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Review article

Preventing delirium in dementia: Managing risk factors

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ABSTRACT

Delirium is a common, disabling medical condition that is associated with numerous adverse outcomes. A number of inter-related factors, including pre-existing cognitive impairment, usually contribute to the development of delirium in a particular susceptible individual. Non-pharmacological approaches to prevention typically target multiple risk factors in a systematic manner (multicomponent interventions). There is generally good evidence that multicomponent interventions reduce the incidence of delirium in hospital populations but there are limited data in people with dementia and those living in the community. It is likely that there is a differential effect of specific interventions in those with cognitive impairment (e.g. people with dementia may respond better to simpler, more pragmatic interventions rather than complex procedures) but this cannot be determined from the existing data. Targeted interventions focussed on hydration, medication rationalization and sleep promotion may also be effective in reducing the incidence of delirium, as well as the active involvement of family members in the care of the elderly hospitalized patient. Hospitalization itself is a potential risk factor for delirium and promising data are emerging of the benefits of home-based care as an alternative to hospitalization but this is restricted to specific sub-populations of patients and is reliant on these services being available.

Contents

1. Introduction

Delirium is a serious medical condition associated with alterations in consciousness together with cognitive impairment and attention deficits. It usually develops over a short period of time and fluctuations in intensity and clinical presentation are characteristic of its course. Other associated symptoms include agitation, psychosis, disturbed sleep and mood changes [1]. Delirium has an overall prevalence of 15% among hospitalized older adults although

Abbreviations: CI, confidence interval; CAM, Confusion Assessment Method; CGA, comprehensive geriatric assessment; HELP, Hospital Elder Life Program; HITH, hospital in the home; ICU, intensive care unit; MCI, mild cognitive impairment; MI, multicomponent intervention; MMSE, mini-mental state examination; OR, odds ratio; RR, relative risk; RCT, randomized controlled trial; vs, versus.

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this is considerably higher in certain patient populations, such as those undergoing major surgical procedures [2]. Community prevalence is lower although prevalence in newly admitted nursing home residents is similar to hospital-based populations and estimated at around 16% [3]. Delirium is frequently under-diagnosed and can go unrecognized in 32–66% of individuals [4].

Once established, few treatments are available to lessen the duration and severity of delirium. Typical approaches involve identifying a presumed underlying cause and manipulation of the environment to lessen confusion and associated distress [5]. Targeted pharmacological approaches are usually aimed at symptom reduction in the more severe cases but appear to have little impact on altering the course of delirium and in some cases may aggravate the confusion associated with this [6].

Dementia is a leading cause of disability worldwide and affects approximately 6.5% of the population over the age of 65 [7]. Cognitive impairment that is not severe enough to meet criteria for dementia (mild cognitive impairment – MCI) is a more frequent occurrence with prevalence rates of around 20% in elderly population cohorts [8,9]. Pre-existing cognitive impairment is one of the principal risk factors for delirium and greatly increases the likelihood of delirium developing in a particular individual. The prevalence of delirium superimposed on dementia is clearly higher than that in cognitively unimpaired populations with estimates ranging from 13% to 89% depending on whether the population is hospital or community-based [10,11].

Delirium contributes to poorer outcomes for patients, their families and the health system in general [12]. Delirious patients have longer hospital stays [13], increased morbidity and mortality [14], and are more likely to have a failed discharge [15]. Adverse outcomes associated with delirium may be accentuated in those with pre-existing cognitive impairment. Delirium may impact negatively on the prognosis of dementia and may accelerate the trajectory of cognitive decline with patients not returning to their premorbid baseline once the acute delirium resolves [16,17]. The presence of delirium in patients with dementia leads to longer periods of hospitalization, increased morbidity, greater likelihood of entry to residential care following discharge and a greater than 5-fold increased risk of death [10,18]. Recognition rates may also suffer given the difficulties establishing a clear baseline of cognitive function and misattributing the symptoms of delirium to the underlying dementia [19]. The management of delirium in the setting of dementia is broadly similar to that in all individuals although consideration of increased susceptibility to side effects of pharmacological agents needs to be considered.

Prevention of delirium is clearly the preferred outcome. A number of risk factors (including cognitive impairment) predispose the individual to delirium and thus make them susceptible to its development in the face of a precipitating event (see Table 1). The cause of delirium is usually multifactorial with a variety of risk factors likely contributing to its development [20–23].

The purpose of this review is to provide an overview of non-pharmacological interventions aimed at preventing delirium in older people with underlying cognitive impairment and dementia with a focus on relevant risk factors.

2. Methods

A systematic review of Medline, PsychInfo, Embase and Cochrane databases, from inception to 10 May 2016 was completed, using the following strategy and search terms:

(delirium OR acute confusion) AND (prevent OR preventing OR prevention OR prophylaxis) AND (dementia OR Alzheimer OR cognitive impairment). The electronic search was supplemented by a hand search of the available references. All citations were reviewed, including systematic and narrative reviews, case-reports, case-series, case-control studies and clinical trials. A meta-analysis was not undertaken due to the heterogeneity of the various studies and variable nature of the interventions.

3. Results and discussion

The electronic and manual search yielded 1171 citations (519 from Medline). Two hundred and forty three of these were retained after excluding duplicates, those reporting pharmacological interventions, those reporting treatment rather than prevention, opinion pieces/editorials and studies in younger age groups. The majority of these 243 articles referred to the prevention of delirium in the general older population rather than in those with pre-existing cognitive impairment. Interventions aimed at modifying risk factors for delirium varied widely as did patient populations and study duration.

Some studies specifically excluded people with existing dementia but these were generally in the minority given that this is a clear risk factor for delirium. Studies that included those with existing cognitive however did not always define this categorically and few studies reported outcomes in this group of individuals. The types of interventions could be broadly divided into those that addressed multiple risk factors in a systematic manner (multicomponent interventions – MI) and those that targeted specific factors in at-risk populations (single component interventions). Interventions were also categorized by whether they were delivered in hospital or at home.

3.1. Multicomponent interventions

Multicomponent interventions are a fairly heterogeneous group of measures that typically target multiple delirium risk factors in a systematic manner [24]. Examples of these may include actively looking for and treating infection, improving communication and environmental cues, cessation of possibly harmful medications, geriatrician review, managing pain, avoiding other iatrogenic causes of delirium e.g. unnecessary catheterisation, addressing sensory impairment, avoiding dehydration and reorientation. These have been incorporated into a number of guidelines, including those published by the National Institute for Clinical Excellence [25]. The origin of MI is often attributed to the trial by Inouye et al. published in 1999 [26] although earlier work systematically addressing risk factors in specific patient populations exists [27,28].

Inouye and colleagues tested a MI (the Hospital Elder Life Program – HELP) in 852 individuals aged 70 years and older admitted to general medical wards in a large teaching hospital. The intervention targeted six common risk factors (cognitive impairment, immobility, sleep deprivation, visual and hearing impairment and dehydration) and patients were non-randomly allocated to intervention or usual care wards. Patients were however matched according to age, gender and delirium risk to ensure an even distribution between the groups. The intervention resulted in a modest reduction in the incidence of delirium (9.9% vs 15% in the intervention vs usual care group; odds ratio (OR): 0.60, 95% confidence interval [95%CI]: 0.39–0.92) and individuals in the intervention group spent fewer days with delirium than those in the control arm (105 days vs 161 days, $p = 0.02$). Two hundred and fifty-three individuals had dementia and the prevalence of this was similar between the groups (125/426, 29.3% usual care vs 128/426, 30% intervention). Thirty-two percent (40/125) of people with dementia in the usual care group developed delirium as compared to just 17% (22/128) in the intervention group ($\chi^2 = 7.50$, $p = 0.006$).

Table 1
Predisposing and precipitating factors for delirium.

Predisposing		Precipitating	
Non-modifiable	Potentially Modifiable	Non-modifiable	Potentially modifiable
Older age	Sensory impairment	Surgical factors e.g. type, urgency, use of cardiopulmonary bypass	Surgical factors e.g. post-operative complications, choice of anaesthetic and analgesia, transfusion requirements
Male gender	Depression	Trauma, especially head trauma	Dehydration
Pre-existing cognitive impairment	Frailty	Environmental e.g. admission to hospital, admission to intensive care	Environmental e.g. disorientation, noise, frequent ward changes, physical restraint, poor environmental cues, inadequate staffing and training
Prior history of delirium	Chronic pain	Non-treatable medical conditions e.g. stroke, myocardial infarct, Parkinson's disease	Acute medical illness e.g. chest infection, heart failure, urinary tract infections, hypoxia, anaemia, renal failure, seizures
History of alcohol and substance abuse	Dependence and immobility	Low albumin	Pain
Medical comorbidity such as stroke, terminal illness, HIV, neurological disease, multi-morbidity, renal and hepatic disease, respiratory disease	Medications e.g. anticholinergics and polypharmacy		Constipation
History of falls/inactivity	Constipation Malnutrition/dehydration		Sleep deprivation Metabolic derangements Iatrogenic causes e.g. inappropriate medications, unnecessary catheterization, abrupt medication withdrawal, prolonged hospitalization Alcohol and drug withdrawal/toxicity Emotional stress

Marcantonio et al. [29] enrolled 126 individuals aged 65 and older undergoing emergency hip fracture surgery and randomized them to proactive geriatric consultation or usual care. The intervention consisted of 'targeted recommendations according to a structured protocol' and included things such as adequate oxygen delivery, transfusions when required, optimal fluid and electrolyte balance, pain management, medication rationalization, treatment of constipation, nutrition, early mobilization, environmental optimization and increased surveillance for post-operative complications such as infections. Nearly 40% of the sample had pre-existing dementia (50/126) but this was slightly more prevalent in the usual care group (51% vs 37%, p = 0.13). Delirium incidence overall was lower in the intervention group (20/62, 32%) as compared to the usual care group (32/64, 50%; p = 0.04) but this effect was not apparent in those with pre-existing dementia. Sixty-two percent (13/21) of those with pre-existing dementia developed delirium in the intervention group compared to 69% (20/29) of those in the usual care arm (p = 0.60).

Harari et al. [30] studied patients 65 years and older undergoing elective orthopaedic surgery before (n = 54) and after (n = 54) the introduction of a comprehensive geriatric assessment (CGA) service. This was delivered via a multi-disciplinary team of a consultant geriatrician, nurse specialist, occupational therapist, physiotherapist and social worker and was targeted towards the individual's specific needs. Ten patients (18.5%) developed delirium in the non-intervention cohort compared to just 3 (5.6%) in those once the CGA service was introduced (p = 0.036). The presence of pre-existing cognitive impairment was not determined. Similar results were reported by Lundstrom et al. [31] who randomly assigned 199 hip fracture patients aged 70 and older to postoperative care in a conventional orthopaedic or specialized geriatric ward. The number of days of postoperative delirium was fewer among intervention participants compared with controls (5 ± 7.1 days vs 10.2 ± 13.3 days, p = 0.009).

A Spanish study [32] enrolled 542 medical inpatients and allocated them to an intervention consisting of staff education and targeted risk factor reduction (n = 170) or usual care (n = 372). The prevalence of pre-existing cognitive impairment (MMSE < 24) was quite high (62.5% in intervention and 55% in control, p = 0.14). The intervention was associated with a lower incidence of delirium (intervention, 11.7% vs 18.5%, control; OR 0.4, 95%CI 0.24–0.77). The intervention was delivered in a specific geriatric unit compared to general medical units for the control condition. The assessment of delirium was also unblinded as the assessors interviewed the participants in the units and were therefore aware of allocation.

More recently, an Australian RCT [33] enrolled 648 consecutive medical inpatients and randomised them to a twice daily intervention of exercise, mobilisation and orientation or usual care. Delirium occurred in 4.9% (95%CI 2.3% to 7.3%) of the intervention group and in 5.9% (95%CI 3.8% to 9.2%) of the control group (p = 0.5). The prevalence of pre-existing cognitive impairment was similar between the groups (38/306, 13% in the intervention and 50/343, 15% in the control). Differential rates of delirium were not reported in those with cognitive impairment although the authors did perform a sub-group analysis in those at intermediate to high risk of delirium at baseline (this presumably included people with cognitive impairment) and found no difference in the rate of delirium between the groups (intervention 15/249 vs control, 21/280; p = 0.6).

Many MIs recognise the need to involve those most familiar to patients although few studies have investigated the efficacy of this in reducing the risk of delirium. Martinez et al. [34] enrolled 287 medical patients older than 70 years and randomised them to a family-led intervention (n = 144) or standard management (n = 143). The intervention consisted of 6 elements: education of the family member, provision of a clock or calendar in the room, avoidance of sensory deprivation, provision of familiar objects in the

room e.g. photographs, reorientation and extended visitation times. Delirium developed in 8/144 (5.6%) patients in the MI group compared to 19/143 (13.3%) of the control group (relative risk [RR] 0.41, 95%CI 0.19–0.92). Forty participants were judged to have dementia or MCI on admission but delirium incidence was not reported in this sub-group.

Few studies have specifically investigated the role of MI in people with dementia. Andro et al. [35] investigated the role of a 'temporospatial orientation and communication program' in patients with established dementia admitted to a 26 bed acute care geriatric unit. They compared the incidence of delirium (as diagnosed by the CAM) before and after the introduction of this program during a 6-month period. Nineteen out of 123 (15.5%) patients developed delirium pre-intervention and 7 out of 133 (5.3%) during the post-intervention period. The authors reported a 66% reduction in the risk of delirium (RR 0.34, 95%CI 0.15–0.78).

A Swiss study [36] of delirium-free medical patients with existing cognitive impairment aged 70 and older, utilised a pre- and post-intervention approach (8-month period in 2 consecutive years). The intervention consisted of an educational package for nurses and physicians on the prevention and treatment of delirium. This was aimed at avoiding potential precipitants of delirium in a systematic manner (e.g. dehydration, inappropriate medications, pain) and improved surveillance for signs of delirium. One hundred and thirty participants were enrolled prior to initiation of the intervention and of these, 43 (33.1%) developed delirium during the admission. This was not vastly different to the intervention group where 44/138 (31.9%) developed delirium ($p = 0.896$). The authors did however report less severity of delirium and a shift towards a less harmful medication strategy in the post-intervention period. The groups were well matched for age, gender and degree of existing cognitive impairment.

Two recent systematic reviews of MI for delirium prevention have been published. Hshieh et al. [37] included 14 studies of 4267 participants aged 65 and older in their review. Eleven of these measured delirium incidence and overall demonstrated significant reductions in delirium incidence (OR 0.47, 95%CI 0.38–0.58). The interventions were also effective in falls reduction (OR 0.38, 95%CI 0.25–0.60) and showed a trend towards a decrease in length of stay (0.16 days shorter, 95%CI −0.97–0.64) and institutionalization (OR 0.95, 95%CI 0.71–1.26). The effect of MI was not specifically studied in those with existing cognitive impairment but did appear to confer a modest but statistically non-significant benefit for cognition in the three trials that reported this (mean difference 0.97, 95%CI −0.46–2.41).

Martinez et al. [24] performed a systematic review of seven randomised controlled trials. The trials were conducted in medical ($n = 2$), coronary ($n = 1$), intensive care (ICU) ($n = 1$) and orthopaedic wards ($n = 2$) and included a variety of interventions such as early mobilisation, reorientation, family involvement in care and other elements of a typical MI. The pooled meta-analysis for all trials ($n = 1619$) showed a RR for delirium of 0.73 (95%CI 0.63–0.85). The effect of the interventions was marginally less in those studies defined as having 'high dementia rates' (OR 0.75, 95%CI 0.64–0.88) as compared to 'low dementia rate' (OR 0.48, 95%CI 0.25–0.90).

Taken together, these studies suggest a role for MI in the prevention of delirium in elderly hospitalized patients with and without pre-existing cognitive impairment although few data exist specifically in cognitive impaired populations. It is quite likely that there may be a differential effect of specific interventions in those with cognitive impairment compared to those without (e.g. people with dementia may respond better to simpler, more pragmatic interventions rather than complex reorientation procedures) but this cannot be determined from the existing data.

3.2. Single component interventions

The development of delirium is undoubtedly a complex process resulting from the interplay of various individual and environmental risk factors together with individual vulnerability. It would therefore seem logical that successful interventions would need to address multiple risk factors in a systematic manner, targeted towards the specific individual. Some studies have however addressed individual risk factors in specified populations with mixed results.

Culp et al. [38] enrolled 98 nursing home residents into a weight-based hydration management program ($n = 53$) or usual care ($n = 45$) over 4 weeks. Very few participants developed delirium (3 in treatment and 3 in control) with no statistical difference between the groups. In another nursing home based cluster-randomized trial, Lapane et al. [39] introduced risk assessment medication software to reduce the potential of medication effects on delirium and falls incidence. Newly admitted residents in the intervention homes experienced a lower rate of delirium compared to usual care homes (HR 0.42, 95%CI 0.35–0.52). Thirty-five percent of residents in the intervention homes had dementia compared with 43% of residents in the usual care homes.

One of the cardinal symptoms of delirium is disruption to circadian sleeping patterns, especially in stimulating environments such as intensive care units. Van Rompaey et al. [40] showed improved sleep perception and reduced incidence of delirium in ICU patients randomized to the use of ear plugs at night ($n = 69$) compared to usual care ($n = 67$) – hazard ratio (HR) 0.47, 95%CI 0.27–0.82. Participants with dementia were excluded and the mean age was 57 (range 19–81). Kamdar et al. [41] enrolled 300 medical ICU patients in a before and after 'quality improvement multi-faceted sleep-promoting' study. The intervention included ear plugs, eye masks, soothing music and in some cases, pharmacological sleeping aids. They reported a reduced incidence of delirium in the 175 participants admitted during the quality improvement period compared to the 110 admitted prior to this (49% vs 69%, OR 0.46, 95%CI 0.23–0.89). Participants again were relatively young (age range 43–63) and unlikely to have underlying cognitive impairment.

3.3. Home-based care

Rates of delirium in hospital populations are clearly higher than in the community. This is most likely due to increased morbidity in these populations but may also be related to the hospitalisation itself. An earlier trial in Sydney, Australia [42] of 100 older adults randomised to treatment at home (hospital-in-the-home; HITH) or usual care (admission to hospital) showed lower delirium incidence in the intervention group (0% vs 20.4%, 95%CI 9.1% to 31.7%) although the diagnosis of delirium was based on review of case notes. A later trial by the same authors [43] randomised 104 consecutive referred geriatric patients to rehabilitation at home or in hospital. The home group had lower odds of developing delirium (as detected by the CAM) compared to the hospitalised group (OR 0.17, 95%CI 0.03–0.65). A quarter of the sample had dementia at study baseline (26/104) but a sub-group analysis of this group was not possible given the rather low incidence of delirium overall (4/104, 3.8%).

Isaia et al. [44] compared delirium incidence in an elderly (≥75 years) patient cohort at medium to high risk of delirium treated for various acute illnesses either in hospital or at home. The incidence of delirium was higher in the hospitalized group compared to those treated at home (16.6% vs 4.7%, RR 3.8, 95%CI 1.8–3.7) and they tended to have longer durations of delirium (7.2 ± 17.3 days vs 1.1 ± 5.1 days, $p < 0.001$). The study was not randomized however and selection bias may have been an issue. Interestingly though, the HITH group had poorer physical and

cognitive function at baseline than the hospitalized group (mean MMSE 18.1 vs 21.6, p = 0.05).

More recently, Verloo et al. [45] piloted a specialist geriatric nurse-led intervention compared to usual at home care in 103 recently discharged elderly patients. The intervention group (n = 51) received 5 additional patient-centred nursing interventions but this had no impact on the incidence of delirium symptoms over one month as compared to the control (n = 52) group (1.90 ± 1.56 vs 2.50 ± 1.90, p = 0.084). This difference was statistically significant after adjustment for age, polypharmacy, cognitive impairment and comorbidities (p = 0.046).

4. Concluding remarks

Delirium is a significant medical condition that significantly adds to morbidity, mortality and health expenditure and is especially problematic in those with pre-existing cognitive impairment. The aetiology of delirium is complex and usually relies on the complex inter-play of multiple risk factors in a vulnerable individual. A number of strategies have been explored to reduce the risk of delirium with perhaps the greatest evidence favouring the use of multicomponent strategies implemented in a systematic and patient-centred manner. These can however be difficult and cumbersome to implement and even simple interventions (e.g. ear plugs, medication software) can be effective although the existing body of evidence in this area is relatively modest. Promising data are emerging of the benefits of home-based care as an alternative to hospitalization but this is restricted to specific sub-populations of patients.

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References

[1] S. Saxena, D. Lawley, Delirium in the elderly: a clinical review, Postgrad. Med. J. 85 (1006) (2009) 405–413.
[2] G. Bucht, Y. Gustafson, O. Sandberg, Epidemiology of delirium, Dement. Geriatr. Cogn. Disord. 10 (5) (1999) 315–318.
[3] D.K. Kiely, M.A. Bergmann, K.M. Murphy, R.N. Jones, E.J. Orav, E.R. Marcantonio, Delirium among newly admitted postacute facility patients: prevalence, symptoms, and severity, J. Gerontol. A. Biol. Sci. Med. Sci. 58 (5) (2003) M441–M445.
[4] S.K. Inouye, Delirium in hospitalized older patients: recognition and risk factors, J. Geriatr. Psychiatry Neurol. 11 (3) (1998) 118–125, discussion 57–58.
[5] S.K. Inouye, R.G. Westendorp, J.S. Saczynski, Delirium in elderly people, Lancet 383 (9920) (2014) 911–922.
[6] J.I. Friedman, L. Soleimani, D.P. McGonigle, C. Egol, J.H. Silverstein, Pharmacological treatments of non-substance-withdrawal delirium: a systematic review of prospective trials, Am. J. Psychiatry 171 (2) (2014) 151–159.
[7] C.P. Ferri, M. Prince, C. Brayne, H. Brodaty, L. Fratiglioni, M. Ganguli, et al., Global prevalence of dementia: a Delphi consensus study, Lancet 366 (9503) (2005) 2112–2117.
[8] K. Ritchie, S. Artero, J. Touchon, Classification criteria for mild cognitive impairment: a population-based validation study, Neurology 56 (1) (2001) 37–42.
[9] O.L. Lopez, W.J. Jagust, S.T. DeKosky, J.T. Becker, A. Fitzpatrick, C. Dulberg, et al., Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 1, Arch. Neurol. 60 (10) (2003) 1385–1389.
[10] D.M. Fick, J.V. Agostini, S.K. Inouye, Delirium superimposed on dementia: a systematic review, J. Am. Geriatr. Soc. 50 (10) (2002) 1723–1732.
[11] D.M. Fick, A.M. Kolanowski, J.L. Waller, S.K. Inouye, Delirium superimposed on dementia in a community-dwelling managed care population: a 3-year retrospective study of occurrence, costs, and utilization, J. Gerontol. A. Biol. Sci. Med. Sci. 60 (6) (2005) 748–753.
[12] J. Witlox, L.S. Eurelings, J.F. de Jonghe, K.J. Kalisvaart, P. Eikelenboom, W.A. van Gool, Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis, JAMA 304 (4) (2010) 443–451.
[13] J. McCusker, M.G. Cole, N. Dendukuri, E. Belzile, Does delirium increase hospital stay? J. Am. Geriatr. Soc. 51 (11) (2003) 1539–1546.
[14] S.T. Pendlebury, N.G. Lovett, S.C. Smith, N. Dutta, C. Bendon, A. Lloyd-Lavery, et al., Observational, longitudinal study of delirium in consecutive unselected acute medical admissions: age-specific rates and associated factors, mortality and re-admission, BMJ Open 5 (11) (2015) e007808.
[15] J. Tropea, D. LoGiudice, D. Liew, A. Gorelik, C. Brand, Poorer outcomes and greater healthcare costs for hospitalised older people with dementia and delirium: a retrospective cohort study, Int. J. Geriatr. Psychiatry (2016).
[16] T.G. Fong, R.N. Jones, P. Shi, E.R. Marcantonio, L. Yap, J.L. Rudolph, et al., Delirium accelerates cognitive decline in Alzheimer disease, Neurology 72 (18) (2009) 1570–1575.
[17] M.F. Weiner, Impact of delirium on the course of Alzheimer disease, Arch. Neurol. 69 (12) (2012) 1639–1640.
[18] T.G. Fong, R.N. Jones, E.R. Marcantonio, D. Tommet, A.L. Gross, D. Habtemariam, et al., Adverse outcomes after hospitalization and delirium in persons with Alzheimer disease, Ann. Intern. Med. 156 (12) (2012) 848–856, W296.
[19] D. Fick, M. Foreman, Consequences of not recognizing delirium superimposed on dementia in hospitalized elderly individuals, J. Gerontol. Nurs. 26 (1) (2000) 30–40.
[20] J. Bucerius, J.F. Gummert, M.A. Borger, T. Walther, N. Doll, V. Falk, et al., Predictors of delirium after cardiac surgery delirium: effect of beating-heart (off-pump) surgery, J. Thorac. Cardiovasc. Surg. 127 (1) (2004) 57–64.
[21] S.K. Inouye, Delirium in older persons, N. Engl. J. Med. 354 (11) (2006) 1157–1165.
[22] S. Ahmed, B. Leurent, E.L. Sampson, Risk factors for incident delirium among older people in acute hospital medical units: a systematic review and meta-analysis, Age Ageing 43 (3) (2014) 326–333.
[23] J.D. Schor, S.E. Levkoff, L.A. Lipsitz, C.H. Reilly, P.D. Cleary, J.W. Rowe, et al., Risk factors for delirium in hospitalized elderly, JAMA 267 (6) (1992) 827–831.
[24] F. Martinez, C. Tobar, N. Hill, Preventing delirium: should non-pharmacological, multicomponent interventions be used? A systematic review and meta-analysis of the literature, Age Ageing 44 (2) (2015) 196–204.
[25] R. O'Mahony, L. Murthy, A. Akunne, J. Young, G. Guideline Development, Synopsis of the National Institute for Health and Clinical Excellence guideline for prevention of delirium, Ann. Intern. Med. 154 (11) (2011) 746–751.
[26] S.K. Inouye, S.T. Bogardus Jr., P.A. Charpentier, L. Leo-Summers, D. Acampora, T.R. Holford, et al., A multicomponent intervention to prevent delirium in hospitalized older patients, N. Engl. J. Med. 340 (9) (1999) 669–676.
[27] Y. Gustafson, B. Brannstrom, D. Berggren, J.I. Ragnarsson, J. Sigaard, G. Bucht, et al., A geriatric-anesthesiologic program to reduce acute confusional states in elderly patients treated for femoral neck fractures, J. Am. Geriatr. Soc. 39 (7) (1991) 655–662.
[28] C.S. Landefeld, R.M. Palmer, D.M. Kresevic, R.H. Fortinsky, J. Kowal, A randomized trial of care in a hospital medical unit especially designed to improve the functional outcomes of acutely ill older patients, N. Engl. J. Med. 332 (20) (1995) 1338–1344.
[29] E.R. Marcantonio, J.M. Flacker, R.J. Wright, N.M. Resnick, Reducing delirium after hip fracture: a randomized trial, J. Am. Geriatr. Soc. 49 (5) (2001) 516–522.
[30] D. Harari, A. Hopper, J. Dhesi, G. Babic-Illman, L. Lockwood, F. Martin, Proactive care of older people undergoing surgery ('POPS'): designing, embedding, evaluating and funding a comprehensive geriatric assessment service for older elective surgical patients, Age Ageing 36 (2) (2007) 190–196.
[31] M. Lundstrom, B. Olofsson, M. Stenvall, S. Karlsson, L. Nyberg, U. Englund, et al., Postoperative delirium in old patients with femoral neck fracture: a randomized intervention study, Aging Clin. Exp. Res. 19 (3) (2007) 178–186.
[32] M.T. Vidan, E. Sanchez, M. Alonso, B. Montero, J. Ortiz, J.A. Serra, An intervention integrated into daily clinical practice reduces the incidence of delirium during hospitalization in elderly patients, J. Am. Geriatr. Soc. 57 (11) (2009) 2029–2036.
[33] K.J. Jeffs, D.J. Berlowitz, S. Grant, V. Lawlor, M. Graco, N.A. de Morton, et al., An enhanced exercise and cognitive programme does not appear to reduce incident delirium in hospitalised patients: a randomised controlled trial, BMJ Open 3 (6) (2013).
[34] F.T. Martinez, C. Tobar, C.I. Beddings, G. Vallejo, P. Fuentes, Preventing delirium in an acute hospital using a non-pharmacological intervention, Age Ageing 41 (5) (2012) 629–634.

[35] M. Andro, E. Comps, S. Estivin, A. Gentric, Prevention of delirium in demented hospitalized patients, Eur. J. Intern. Med. 23 (2) (2012) 124–125.
[36] W. Hasemann, D. Tolson, J. Godwin, R. Spirig, I.A. Frei, R.W. Kressig, A before and after study of a nurse led comprehensive delirium management programme (DemDel) for older acute care inpatients with cognitive impairment, Int. J. Nurs. Stud. 53 (2016) 27–38.
[37] T.T. Hshieh, J. Yue, E. Oh, M. Puelle, S. Dowal, T. Travison, et al., Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis, JAMA Intern. Med. 175 (4) (2015) 512–520.
[38] K. Culp, J. Mentes, B. Wakefield, Hydration and acute confusion in long-term care residents, West. J. Nurs. Res. 25 (3) (2003) 251–266, discussion 67–73.
[39] K.L. Lapane, C.M. Hughes, L.A. Daiello, K.A. Cameron, J. Feinberg, Effect of a pharmacist-led multicomponent intervention focusing on the medication monitoring phase to prevent potential adverse drug events in nursing homes, J. Am. Geriatr. Soc. 59 (7) (2011) 1238–1245.
[40] B. Van Rompaey, M.M. Elseviers, W. Van Drom, V. Fromont, P.G. Jorens, The effect of earplugs during the night on the onset of delirium and sleep perception: a randomized controlled trial in intensive care patients, Crit. Care 16 (3) (2012) R73.
[41] B.B. Kamdar, L.M. King, N.A. Collop, S. Sakamuri, E. Colantuoni, K.J. Neufeld, et al., The effect of a quality improvement intervention on perceived sleep quality and cognition in a medical ICU, Crit. Care Med. 41 (3) (2013) 800–809.
[42] G.A. Caplan, J.A. Ward, N.J. Brennan, J. Coconis, N. Board, A. Brown, Hospital in the home: a randomised controlled trial, Med. J. Aust. 170 (4) (1999) 156–160.
[43] G.A. Caplan, J. Coconis, N. Board, A. Sayers, J. Woods, Does home treatment affect delirium? A randomised controlled trial of rehabilitation of elderly and care at home or usual treatment (The REACH-OUT trial), Age Ageing 35 (1) (2006) 53–60.
[44] G. Isaia, M.A. Astengo, V. Tibaldi, M. Zanocchi, B. Bardelli, R. Obialero, et al., Delirium in elderly home-treated patients: a prospective study with 6-month follow-up, Age (Dordr.) 31 (2) (2009) 109–117.
[45] H. Verloo, C. Goulet, D. Morin, A. von Gunten, Effect estimation of an innovative nursing intervention to improve delirium among home-Dwelling older adults: a randomized controlled pilot trial, Dement. Geriatr. Cogn. Dis. Extra 5 (1) (2015) 176–190.