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NON-PHARMACOLOGICAL INTERVENTIONS TO PREVENT OR TREAT DELIRIUM IN OLDER PATIENTS: CLINICAL PRACTICE RECOMMENDATIONS THE SENATOR-ONTOP SERIES

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Abstract: *Description:* The ONTOP project aims to undertake a literature search of systematic reviews concerning evidence-based non-pharmacological interventions of prevalent medical conditions affecting older people, including delirium. *Objectives:* To develop explicit and transparent recommendations for non-pharmacological interventions in older subjects at risk of developing delirium, as well as in older subjects with delirium, based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach to rating the quality of evidence and the strength of recommendations. *Methods:* A multidisciplinary panel was constituted comprising geriatricians, research nurse and a clinical epidemiologist. The panel developed a systematic overview of non-pharmacological interventions to prevent or treat delirium. The GRADE approach was used to rate the evidence and to formulate recommendations. *Results:* The critical outcomes were delirium incidence, for delirium prevention, and delirium improvement and functional status, for delirium treatment. The non-pharmacological interventions were identified and categorized as multicomponent and single component. Strong recommendations in favor of multicomponent interventions to prevent delirium, in surgical or medicals wards, were formulated. In the latter case the evidence applied to older patients at intermediate - high risk of developing delirium. Weak recommendations, to prevent delirium, were formulated for multicomponent interventions provided by family members (medical ward), staff education (medical ward), ear plugs (intensive care unit), reorientation protocol (intensive care unit), and the use of a software to perform drug review. Weak recommendations were provided for the use of multicomponent interventions to prevent delirium in medical wards in patients not selected according to the risk of delirium. Strong recommendations not to use bright light therapy to prevent delirium in intensive care unit settings were articulated. Weak recommendations not to use music therapy to prevent delirium for patients undergoing surgical interventions were specified. The ability to make strong recommendations was limited by the low quality of evidence and the presence of uncertainty. Moreover, weak recommendations were provided for the use of multicomponent interventions to treat delirium of older patients (medical wards). *Conclusions:* Overall, the panel developed 12 recommendations for the delivery of non-pharmacological interventions to older patients at risk of developing or, with delirium.

Key words: Delirium, non-pharmacological intervention, multicomponent intervention, clinical practice recommendation.

Background

Delirium, also known as acute confusional state, is a geriatric syndrome commonly occurring in hospitalized older patients (1). The prevalence of delirium varies from 10% to 30% in patients admitted to general hospitals (2, 3) and may reach 60% among older patients (4) or in subjects undergoing major surgery (5). Delirium is associated with prolonged hospital stay (6), functional and cognitive decline (7), as well as with increased morbidity and mortality (8, 9). The estimated direct health care costs associated with this syndrome are between $60,516 and $64,421 per delirious patient per year (10).

Since there is no conclusive evidence that drugs are effective to prevent or treat delirium and they have potentially severe adverse effects (11), in the last few decades, non-pharmacological interventions have been proposed as valid alternative approaches.

The purpose of the present article was to develop explicit and transparent, clinical practical recommendations, to prevent and treat delirium using non-pharmacological interventions in older patients on the basis of the current best evidence. For the purpose of this clinical guidance, we developed a systematic overview of reviews from which we gathered the evidence regarding the efficacy of non-pharmacological interventions to prevent or treat delirium in any setting (12, 13).

The present work was carried out as part of the ONTOP project (12) which is a work package of a large European Union funded FP 7 research project named SENATOR (Software ENgine for the Assessment & optimization of drug and non-drug Therapy in Older persons; http://www. senator-project.eu/) that aims to build a software engine with the capacity to optimize non-pharmacological as well as pharmacological therapies and simultaneously

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minimize adverse drug reactions, inappropriate prescribing, polypharmacy and excessive costs in older patients with multimorbidity. The efficacy of the SENATOR software will be tested in a randomized controlled clinical trial, starting in 2015. The clinical conditions of interest in the ONTOP work package include delirium (13), falls, pressure sores (14), urinary incontinence, dementia, heart failure, orthostatic hypotension, sarcopaenia and stroke.

Methods

The ONTOP Panel composition

The ONTOP Panel comprised professionals (geriatricians, a research nurse and a clinical epidemiologist) from 4 European countries (Italy, Spain, UK, and Ireland).

Evidence Review

Defining the clinical questions and deciding important and critical outcomes

In order to formulate appropriate clinical questions, the evidence expert group identified a list of relevant outcomes and submitted the list to a larger group of experts according to the GRADE criteria (15).

After two rounds of consultations, the panel concluded that the importance of the listed outcomes could change in relation to delirium treatment or prevention. Therefore, a decision was made to provide separate surveys for the two different approaches. In a third and final survey, critical outcomes were identified: delirium incidence, for delirium prevention, and delirium improvement and functional status, for delirium treatment.

The panel classified the types of interventions as (a) multicomponent and (b) single component. For the latter, the panel decided to generate a clinical question for each single component intervention identified from the evidence.

Conversely, for multicomponent interventions, the evidence expert group was aware that a uniform definition did not exist and decided to de-itemize the elements included in each multicomponent intervention. De-itemization was important to perform meta-analyses (13) and to identify critical elements to be included in the recommendation. The evidence group also considered the setting an important element in the formulation of the clinical questions.

For each clinical question, in addition to critical outcomes, the evidence group defined the relevant population, alternative management strategies (intervention and comparator), and the setting. The panel decided to consider any experimental comparative study for inclusion (e.g., Clinical Controlled Trials (CCTs) and Before-After Studies (BAS)), as a limited number of randomized clinical trials were expected to be found. The panel decided to give priority to the latter type of trial, while other experimental designs would be considered only when randomized trials were absent. Before after studies with historical controls were excluded.

Identifying the evidence

A detailed description of the process used to identify the evidence has been already published (12, 13).

Grading the evidence

GRADE is a systematic, standardized approach to assess the quality of the evidence. The quality is evaluated according to the study design and the execution (the risk of bias), consistency, directness in the applicability of the evidence, precision of the estimate of the treatment effect, and publication bias. Limitations in any of these categories can lower the quality of the evidence by 1 or 2 levels. Box 1 shows the 4 levels of the quality of the evidence and the corresponding definitions. According to GRADE, the evidence can also be rated up, when the treatment effect is very large, when there is a dose-response gradient, or when the treatment effect is maintained despite the presence of confounding factors (16). In addition, the quality of the evidence across all critical outcomes is assessed, including both benefits and harms. The overall quality of evidence is determined by the lowest quality of evidence for each of the critical outcomes.

Box 1
Quality of evidence and definitions

Quality of Evidence	Definition
High	We are very confident that the true effect lies close to that of the estimated effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimated effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimated effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimated effect.

Evaluating Quality of Bodies of Evidence

The ONTOP Panel held workshops and teleconferences to discuss the available evidence, the presentation of the results and their impact on making recommendations.

For each critical outcome, GRADE evidence profiles were prepared containing information about the quality of the evidence and the estimate of the treatment effect. These profiles

were assessed by the members of the ONTOP Group when preparing the recommendations. The group provided standard decision tables to allow the panel to judge the evidence and to generate recommendations. One table (the Summary of Findings Table) was prepared for each recommendation to record decisions and ensure that the panel uniformly considered the quality of the evidence, the certainty regarding the balance of benefits versus harms,. The strength of a recommendation (strong or weak) was determined by the balance between desirable and undesirable effects, and likely values and preferences of the patients. Box 2 displays the definitions of weak and strong recommendations.

Box 2
Assessment of the strength of a recommendation

Strength	Definition
Strong	The Panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects.
Weak	The Panel concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects.

Results

After identifying the critical outcomes, based on the type of intervention (single or multicomponent), setting (medical or surgical) and the aim of the intervention (prevention or treatment) the following clinical questions and the related recommendations were formulated.

Recommendation 1

Clinical question: Should multicomponent non-pharmacological interventions be recommended to prevent the incidence of delirium in older patients receiving urgent surgical treatment?

Evidence profile

From the systematic overview of reviews, the evidence expert group identified two randomized trials (17, 18), one controlled clinical trial (19) and four before-after studies (20-23).

The expert group decided to consider only the randomized trials while formulating the clinical recommendation.

The two randomized trials were similar in terms of characteristics of the population (17, 18) and the investigated interventions, which had in common the application of comprehensive geriatric assessment, management and rehabilitation; prevention, early detection and treatment of major postoperative complications; oxygen therapy; regulation of bowel/bladder function; and nutrition and hydration (13).

The studies used different approaches to assess delirium (Marcantonio used the Confusion Assessment Method daily (24); Lundstrom used nurses'judgment and applied a modified Organic Brain Syndrome (OBS) Scale - a combined observation and interview scale – administered between 3-5 days after admission).

In an intention-to-treat analysis, 325 subjects were analyzed. The results indicated a statistically significant reduced rate of delirium incidence in patients who received a non-pharmacological multicomponent intervention, with 19 fewer cases of delirium per 100 patients receiving the treatment [RR 0.71 (95% CI, 0.59 to 0.86)]

The two included studies were randomized and should potentially be considered of high quality. However, two concerns were highlighted by the evidence expert group: allocation concealment was not clear in Marcantonio and both studies were susceptible to performance bias, given the nature of the intervention, although these studies were less exposed to detection bias, since the outcome assessor was blinded.

The panel did not find any concern regarding inconsistency, indirectness and imprecision. Consequently, due to the aforementioned risk of bias, the panel downgraded the evidence by one level resulting in a moderate level of quality.

Expert Group Recommendations

Clinical question:
Should multicomponent non-pharmacological interventions be recommended to prevent the incidence of delirium in older patients receiving urgent surgical treatment?

Recommendation:
In patients, aged 65 years or older, receiving an urgent surgical intervention, we recommend multicomponent non-pharmacological interventions, to prevent delirium, containing at least the following components: early mobilization, hydration and nutrition, oxygen delivery, pain control, regulation of bladder and bowel function and prevention, early detection, and treatment of major postoperative complications (strong recommendation | moderate-quality evidence).

Underlying values and preferences:
This recommendation places a high value on the capacity of non-pharmacological interventions to prevent delirium, while not generating adverse events.

Remarks:
The two randomized trials and the majority of the other studies were performed in older patients undergoing surgical repair for hip fracture.

Recommendation 2

Clinical question: Should a multicomponent non-pharmacological intervention, performed by family members, be recommended to prevent delirium in older patients, at intermediate/high risk of developing delirium, hospitalized in

medical wards?

Evidence profile

Available data were obtained only from one randomized trial. In this trial, 287 hospitalized patients (mean age 78.2 ± 6.2 years, 62.7% female) with intermediate/high risk of developing delirium were selected, defined by the presence of at least one of the following risk factors: more than 70 years of age, documented cognitive impairment, alcoholism and metabolic imbalances (25).

The occurrence of delirium was measured daily with the Confusion Assessment Method (CAM). There was a statistically significant reduction of delirium incidence in patients that received a non-pharmacological multicomponent intervention, with 8 fewer cases of delirium per 100 patients receiving the treatment [RR 0.42 (95% CI 0.19-0.92)].

The study was adequately randomized, but it was unclear as to whether the outcome assessor was blinded. However, the expert panel decided not to downgrade this study because of risk of bias.

The panel did not find any issues regarding inconsistency and indirectness, but identified serious imprecision due to a large confidence interval, leading to downgrading this study by two levels. Hence, the overall quality of the evidence for 'Delirium incidence' was rated low.

Expert Group Recommendations

Clinical question:

Should a multicomponent non-pharmacological intervention, performed by family members, be recommended to prevent delirium in older patients, at intermediate/high risk of developing delirium, hospitalized in medical wards?

Recommendation:

In patients aged 65 or older, at intermediate-high of developing delirium (previous history of cognitive impairment documented in patient medical record, with a score on the Mini-Mental State Examination <24 prior to hospitalisation, alcoholism or metabolic imbalances at admission) admitted to a medical ward, we recommend a non-pharmacological intervention provided by patients' trained family members, containing at least the following components: provision of a clock, avoidance of sensory deprivation, presence of familiar objects in the room, reorientation of patients, extended visitation times, to prevent delirium (weak recommendation | low-quality evidence).

Underlying values and preferences:

This recommendation places a high value on the capacity of non-pharmacological interventions to prevent delirium, while not generating adverse events.

Recommendation 3

Clinical question: Should a multicomponent non-pharmacological intervention, performed by a trained interdisciplinary team, be recommended to prevent delirium in older patients, at high or intermediate risk of developing delirium, hospitalized in medical wards?

Evidence profile

From the systematic search of reviews, we identified two CCTs (26, 27) and two BAS (28, 29) with patients at high/intermediate risk of developing delirium.

When formulating the present recommendations, the panel considered only the two CCTs.

Inouye 1999 evaluated 852 subjects (mean age 80 years, 61% female) at intermediate or high risk of developing delirium (with at least one of the following characteristics: visual impairment, severe illness, cognitive impairment, high ratio of blood urea nitrogen to creatinine). Vidan 2009 (27) evaluated 542 patients (mean age 84 years, 56% female) at intermediate or high risk of developing delirium (with at least one of the following characteristics: visual impairment, acute severe disease, cognitive impairment, dehydration).

The multicomponent non-pharmacological intervention employed in both studies consisted of a trained interdisciplinary team that implemented standardized interventions to target several risk factors (cognitive impairment, sleep deprivation, immobility, sensory impairment, dehydration and daily monitoring of adherence shared by both studies plus malnutrition and inappropriate drug use in Vidan 2009 (27)).

Given the absence of randomization, the two studies were exposed to the risk of selection bias, but the basic characteristics of the allocated groups were similar. In addition, due to the nature of the intervention, both studies were exposed to the risk of performance bias. However, while Inouye (26) was at low risk of detection bias, in Vidan (27), it was not clear whether the assessor was aware of the patient allocation and the objectives of the study.

In an intention-to-treat analysis, 1394 subjects were analyzed in the two controlled clinical trials. Delirium incidence, measured with the CAM, was a primary outcome in both trials. It was assessed daily in Inouye (26), while Vidan (27) evaluated delirium daily in the morning and interviewed family members and nurses and reviewed medical records for the afternoon/night.

There was a statistically significant reduction of delirium incidence in patients that received a non-pharmacological multicomponent intervention, with 6 fewer cases of delirium per 100 patients receiving the treatment [RR 0.65 (95% CI 0.49, 0.86); I^2 0%].

The panel downgraded the quality of evidence by one level for serious risk of bias due to the absence of randomization, while there were no issues concerning inconsistency, indirectness and imprecision.

Overall, the quality of evidence for 'Delirium incidence' was

rated moderate.

Expert Group Recommendations

Clinical question:
Should a multicomponent non-pharmacological intervention, performed by a trained interdisciplinary team, be recommended to prevent delirium in older patients, at high or intermediate risk of developing delirium, hospitalized in medical wards?

Recommendation:
In patients, aged 65 or older, hospitalized in medical wards, at intermediate-high risk of developing delirium (with one of the following characteristics: visual impairment, severe illness, cognitive impairment, dehydration), we recommend non-pharmacological interventions, provided by a trained interdisciplinary team (targeting the following risk factors: cognitive impairment, sleep deprivation, immobility, sensory impairment, and dehydration), to prevent delirium (strong recommendation | moderate-quality evidence).

Underlying values and preferences:
This recommendation places a high value on the capacity of non-pharmacological interventions to prevent delirium, while not generating adverse events.

Recommendation 4

Clinical question: Should a multicomponent non-pharmacological intervention, delivered in a geriatric ward, be recommended to prevent delirium in older patients, not selected on the basis of delirium risk, hospitalized in medical departments?

Evidence profile

The expert group identified only one study (30) that evaluated the effect of treatment provided in an acute geriatric ward with emphasis on early rehabilitation and discharge planning for older patients with acute medical illnesses compared to admission to a general ward. In this study, 1201 patients, older than 70 years of age, were included and the primary measure was poor global outcome at 3-months follow-up, defined as death and/or severe primary ADL and/or poor psychological well-being.

The study was at high risk of bias because the personnel could have been aware of the group allocation with block randomization and it was at high risk of attrition bias, because the data were analyzed per protocol.

Delirium incidence, measured using the CAM instrument, was assessed as a secondary outcome . The proportion of patients with delirium at entry was 4.3% in the intervention group and 5.0% in the control group. After 3 months follow-up, the incidence of delirium between the two groups did not differ significantly (3.3% in the acute geriatrics-based ward and 1.9% in the general medical ward; RR 1.75, 95% CI 0.5 to 6.1).

The panel downgraded the quality of evidence by two levels for serious risk of bias due to selection and high attrition, and a per-protocol analysis. In addition, due to a large confidence interval, the panel further downgraded the evidence by 1 level.

Overall, the quality of evidence was rated very low.

Expert Group Recommendations

Clinical question:
Should a multicomponent non-pharmacological intervention delivered in a geriatric ward be recommended to prevent delirium in older patients, not selected on the basis of delirium risk, hospitalized in medical departments?

Recommendation:
In patients, aged 65 or older, not selected on the basis of delirium risk, we recommend multicomponent non-pharmacological interventions delivered in a geriatric ward to prevent delirium (weak recommendation | very low-quality evidence).

Underlying values and preferences:
This recommendation places a high value on the fact that the intervention represented good clinical practice in the treatment of acutely ill older patients, which resulted in a shorter length of stay in the hospital although it was not effective in preventing delirium.

Recommendation 5

Clinical question: Should a multicomponent non-pharmacological intervention be recommended to treat delirium in older patients hospitalized in medical wards?

Evidence profile

Delirium improvement

Four randomized clinical studies evaluated the efficacy of non-pharmacological interventions to treat delirium in patients hospitalized for acute illness in medical wards (31-34). The number of patients ranged from 88 to 227, the mean age was around 80, and the percentage of women ranged from 61% to 75%.

The primary concern that arose when evaluating the studies that addressed delirium treatment, was the absence of a clear definition of delirium remission. Although Lundstrom 2005 (34) was the only study to report delirium remission, the schedule of delirium assessment was not adequate to detect complete remission, thus potentially leading to overestimation.

The remaining three trials reported delirium improvement without clearly providing the number of patients who had improved. In fact, Pitkala 2006 (33) used a sustained improvement of four points or more in the Memorial Delirium Assessment Scale (MDAS) score to detect significant improvement in symptoms of delirium. Despite the significant

statistical difference between the two groups, the number of patients that had improved was not reported.

Cole 1994 (32) used the Short Portable Mental Status Questionnaire (SPMSQ) to identify patients, with moderate to severe cognitive impairment, to whom the CAM instrument was to be administered to assess delirium. After allocation, the patients were evaluated with the Crichton Geriatric Behavioral Rating Scale and the SPMSQ. The study reported a significant difference in improvement on the SPMSQ after 8 weeks, between the treatment and control groups, without providing the number of patients with delirium improvement.

To identify patients with delirium, Cole 2002 (31) screened patients using the SPMSQ and applied the CAM, to those that scored 3 to 9 or had symptoms of delirium recorded in the nursing notes. The study reported that 48% of patients in the intervention group and 45% of patients in the usual care group, met the criteria for improvement with no significant difference.

In conclusion, despite the limitation of the data presentation in three trials, which hindered the conduction of a meta-analysis, it appeared that there was no significant improvement in delirium in the patients that received the multicomponent intervention. The overall quality of the evidence for delirium improvement was judged by the panel to be very low due to very serious limitations in the study design and execution (inadequate or unclear allocation concealment) and imprecision.

Expert Group Recommendations

Clinical question:
Should a multicomponent non-pharmacological intervention be recommended to treat delirium in older patients hospitalized in medical wards?

Recommendation:
In patients with delirium aged 65 years or older admitted to medical wards, we recommend multicomponent non-pharmacological interventions to treat delirium (weak recommendation | very low-quality of evidence).

Underlying values and preferences:
This recommendation places a high value on the absence of adverse effects when non-pharmacological interventions are delivered. Moreover, the multicomponent intervention represents good clinical practice in the treatment of acutely ill older patients.

Recommendation 6

Clinical question: Should a multicomponent non-pharmacological intervention be recommended to improve functional status in older patients with delirium, hospitalized in medical departments?

Evidence profile

Functional status

Cole 2002 (31) and Pitkala 2006 (33) measured functional status as a secondary outcome using the Barthel Index. However, no significant differences between the two study groups. The other two studies did not report any data.

The overall quality of the evidence, for functional status, was judged by the panel to be very low, due to very serious limitations in the study design, study execution (inadequate or unclear allocation concealment) and imprecision.

Expert Group Recommendations

Clinical question:
Should a multicomponent non-pharmacological intervention be recommended to improve functional status in older patients with delirium, hospitalized in medical departments?

Recommendation:
In patients aged 65 or older with delirium admitted to a medical setting, we recommend multicomponent non-pharmacological interventions to improve functional status in older patients with delirium (weak recommendation | very low-quality of evidence).

Underlying values and preferences:
See above Recommendation n° 5.

Recommendation 7

Clinical question: Should staff education be recommended to prevent delirium in older patients, not selected according to the baseline risk of developing delirium, and hospitalized in medical departments?

Evidence profile

We found only one controlled clinical trial (35) that evaluated the efficacy of staff education to prevent delirium in older patients. The study included 250 patients in a medical ward (mean age 80, 40% women) and assessed delirium incidence with the modified delirium rating Scale. The incidence of delirium was reduced by 50% in the group allocated to staff education (RR 0.50, 95% CI 0.26 to 0.96) which means that for 100 patients receiving the treatment there will be on average, 10 fewer cases of delirium (ranging from 1 fewer to 14 fewer).

The panel was concerned, however, because the limitation in study design and execution (the absence of randomization) and the large confidence interval (imprecision) could have influenced the treatment effect and therefore downgraded the evidence by 2 levels. No further concerns were expressed in terms of inconsistency and indirectness. Hence, the level of evidence for staff education to prevent delirium incidence was rated low.

Expert Group Recommendations

Clinical question:
Should staff education be recommended to prevent delirium in acutely ill older patients, not selected according to the baseline risk of developing delirium, and hospitalized in medical wards?

Recommendation:
In patients aged 65 years or older, admitted to a medical ward, we recommend staff education to prevent delirium (weak recommendation | low-quality evidence).

Underlying values and preferences:
This recommendation places a high value on the capacity of staff education to prevent delirium and the absence of adverse events. However, the panel recognizes that staff education usually should be provided in the context of a multicomponent non-pharmacological intervention, for which there is stronger evidence (see Recommendation n° 1, 2).

Recommendation 8

Clinical question: Should bright light therapy be used to prevent delirium in older surgical patients admitted to an intensive care unit?

Evidence profile

Two small randomized trials, Ono 2011 (36) and Taguchi 2007 (37), considered the efficacy of Bright light therapy in an Intensive Care setting, in 41 men who underwent surgery for oesophageal cancer.

The method of randomization was unclear in both trials (36, 37). Given the nature of the intervention, the studies were exposed to performance bias. In addition, both studies were judged unclear in terms of detection, attrition and selective reporting bias.

In both studies, delirium incidence was measured using the NEECHAM scale, consisting of 4 categories 'Moderate to severe confusion', 'Mild or initial confusion', 'Not confused but high risk' or 'A state with normal functions'. There was a reduction in the risk of developing delirium in patients receiving bright light therapy without, however, reaching statistical significance in a meta-analysis [OR 0.20 (95% CI, 0.04 – 1.18)].

The panel judged the quality of evidence very low due to serious limitations in the study design (none of the items was of low risk of bias), indirectness (patients affected by esophageal cancer), imprecision (the size of both studies was too small with very few events reflected in a large confidence interval).

Expert Group Recommendations

Clinical question:
Should bright light therapy be used to prevent delirium in older surgical patients admitted to an intensive care unit?

Recommendation:
In older surgical patients, admitted to an intensive care unit setting, we do not recommend the use of bright light therapy to prevent delirium (weak recommendation | very low-quality of evidence).

Recommendation 9

Clinical question: Should ear plugs be used to prevent delirium in older surgical patients admitted to an intensive care unit?

Evidence profile

One randomized trial (Van Rompaey 2012) evaluated the efficacy of using Ear Plugs, to prevent delirium, in 136 patients in an intensive care unit (mean age 60; 34 % male). Delirium incidence was evaluated using the NEECHAM scale (38). The study hypothesis was that earplugs could reduce noise during the night thus preventing delirium .

Despite the study being methodologically sound, the trial was not able to demonstrate the efficacy of ear plugs to prevent delirium [RR 1.05(95%CI 0.53 to 2.06)].

The panel rated the evidence low due to imprecision (the sample size of the studies was too low; wide confidence interval).

Expert Group Recommendations

Clinical question:
Should ear plugs used to prevent delirium in older surgical patients admitted an intensive care unit?

Recommendation:
In patients aged 65 or older, admitted in an intensive care unit, we do not recommend the use of ear plugs to prevent delirium (weak recommendation | low-quality of evidence).

Recommendation 10

Clinical question: Should music therapy be recommended to prevent delirium in older surgical patients admitted to an intensive care unit?

Evidence profile

The evidence concerning the benefit of music therapy, for patients undergoing surgery, was based on three randomized trials. The overall number of participants was 212 ranging from 22 to 124, with a mean age from 73 to 77 years. The populations in the three studies underwent elective surgery. Delirium was evaluated using the NEECHAM scale in one

study (39), but in the other two trials, the method of evaluation was not specified (40, 41). All three studies were performed by the same group of authors, however, despite concluding that music therapy had some benefit, the results were not clearly reported in any of the studies.

The panel judged the level of evidence very low due to study design limitations (allocation concealment was unclear in 2 studies and inadequate in 1; incomplete outcome data) and imprecision (small sample size in the included studies), leading to a downgrading of 3 levels.

Expert Group Recommendations

Clinical question:
Should music therapy be recommended to prevent delirium in older surgical patients admitted to an intensive care unit?

Recommendation:
In older surgical patients admitted to an intensive care unit, we do not recommend the use of music therapy to prevent delirium (weak recommendation | very low-quality of evidence).

Recommendation 11

Clinical question: Should the use of a software to perform drug review be recommended to prevent delirium in nursing home residents?

Evidence profile

One study evaluated the use of a clinical informatics tool that implemented prospective monitoring plans to prevent delirium, falls and hospitalizations potentially due to adverse drug events, and mortality (42). This was a software known as a Geriatric Risk Assessment Med. Guide (GRAM) which correlated medication used, with physical, functional, and cognitive decline, to foster early recognition of potential adverse effects.

GRAM was designed to assist healthcare professionals to identify, prevent or resolve medication-related adverse events in patients with complex drug regimens. The study was a cluster-randomised trial that included 3201 residents living in nursing homes (median age 85; 28% men).

The panel judged the level of evidence moderate due to study design limitations (allocation concealment was unclear; outcome assessor was not blinded).

The results showed a statistically significant reduction of delirium incidence in patients allocated to GRAM software, with 9 fewer cases of delirium per 100 patients receiving the treatment [HR 0.42 (95% CI 0.35, 0.52)].

Expert Group Recommendations

Clinical question:
Should the use of a software to perform drug review, be recommended to prevent delirium in nursing home residents?

Recommendation:
In residents aged 65 or older, living in nursing homes, we recommend use of a software supporting medication review to prevent delirium (weak recommendation | moderate-quality of evidence).

Remarks:
The recommendation is based on only one properly conducted study.

Recommendation 12

Clinical question: Should a Reorientation Protocol be recommended to prevent delirium, in surgical or medical patients, admitted to an intensive care unit?

Evidence profile

One before-after study assessed the efficacy of a reorientation protocol to prevent delirium in 314 older medical or surgical patients admitted to an intensive care unit (43). The study enrolled critically-ill patients with a median age of 70 years and evaluated delirium using the CAM scale.

The panel judged the level of evidence concerning reorientation protocol to be very low, due to study design limitations (high risk of selection bias caused by an absence of randomization; high risk of detection bias/outcome assessor not blinded) and imprecision (the sample size did not reach the optimal information size (44)).

The results showed a statistically significant reduction of delirium incidence in patients that received the reorientation protocol with 13 fewer cases of delirium per 100 patients receiving the treatment [RR 0.63 (95% CI 0.44 to 0.91)].

Expert Group Recommendations

Clinical question:
Should Reorientation Protocol be recommended to prevent delirium in surgical patients in intensive care unit?

Recommendation:
In medical or surgical patients aged 65 or older, admitted to an intensive care unit, we recommend the use of a reorientation protocol to prevent delirium (weak recommendation | very low-quality of evidence).

Discussion

Delirium is a common geriatric syndrome in older patients, which is a cause of increased morbidity, mortality and financial costs (11). Moreover, the experience of delirium is reported

to be extremely distressing by older patients, who are able to remember it, caregivers and staff involved in patient care (45).

Based on a systematic literature search and an exhaustive evidence evaluation, we provide 12 recommendations for non-pharmacological interventions to prevent or treat delirium in older patients. Critical outcomes, together with the aim of the intervention (prevention or treatment), the setting and the type of intervention (multicomponent or single component), were used to produce sensible clinical questions for which clear and complete recommendations were developed.

There was a considerable body of evidence that supported multicomponent non-pharmacological interventions to prevent delirium both in medical and surgical settings. We limited our body of evidence to experimental trials with moderate quality of evidence to formulate recommendations. However, there were several non-randomized studies, that when pooled, provided estimates of the treatment effect that had the same direction and magnitude as the results of the meta-analyses of trials on which we based our recommendations (13).

Furthermore, by de-itemizing the elements of the multicomponent interventions, meta-analyses were justified (13), and more importantly, we were able to formulate specific recommendations that highlighted the components physicians might consider important when delivering multicomponent interventions. For example, in surgical settings, we strongly recommended a non-pharmacological intervention that has at least the following elements: early mobilization, hydration and nutrition, oxygen delivery, pain control, regulation of bladder and bowel function and prevention, early detection, and treatment of major postoperative complications. We are unsure whether the different elements have a particular weight in determining the positive effect. Future research is needed to address the relevance of each element within the multicomponent interventions to prevent delirium.

The use of the GRADE methodology is another advantage for the applicability of our recommendations. GRADE provides a systematic and transparent approach to identifying populations and outcomes of interest, provides a definition for the quality of evidence and evaluates the evidence based on factors that reduce or enhance the quality. Furthermore, to formulate recommendations, GRADE articulates the effect estimates for desirable and undesirable outcomes of interest, confidence in the effect estimates and consideration of values and preferences (46). The GRADE methodology is now used among different organizations including the World Health Organization and the Agency for Healthcare Research and Quality. Compared to other guidelines concerning non-pharmacological interventions to prevent or treat delirium, our recommendations provide a more systematic and transparent way to judge the evidence and an explicit presentation of how the panel viewed the domains when considering the direction and strength of recommendations.

Limitations

Our main limitation was that, owing to limited time and resources, no cost-effectiveness evaluation was performed.

Conclusions

The present paper provides transparent, evidence-based recommendations for the prevention and treatment of delirium in older patients. The ONTOP panel reached consensus on critical outcomes and provided strong recommendations for the use of multicomponent interventions to prevent delirium either in medical or surgical settings. Specific areas for additional research, include the role of elements within the multicomponent interventions and conducting studies with adequate sample size and methodological standards to clarify the role of single component interventions in the prevention of delirium and multicomponent interventions in the treatment of delirium.

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