence was significantly lower in the experimental group [RR 0.63 (95%CI 0.44 to 0.91)].

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In a CCT, Tabet et al.\[94\] evaluated the efficacy of Staff Education to prevent delirium in a medical ward. The incidence of delirium was significantly lower on the intervention ward despite a wide confidence interval [RR 0.50 (95%CI 0.26 to 0.96)]\[94\].

In a controlled BA study, Colombo et al.\[96\] evaluated the efficacy of a Reorientation protocol in 314 critically-ill patients admitted to an ICU. Delirium occurrence was significantly lower in the experimental group [RR 0.63 (95%CI 0.44 to 0.91)].

Table 8 displays the summary of finding with GRADE evidence profile for each single component.

---

**Discussion**

This systematic review was aimed at identifying systematic reviews and meta-analyses of non-pharmacological interventions used to prevent or treat delirium in patients aged 60 years or older to provide a summary for decision makers and guideline developers.

From 26 SRs or meta-analyses meeting our inclusion criteria, we analyzed data from 31 primary studies published in the last 20 years.

We found evidence of moderate quality supporting the efficacy of multicomponent non-pharmacological interventions to prevent delirium in older patients acutely admitted to a surgical or a medical ward. It must be emphasized, however, that these interventions are effective...
<table>
<thead>
<tr>
<th>Comparison</th>
<th>No of patients</th>
<th>Effect</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bright light therapy</td>
<td>2/21 (9.5%)</td>
<td>0.29 (0.07 to 1.25)</td>
<td>25 fewer per 100 (from 33 fewer to 9 more)</td>
<td>+ Very low (a)</td>
</tr>
<tr>
<td>Ear plugs</td>
<td>14/69 (20.3%)</td>
<td>1.05 (0.53 to 2.06)</td>
<td>1 more per 100 (from 9 fewer to 21 more)</td>
<td>++ Low (b)</td>
</tr>
<tr>
<td>Geriatric Risk Assessment MedGuide software</td>
<td>169/1769 (9.6%)</td>
<td>HR 0.42 (0.35 to 0.52)</td>
<td>9 fewer per 100 (from 8 fewer to 11 fewer)</td>
<td>+++ Moderate (c)</td>
</tr>
<tr>
<td>Hydration</td>
<td>3/53 (5.7%)</td>
<td>0.85 (0.18 to 4)</td>
<td>1 fewer per 100 (from 5 fewer to 20 more)</td>
<td>+ Very low (d)</td>
</tr>
<tr>
<td>Music therapy</td>
<td>-</td>
<td>-</td>
<td>+ Very low (e)</td>
<td>Critical</td>
</tr>
<tr>
<td>Staff education</td>
<td>12/122 (9.8%)</td>
<td>0.5 (0.26 to 0.96)</td>
<td>10 fewer per 100 (from 1 fewer to 14 fewer)</td>
<td>++ Low (f)</td>
</tr>
<tr>
<td>Reorientation protocol</td>
<td>32/144 (22.2%)</td>
<td>0.63 (0.44 to 0.91)</td>
<td>13 fewer per 100 (from 3 fewer to 20 fewer)</td>
<td>+ Very low (g)</td>
</tr>
</tbody>
</table>

(a) Allocation concealment not clear; blinding of outcome assessor; Japanese with esophageal cancer (indirectness); more than 20% exclusions; large confidence interval.
(b) Unclear number of included patients in final analysis; large confidence interval.
(c) Allocation concealment unclear.
(d) Inadequate randomization; outcome assessor not blinded; unclear final analysis; significant different at baseline (blood urea nitrogen and creatinine ratio).
(e) Inadequate/unclear allocation concealment; outcome assessor not blinded/unclear; results inadequately reported.
(f) High risk of selection bias (controlled clinical trial); outcome assessor not blinded; large confidence interval.
(g) High risk of selection bias (before-after study); outcome assessor not blinded; differences in baseline characteristics (diabetes, sepsis, ...); large confidence interval.

doi:10.1371/journal.pone.0123090.t008
when administered to patient at intermediate/high-risk of developing delirium. When single component interventions were considered staff-education, reorientation protocol and the Geriatric Risk Assessment MedGuide software were the only interventions that produced significant reduction in delirium prevention albeit a wide confidence interval, likely due to the fact that only one study has been performed for each of them. However, staff-education, reorientation protocol and drug review were present in trials where the multicomponent interventions resulted effective in reducing the delirium incidence.

On the contrary, evidence was insufficient to determine the benefit of multicomponent interventions in the prevention of delirium in other care settings (i.e., nursing homes). Finally, conflicting but mainly negative evidence was found concerning the utility of multicomponent non-pharmacological interventions to treat delirium in older medical patients.

Strengths and weaknesses of the study

This is the first systematic review to gather evidence from different SRs and meta-analyses concerning non-pharmacological treatments for delirium.

Firstly, most of the reviews included in our analysis had different aims and, consequently, the primary studies were distributed among the different reviews requiring the interested reader to consult all of them. For example, the review of Mak et al.[34], focused on prevention of delirium in patients with hip fracture[34]. Skingleyet al.[33] were interested in music as a single component intervention to prevent delirium[33]; Holroyd-Leduc et al.[38] considered both pharmacological and non-pharmacological interventions without examining the single component intervention[38]; the review by Hempenius et al.[98] was limited only to delirium prevention[30] (S6 Table shows how the primary studies were distributed among the reviews). Thus, our systematic overview provides a unique tool that synthesizes the evidence on non-pharmacological intervention.

Secondly, unlike previously published reviews, we carefully examined the multicomponent intervention in order to identify the components that were common among different studies and used this information to decide whether it was feasible to perform a meta-analysis. In fact, in the assessment of non-pharmacological interventions for delirium prevention in older surgical patients, we were able to combine 2 RCTs [62,63] together with the recently published CCT[64] and from this combination of studies, we obtained a more precise estimate of the efficacy of the interventions. Similarly, in the setting of acute medical wards, we meta-analyzed Inouye and Vidan’s CCTs[76,77] based on the fact that they had at least seven components in common.

Third, we categorized the studies based on study design, the provision of intervention (for prevention or treatment), and the setting in which the intervention was provided as well as the risk of bias for each study. We believe that this classification approach will facilitate the formulation of clinical questions to assist clinicians to make decisions and to help guideline developers produce recommendations.

Fourth, the strength of evidence is evaluated according to the GRADE items of risk of bias, inconsistency, indirectness, imprecision, and publication bias.

We acknowledge that two studies were recently published that compares to our analysis. The first, was a meta-analysis that considered the efficacy of multicomponent interventions on, among other outcomes, delirium prevention[99]. The study pooled the results of 11 studies including randomized, controlled clinical trials and non-randomized studies and found an OR 0.47 (95% CI, 0.38 to 0.58) in favor of non-pharmacological intervention. The second article is a practice statement from the American Geriatrics Society[100] and it deals with the risk factors, diagnosis, and management of delirium including the use of non-pharmacological interventions.
intervention for prevention and treatment of postoperative delirium. The authors identified 11 studies including randomized and non-randomized studies and state that the incidence of delirium was reduced but did not perform a meta-analysis. The conclusions of the two papers about multicomponent interventions to prevent delirium are similar to ours although our approach to meta-analyze data considered the setting in which the intervention is provided, the elements that composed the multicomponent interventions and the study design. In addition, we applied the GRADE approach and provide a summary of findings table that can provide the reader a complete account of the confidence of the evidence for the recommendation of multicomponent interventions.

We acknowledge that our review has some limitations. Firstly, the arbitrary age cut-off that may limit the applicability of the evidence from the present overview to patients with less than 60 years of age. Secondly, the lack of assessment of cost-effectiveness reviews does not allow us to reach any conclusions regarding this topic. Thirdly, the studies examined were heterogeneous in terms of intervention, study design, population, outcome and instrument assessment. To address this issue we adopted the best available methodology, i.e. GRADE, to evaluate and synthesize the available evidence.

Implications for healthcare professionals

Delirium is a geriatric syndrome and as such, it is expected to have a multifactorial etiology in the majority of patients[70,86]. This implies that multicomponent interventions are those with the best chance of being effective. We did find that multicomponent interventions were able to prevent delirium in hospitalized older patients. However, the multicomponent interventions adopted in different studies were quite heterogeneous and therefore difficult to compare. We were able to identify some common elements among different interventions, but no evidence is available to allow either the identification of which multicomponent program is more effective than others, or the relative contribution of each constituent intervention to the positive results in each individual patient. [101].

Unanswered questions and future research

The process of de-itemizing the multicomponent interventions used to provide the rational to pool meta-analyses may have another implication. For example, in delirium prevention in surgical setting, early mobilization, nutrition and hydration, regulation of bowel/bladder function, and early prevention of complications were the items that randomized studies had in common; in medical setting, in addition to early mobilization, nutrition and hydration, the interventions that the two controlled trials had in common were staff education, orientation protocol, avoidance of sensory deprivation. It is conceivable that these items may have more weight in determining the efficacy. Future studies may consider to design different multicomponent modalities in order to understand which items provide the most important contribution to the efficacy of the multicomponent intervention, how they are interrelated and the resources needed to implement the intervention.

Another point worthy of comment is the fact that the multicomponent interventions work well to prevent delirium, but their efficacy to treat delirium is at best controversial, with more negative than positive results from the studies evaluated. There is no simple explanation for these findings. One possibility is that while the risk factors for delirium are well characterized [70] and their management can effectively reduce the incidence of new episodes of this geriatric syndrome, the pathophysiology underlying the onset, development and persistence of confusion is not well understood. Several theories have been proposed, including impairment of cerebral metabolism (metabolic encephalopathy), intoxication by drugs, especially those with...
anticholinergic effects, inflammation, hypercortisolism, and a combination of the former, but no hypothesis has a strong experimental evidence in support of its validity [102].

Therefore, multicomponent interventions investigated in delirium treatment studies are quite similar to those developed for delirium prevention, but they are applied in a very different clinical scenarios. Further research concerning the pathophysiology of delirium is clearly needed to provide the data to support the development of more effective interventions to treat older patients suffering from delirium.

Conclusions
In older patients at intermediate/high risk of delirium multi-component non-pharmacological interventions as well as some single-components intervention (staff education, reorientation and drug review) reduce the incidence of delirium. Evidence for the role of non-pharmacological interventions in the treatment of delirium is inconclusive.

Supporting Information
S1 Box. List of non-pharmacological interventions to prevent or treat delirium.
(DOCX)

S2 Box. List of Search strategies.
(DOCX)

S1 File. Results for secondary outcomes.
(DOCX)

S1 Table. List of non-pharmacological interventions.
(DOCX)

S2 Table. Ranking of possible important outcomes when making decisions on delirium prevention.
(DOCX)

S3 Table. List of excluded reviews with reasons.
(DOCX)

S4 Table. Methodological quality assessment of the included studies systematic reviews (AMSTAR).
(DOCX)

S5 Table. Excluded primary studies with reasons.
(DOCX)

S6 Table. Distribution of Primary Studies (column) across Systematic Reviews (row).
(XLSX)

Acknowledgments
We thank the following panel members that participated in the Delphi process to identify relevant outcomes and non-pharmacological interventions: Hubert Blain, Karen Andersen Ranneberg, Regina Roller-Wirnsberger, Fabio Salvi, Andrea Corsonello, Adalsteinn Gudmundsson, Akner Gunnar, MirkoPetrovic.
Author Contributions
Conceived and designed the experiments: IA AC ACJ RLS DO. Performed the experiments: IA JMR FT ILM VP. Analyzed the data: IA JMR FT AC ACJ PDF VP ILM. Contributed reagents/materials/analysis tools: IA AC JMR AC PDF FT RLS DO FL. Wrote the paper: IA FT JMR AC ACJ ILM RLS VP PDF FL DO.

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on the effectiveness of nonpharmacologic interventions: evidence from the delirium prevention trial. 
Arch Intern Med. 2003 Apr 28; 163(8):958–64. PMID: 12719206


and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients 
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