25. Steenland K, Macneil J, Bartell S, Lah J. Analyses of diagnostic patterns at 30 Alzheimer's disease centers in the US. Neuroepidemiology 2010; 35: 19–27.
26. O Connor DW, Blessed G, Cooper B, Jonker C, Morris JC. Cross-national interrater reliability of dementia diagnosis in the elderly and factors associated with disagreement. Neurology 1996; 47: 1194–9.
27. Nasreddine ZS, Philips NA, Bedirian V *et al*. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc 2005; 53: 695–9.

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Preventing delirium in an acute hospital using a non-pharmacological intervention

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Abstract

Background: delirium is a clinical syndrome associated with multiple short and long-term complications and therefore prevention is an essential part of its management. This study was designed to assess the efficacy of multicomponent intervention in delirium prevention.
Methods: a total of 287 hospitalised patients at intermediate or high risk of developing delirium were randomised to receive a non-pharmacological intervention delivered by family members (144 patients) or standard management (143 patients). The primary efficacy outcome was the occurrence of delirium at any time during the course of hospitalisation. Three validated observers performed the event adjudication by using the confusion assessment method screening instrument.
Results: there were no significant differences in the baseline characteristics between the two groups. The primary outcome occurred in 5.6% of the patients in the intervention group and in 13.3% of the patients in the control group (relative risk: 0.41; confidence interval: 0.19–0.92; $P = 0.027$).
Conclusion: the results of this study show that there is a benefit in the non-pharmacological prevention of delirium using family members, when compared with standard management of patients at risk of developing this condition.

Keywords: *delirium, primary prevention, elderly*

Introduction

Delirium is a clinical syndrome characterised by an altered level of consciousness and cognitive disorders that develop over a short period of time (usually over hours or days) and tend to fluctuate during the course of the day [1]. The etiology of this syndrome is often multifactorial.

What makes delirium important is not only its high occurrence rate among hospitalied patients but also its consequences. The occurrence rate ranges from 6 to 56% [2, 3] in hospitalised patients. Its consequences include the contribution to increased morbidity and mortality, being cause of distress to patients and their families and increased costs [3]. An example of this is that the presence of delirium in hospitalisation is an independent factor for mortality 1 year

after discharge [4]. It is also associated with increased length of hospital stay and institutionalisation. In economic terms, there is an apparent increase in costs due to both prolonged length of hospital stay and management of secondary complications associated with the condition. In the USA, costs attributable to delirium are estimated to be USD$2500 per patient per hospitalisation [5].

Several studies have aimed at the prevention of delirium using multidisciplinary strategies [5, 6], pharmacological, behavioral [7, 8] and environmental [5, 9]. Only a few of them have been proven effective in reducing the overall incidence, length or severity of delirium [5, 9–13]. A recent Cochrane review aims to determine the interventions to prevent delirium in hospitalised patients [13]. Studies suggesting multicomponent interventions have shown positive outcomes [5], but a reduction in the incidence of acute confusional syndromes in medical wards has yet to be proved in randomised controlled trials. We designed our study prophylactic environmental management of in-hospital delirium (PEMID) to determine whether a non-pharmacological intervention delivered by family members could reduce the incidence of delirium, as compared with standard management of elderly inpatients at intermediate or high risk of developing this condition during the course of hospitalisation.

Patients and methods

Study design

PEMID is a single-blind randomised controlled clinical trial designed to assess the efficacy of a multicomponent management protocol, in contrast to standard management, in preventing delirium in patients who have been hospitalised for a general medical disease.

Patients

Eligible patients were older adults hospitalised in the internal medicine ward of the Hospital Naval Almirante Nef from September 2009 to June 2010. We considered for inclusion all patients at risk for delirium on the basis of the presence of at least one risk factor from a clinical prediction rule [14]. Briefly, risk factors considered included being >70 years, previous history of cognitive impairment documented in patient medical record with a score on the Minimental State Examination <24 prior to hospitalisation, alcoholism or metabolic imbalances[1] at the moment of admission.

We excluded any patients with delirium on hospital admission (prevalent delirium), those who did not have family support according to the observer evaluation, who refused consent, admitted to a ward other than general internal medicine and those placed in a room with more than two beds to prevent interference with the non-pharmacological intervention.

Procedures

Full informed consent was obtained from all patients or patient's legally authorised representatives prior to randomisation. Patients were randomised using computer-generated random numbers. Investigators were kept unaware of the randomisation process, which was performed by a statistician who was not involved in data collection.

For each patient the following data were obtained from medical records at admission: age, gender, diagnosis upon admittance, comorbidities measured using the Charlson comorbidity index [15], laboratory tests performed at admission (plasma electrolytes, haematocrit, haemoglobin, serum creatinine, urea, serum C-reactive protein levels and white blood cell count) and ability to cope with basic activities of daily living estimated by the Barthel index [16, 17], which in turn was calculated on the basis of the history provided by a family member having lived with the patient during the last 2 weeks prior to hospital admission (see Figure 2).

The non-pharmacological intervention was performed thoroughly by patient's family members to avoid health-care personnel education. The intervention consisted of following six elements:

(i) Education: the observers conducted brief interviews with each patient's family members, in which the main aspects regarding the clinical features and prognostic implications of acute confusional syndromes were explained. These interviews lasted no more than 10 min overall and were accompanied by a specially designed pamphlet.
(ii) Provision of a clock (analogue or digital as required by the patient) and calendar in the room.
(iii) Avoidance of sensory deprivation (glasses, denture and hearing aids must be available as needed).
(iv) Presence of familiar objects in the room (photographs, cushions and radio).
(v) Reorientation of patient provided by family members (current date and time, recent events).
(vi) Extended visitation times (5 h daily).

The specific treatment for delirium was undertaken by the attending physician. None of the researchers interfered in his therapeutic actions.

Outcomes

Patients included in the study were visited on a daily basis to assess the presence of delirium by the confusion assessment method (CAM) tool [18–20]. The selection of CAM was based on its excellent diagnostic capabilities, ease of use and high interobserver reliability [4, 20]. The date of onset of the first episode, total number of days with delirium, evaluation of compliance with the intervention using a

[1]Metabolic imbalances: serum sodium >145 or <135 mEq/l, serum potassium >4.5 mEq/l or <3.5 mEq/l, glycaemia <60mg/dl or >200 mg/dl.

form designed for this purpose and discharge date or transfer to another unit were recorded. Visits were made by three previously trained independent observers who validated each other to the application of CAM by means of Fleiss' kappa statistic ($K = 1$).

The primary efficacy outcome was defined as the presence of delirium at any time during the course of hospitalisation, diagnosed by one of the independent observers using the CAM tool, in any of its different subtypes: hypoactive, hyperactive and mixed. The secondary outcome of interest was the incidence of falls during hospital stay and complications derived from them (fractures, transfers of patients to intensive care units).

Statistical analysis

A minimum sample size of 226 patients was calculated (113 per group) to demonstrate a reduction of 15% in the incidence of delirium in patients undergoing prevention through multicomponent measures, assuming an incidence of 25% and a statistical power of 80% with standard levels of significance (0.05). All data were analysed on an intention-to-treat basis.

First, descriptive statistics tests were performed to assess the characteristics of the study population. The Fisher's exact test was used to evaluate bivariate association of categorical variables. Quantitative variables were compared using Mann–Whitney or Student's *t*-tests according to data distribution characteristics and variances, which were tested by the Kolmogorov–Smirnov and Levène tests, respectively. Kaplan–Meier curves compared with the log-rank tests were used to evaluate the primary outcome. The analysis was performed by a statistician who was unaware of the clinical evaluation process of patients using Stata v10.0® (StataCorp, 1996–2011). The ethics committee of Naval Hospital Almirante Nef approved this study, which is registered at ClinicalTrials.gov. Its registry number is NCT: 01356810.

Results

Patients were recruited from 15 September 2009 to 30 May 2010, and the follow-up was continued until hospital discharge of the last patient in the study group. Out of the total of 1285 eligible patients in this period of time, 294 did not meet the inclusion criteria and 704 were excluded. The main reasons for exclusion are detailed in Figure 1. Out of the 287 patients who finally underwent the randomisation process, 144 were enrolled in the treatment group and 143 in the control group. Thirteen patients were lost to follow-up, 4 in the treatment group and 9 in the control group.

The study sample consisted mainly of female patients (62.7%) with a mean age of 78.2 ± 6.2 years. The median Barthel index was 95 points (interquartile range, IQR: 85–100), while the median Charlson comorbidity index was 2 (IQR: 1–3) points. The most common comorbidities were heart failure (29.1%), chronic obstructive pulmonary disease (21.7%) and any form of cancer (17%). Previous history of mild cognitive impairment was found in 8.1% of patients, while prior dementia, in any of its forms, was present in 5.9% of patients. A history of delirium in a previous hospitalisation was found in 3.9% of the included patients. Patients were well balanced with respect to all their characteristics, as shown in Table 1.

Effectiveness

Twenty-seven cases of incident delirium were identified during the observation period. Mixed delirium was the most common subtype, as it was found in 11 (41%) cases. Hypoactive delirium was observed in 10 (37%) cases, and the hyperactive subtype in 6 (22%) cases. The median duration of delirium was 2 days overall (IQR: 1–5 days), and there were no significant differences between both groups ($P = 0.34$, Mann–Whitney *U*-test). In the group assigned to receive the multicomponent intervention, delirium developed in 8 (5.6%) cases, while control group had 19 (13.3%) episodes. These differences were found to be statistically significant, with a relative risk (RR) of 0.41 for delirium (95% confidence interval: 0.19–0.92, $P = 0.027$) and an RR reduction of developing delirium of 59%. These differences remained significant when analysed with the log-rank test ($P = 0.008$; Figure 2). In absolute terms, risk reduction was 7.78% and the number needed to treat (NNT) was 13. No significant differences in the median length of hospitalisation were seen ($P = 0.36$). All relevant outcomes are shown in Table 2.

Four falls were reported during follow-up, all of which occurred in the control group ($P = 0.06$). One patient had a fall-related fracture and during the study period no patient needed to be transferred, as a result from fall, to more complex care units.

Discussion

This study shows the benefits of a non-pharmacological preventive strategy of delirium in patients at intermediate or high risk for this condition, hospitalised in an internal medicine ward. Our current study supports the research conducted by Inouye in 1999 [5], which also demonstrated that a multicomponent intervention reduces the development of delirium in a similar magnitude than that in this trial. The most important difference in outcomes was a moderate tendency towards a delayed onset of delirium in our study, which could also be a consequence of the non-pharmacological intervention. Under the same viewpoint, additional important evidence that should be considered comes from trials that have shown a reduction in severity and duration of delirium episodes [11, 12]. This further enforces the idea that multicomponent interventions influence the development of delirium; however, no important changes in its incidence amongst the above-mentioned studies were seen.

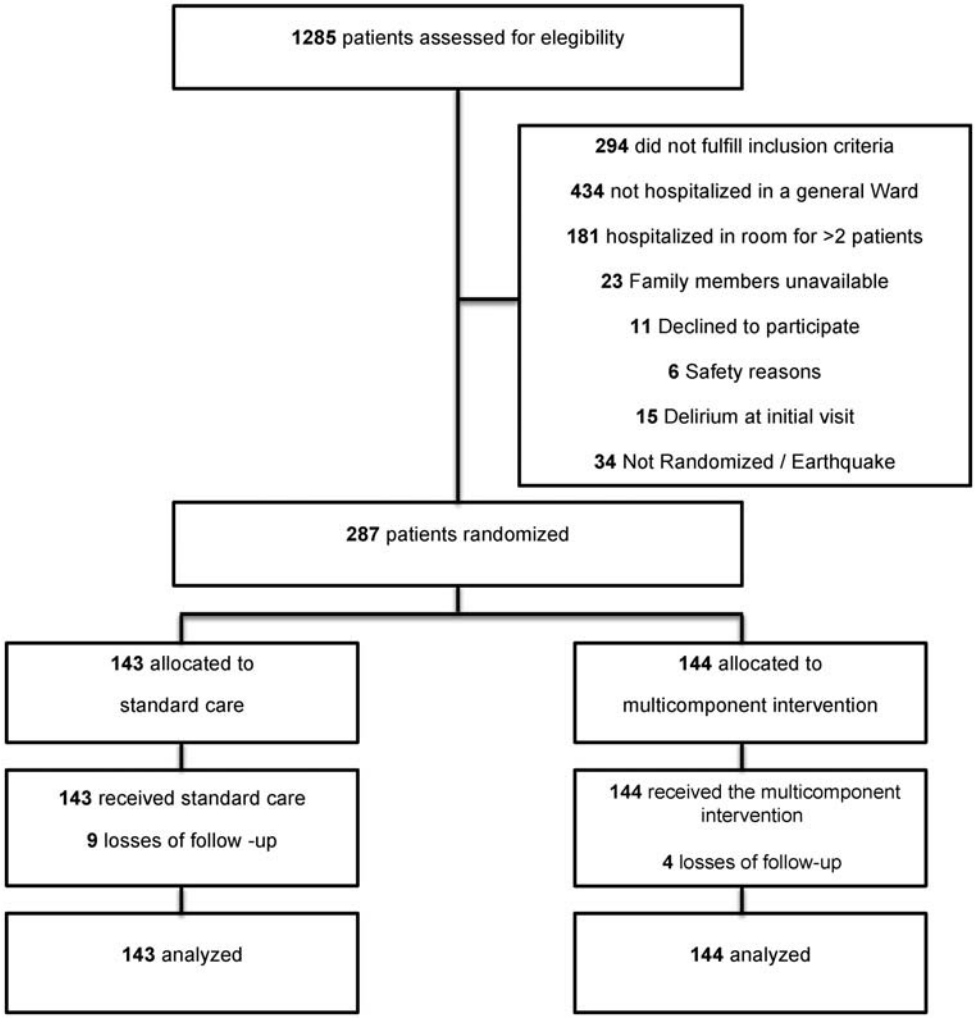

Figure 1. CONSORT flow diagram.

It should be considered that most studies using non-pharmacological interventions [5, 8–12] have employed trained clinical personnel, which is an important difference from our trial. This encourages the widespread application of these preventive measurements due to the fact that only a brief family education session was required amongst the interventional arm; thus making it easily applicable and affordable by most health-care providers.

The incidence of dementia was low [21], roughly affecting 6% of the included patients, as was the prescription of high-risk medications during the hospital stay, present in just about the same proportion (5%). Both these findings are surprising, considering the important role that they play as predisposing and triggering factors of delirium, respectively, and should be kept in mind when analysing results. There are many reasons that could explain this, the first one being the fact that patients with prevalent delirium were excluded from the protocol. We hypothesise that patients with dementia or with a medication-induced episode of delirium could have presented to the emergency room already in delirium, and thus excluded from this trial. A second reason is related to internal policies of the study centre. Patients with moderate to advanced stages of dementia are usually admitted to special care wards, which are four-bed rooms unsuitable for the proper comparison of our non-pharmacological intervention. Another possibility could be linked to the fact that the diagnosis of dementia was solely based on a chart review. Observers did not diagnose cognitive impairment because of the acute processes involved in the hospitalisation.

An additional factor that could have been considered a potential confounder is the use of prophylactic antipsychotics during the hospital stay, a practice that is exceedingly rare at the study centre. Most of the available evidence that could be used for a recommendation in prescribing antipsychotics comes from surgical scenarios, namely the elderly patient with a hip fracture or joint replacement surgery [22, 23] However, a reduction in incident delirium in elderly medical inpatients has yet to be proved, due to the insufficient research that has been conducted in this scenario [13].

The non-significant reduction in the incidence of falls is most likely due to insufficient statistical power to assess this

Table 1. Baseline characteristics of the patients

Characteristic	Control group ($n = 143$)	Intervention group ($n = 144$)	*P*-value
Mean age (years) (SD)	78.3 ± 6.1	78.1 ± 6.3	0.74
Male gender, no. (%)	96 (67)	84 (58)	0.16
Barthel index, median (IQR)	95 (85–100)	95 (85–100)	0.88
Comorbidities[a]			
Charlson comorbidity index, median (IQR)	2 (1–3)	2 (1–4)	0.45
Cancer, no. (%)	28 (19.6)	23 (15.9)	0.44
Metastatic Cancer, no. (%)	6 (4.2)	3 (2.1)	0.33
Heart failure, no. (%)	29 (27.3)	44 (30.6)	0.60
Chronic obstructive pulmonary disease, no. (%)	28 (19.6)	34 (23.6)	0.47
Chronic kidney disease, no. (%)	22 (15.4)	18 (12.5)	0.42
Acute myocardial infarction, no. (%)	11 (7.7)	15 (10.4)	0.41
Mild cognitive impairment, no. (%)	14 (9.8)	9 (6.3)	0.28
Dementia, no. (%)	8 (5.6)	9 (6.3)	1
Diabetes mellitus with end-organ damage, no. (%)	11 (7.6)	13 (9)	0.83
Peripheral vascular disease, no. (%)	7 (4.9)	11 (7.6)	0.34
Previous delirium, no. (%)	3 (2.1)	8 (5.5)	0.22
Mild liver disease, no. (%)	6 (4.2)	4 (2.8)	0.54
Severe liver disease, no. (%)	2 (1.4)	3 (2.1)	1
Mesenchymopathies, no. (%)	3 (2.1)	7 (4.9)	0.34
Peptic ulcer disease, no. (%)	2 (1.4)	8 (5.5)	0.10
Lymphoma, no. (%)	1 (0.7)	1 (0.7)	1
Leukaemia, no. (%)	0 (0)	1 (0.7)	0.5
Hemiplegia, no. (%)	0 (0)	0 (0)	–
Acquired immunodeficiency syndrome, no. (%)	0 (0)	0 (0)	–
Laboratory			
Serum sodium (mEq/l) (SD)	136 ± 5	137 ± 4	0.34
Hyponatremia, no. (%)	29 (20.3)	26 (18)	0.64
Serum potassium (mEq/l) (SD)	4.2 ± 0.7	4.2 ± 0.6	0.95
Serum creatinine (mEq/l) (SD)	1.4 ± 1.1	1.3 ± 1	0.42
Uremia (mg/dl) (SD)	52 ± 38	48 ± 42	0.45
Haemoglobin (g/dl) (SD)	12 ± 2.2	12.1 ± 0.7	0.61
C reactive protein (mg/l) (SD)	11.7 ± 19.8	15.9 ± 30.7	0.22
White cell count (cells/mm^3)	9.580 ± 4.570	9.820 ± 4.185	0.67
Medications			
Patients started on risky medications, no. (%)	7 (4.9)	8 (5.5)	0.80
Benzodiazepines, no. (%)	4 (2.8)	5 (3.5)	0.75
Antihistamines, no. (%)	0 (0)	2 (1.4)	0.25
Anticholinergics, no. (%)	2 (1.4)	1 (0.7)	1
Opioids, no. (%)	1 (0.7)	0 (0)	1

SD, standard deviation.
[a]As defined in the Charlson comorbidity index.

outcome, given that the sample size was not conceived to detect differences in a complication considerably less frequent than delirium. Further studies should be done on the potential association between reduction in falls and implemented multicomponent interventions, because this is also a highly relevant complication to the hospitalised patient.

The strengths of this study include: daily assessment of patients with a validated instrument (CAM), validated observers, the fact that it is a randomised controlled study and that this intervention involves no costs in terms of money or increased health risks.

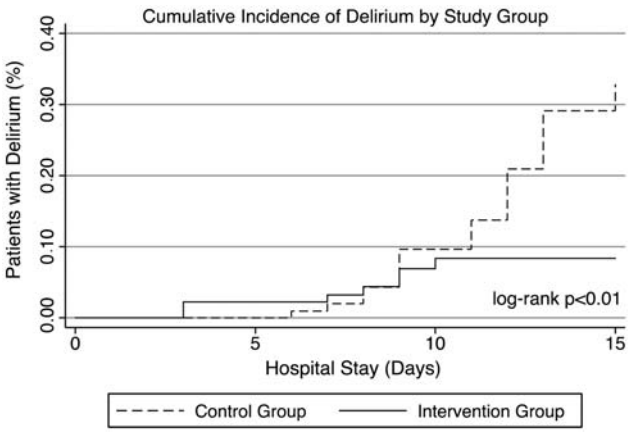

Figure 2. Time-to-event curves of the studied patients.

Table 2. Study outcomes

Outcome	Control group ($n = 143$)	Intervention group ($n = 144$)	*P*-value
Incident delirium, no. (%)	19 (13.3)	8 (5.6)	0.027
Mixed delirium, no. (%)	9 (6.3)	2 (1.4)	
Hypoactive delirium no. (%)	8 (5.6)	2 (1.4)	
Hyperactive delirium, no. (%)	2 (1.4)	4 (2.8)	
Median delirium duration (days) (IQR)	3 (1–5)	2 (1–2)	0.37
Falls, no. (%)	4 (2.8)	0 (0)	0.06
Median hospital stay (days) (IQR)	9 (5–12)	9 (6–13)	0.36

There are some limitations that must be considered. Although this is a randomised controlled trial, family members of the patients in the control group were allowed to implement certain measures that could influence delirium development (daily visits, provision of orientation objects, sensory support equipment, etc.). The incidence of delirium was lower than expected, a fact that is most likely related to this phenomenon. This could have made our statistical power insufficient to detect differences between groups, but the protective effects of the intervention remained significant. It should also be considered that the generation of randomisation sequences by means other than patient inclusion, such as ward location or room number, would have been an inappropriate way to achieve true random allocation.

Simple data masking was another major limitation. The event adjudicants were aware of treatment assignment, which has obvious implications when analysing conclusions. Nevertheless, masking adjudicants would have meant moving patients out of the multicomponent intervention place, which in turn would have interfered with the appropriate interpretation of the study outcomes.

Another factor to be considered is the small number of patients per room [2] where the research was made. This reality is hard to find in other hospitals. Although the intervention was simple enough to be carried out solely by family members, it should be highlighted that cooperation

from their part was obviously required, making proper motivation an important aspect to consider. In our trial, this was achieved through the educational interview that was conducted in the interventional arm, but further strategies should be researched in the future in order to improve this method of prevention.

Conclusions

Our non-pharmacological intervention carried out by family members reduced the risk of developing delirium in patients in general medicine wards. The observed NNT of 13 makes it absolutely applicable with tangible benefits. The application of this kind of intervention seems to be cost-effective and could improve prognosis of hospitalised older patients.

Key points

- Delirium is a common neuropsychiatric syndrome that is most frequently seen in elderly patients.
- It has been associated with increased morbidity and mortality, functional impairment, cognitive decline and increased health-care costs.
- In this study, a multicomponent intervention delivered by family members significantly reduced the incidence of delirium in a group of elderly medical inpatients.

Conflicts of interest

None declared.

References

1. Inouye SK. Delirium in older persons. N Engl J Med 2006; 354: 1157–65.
2. Maldonado JR. Delirium in the acute care setting: characteristics, diagnosis and treatment. Crit Care Clin 2008; 24: 657–722, vii.
3. Young J, Inouye SK. Delirium in older people. BMJ 2007; 334: 842–46.
4. Wong C, Holroyd J, Simel D, Straus S. Does this patient have delirium? Value of bedside instruments. JAMA 2010; 304: 779–86.
5. Inouye SK *et al* A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med 1999; 340: 669–76.
6. Cole MG *et al* Systematic detection and multidisciplinary care of delirium in older medical inpatients: a randomized trial. CMAJ 2002; 167: 753–9.
7. Yang FM *et al* Participation in activity and risk for incident delirium. J Am Geriatr Soc 2008; 56: 1479–84.
8. McDowell JA, Mion LC, Lydon TJ, Inouye SK. A nonpharmacologic sleep protocol for hospitalized older patients. J Am Geriatr Soc 1998; 46: 700–5.
9. Inouye SK. A practical program for preventing delirium in hospitalized elderly patients. Cleve Clin J Med 2004; 71: 890–6.
10. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. J Am Geriatr Soc 2001; 49: 516–22.
11. Milisen K, Foreman MD, Abraham IL *et al* A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients. J Am Geriatr Soc 2001; 49: 523–32.
12. Lundström M, Edlund A, Karlsson S, Brännström B, Bucht GGustafson Y. A multifactorial intervention program reduces the duration of delirium, length of hospitalization, and mortality in delirious patients. J Am Geriatr Soc 2005; 53: 622–8.
13. Siddiqi N, Holt R, Britton AM, Holmes J. Interventions for preventing delirium in hospitalized patients. Cochrane Database of Systematic Reviews. In: The Cochrane Library, Issue 03, Art. No. CD005563.
14. Marcantonio ER *et al* A clinical prediction rule for delirium after elective noncardiac surgery. JAMA 1994; 271: 134–9.
15. Charlson ME *et al* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373–83.
16. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. Md State Med J 1965; 14: 61–5.
17. Sainsbury A *et al* Reliability of the Barthel index when used with older people. Age Ageing 2005; 34: 228–32.
18. Cole MG *et al* An exploratory study of diagnostic criteria for delirium in older medical inpatients. J Neuropsychiatry Clin Neurosci 2007; 19: 151–6.
19. Wei LA *et al* The confusion assessment method: a systematic review of current usage. J Am Geriatr Soc 2008; 56: 823–30.
20. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990; 113: 941–8.
21. Sampson E, Blanchard M, Jones L, Tookman A, King M. Dementia in the acute hospital: prospective cohort study of prevalence and mortality. Br J Psychiatry 2009; 195: 61–6.
22. Kalisvaart KJ, De Jonghe JFM, Bogaards MJ *et al* Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc 2005; 53: 1658–666.
23. Larsen KA, Kelly SE, Stern TA *et al* Administration of olanzapine to prevent postoperative delirium in elderly joint-replacement patients: a randomized, controlled trial. Psychosomatics 2010; 51: 409–18.

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