Interventions for preventing delirium in older people in institutional long-term care (Review)

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[Intervention Review]

Interventions for preventing delirium in older people in institutional long-term care

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ABSTRACT

Background

Delirium is a common and distressing complication of a range of stressor events including infection, new medications and environment change that is often experienced by older people with frailty and dementia. Older people living in institutional long-term care (LTC) are at high risk of delirium, which increases the risk of admission to hospital, development of or worsening of dementia, and mortality. Delirium is also associated with substantial healthcare costs. Although it is possible to prevent delirium in the hospital setting by providing multicomponent delirium prevention interventions it is currently unclear whether interventions to prevent delirium in LTC are effective.

Objectives

To assess the effectiveness of interventions for preventing delirium in older people in long term care.

Search methods

We searched ALOIS (www.medicine.ox.ac.uk/alois) - the Cochrane Dementia and Cognitive Improvement Group's Specialised Register - on 23 April 2013. The search was as sensitive as possible to identify all studies on ALOIS relating to delirium. We ran additional separate searches in major healthcare databases, trial registers, the Cochrane Central Register of Controlled Trials (CENTRAL) and grey literature sources, to ensure that the search was as comprehensive as possible.

Selection criteria

We included randomised controlled trials (RCTs) and cluster-randomised controlled trials (cluster-RCTs) of single- and multicomponent non-pharmacological and pharmacological interventions for preventing delirium in older people (aged 65 years and over) in permanent LTC residence.

Data collection and analysis

Two independent review authors examined the titles and abstracts of citations identified by the search for eligibility and extracted data, with any disagreements settled by consensus. Primary outcomes were prevalence, incidence and severity of delirium. Secondary outcomes included new diagnosis of dementia, activities of daily living, quality of life and adverse outcomes. We used risk ratios (RRs) as measures of treatment effect for dichotomous outcomes and hazard ratios (HR) for time to event data.

Main results

We included two trials that recruited 3636 participants. Both were complex single-component non-pharmacological delirium prevention interventions. Risk of bias for many items was unclear due to inadequate reporting. Notably, there was no evidence of blinding of trial participants or assessors in either trial. One small cluster-RCT (n = 98) of a hydration-based intervention reported no reduction in delirium incidence in the intervention group compared to control (RR 0.85, 95% confidence interval (CI) 0.18 to 4.00, analysis not adjusted for clustering, very low quality evidence). Results were imprecise and there were serious limitations evident in trial design. One large cluster-RCT (n = 3538) of a computerised system to identify medications that may contribute to delirium risk and trigger a pharmacist-led medication review reported a large reduction in delirium incidence (12-month HR 0.42, CI 0.34 to 0.51, moderate quality evidence) but no clear evidence of reduction in hospital admissions (HR 0.89, CI 0.72 to 1.10, moderate quality evidence), in mortality (HR 0.88, CI 0.66 to 1.17, moderate quality evidence) or in falls risk (HR 1.03, CI 0.92 to 1.15, moderate quality evidence).

Authors' conclusions

Our review identified very limited evidence on interventions for preventing delirium in older people in LTC. Introduction of a software-based intervention to identify medications that could contribute to delirium risk so that a pharmacist-led medication review and monitoring plan can be initiated may reduce incidence of delirium for older people in institutional LTC. This is based on one large RCT in the United States and may not be practical in other countries which do not have comparable information technology services available in care homes. Our review identified only one ongoing pilot trial of a multicomponent delirium prevention intervention and no trials of pharmacological agents. Future trials of computerised medication management systems and multicomponent non-pharmacological and pharmacological delirium prevention interventions for older people in LTC are needed to help inform the provision of evidence-based care for this vulnerable group.

PLAIN LANGUAGE SUMMARY

Interventions for preventing delirium in older people in institutional long-term care (LTC)

Review question

We reviewed the evidence about the effectiveness of interventions for preventing delirium in older people living in long-term care (LTC).

Background

LTC is the name used for residential homes, which provide personal care, supervision with medications and some help with day to day activities, and nursing homes, which provide 24-hour nursing care. Delirium is a common and serious illness for older people living in LTC. People with delirium usually become more confused over a few hours or a couple of days. Some people with delirium become quiet and sleepy but others become agitated and disorientated, so it can be a very distressing condition. It can also increase the chances of being admitted to hospital and developing dementia, and LTC residents who develop delirium are at increased risk of death.

Importantly, studies of people in hospital have shown that it is possible to prevent around a third of cases of delirium by providing an environment and care plan that target the main risk factors for delirium. For example: providing better lighting and signs to avoid disorientation; avoiding unnecessary use of catheters to help prevent infection; avoiding medications which increase delirium risk.

This review has searched for and assessed research on preventing delirium in older people living in LTC.

Study characteristics

The evidence is current to 04/2013. We found two studies that included 3636 participants. Both studies were done in the United States.

The first study tested whether delirium can be prevented by calculating how much fluid an older person in a care home needs each day and ensuring that hydration was provided by giving regular drinks. 98 people participated in the study, which lasted four weeks.

The second study tested the effect of a computer programme which searched prescriptions for medications that might increase the chance of developing delirium so that a pharmacist could adjust or stop them. 3538 people participated in the study, which lasted 12 months.

Key findings

The first study found that the hydration intervention did not reduce delirium. However, this was a small study of short duration with serious design problems.

The second study found that the computerised medication search programme and pharmacist review reduced delirium but there was no clear reduction in hospital admissions, deaths or falls. One problem with the findings of this study is that it might not be possible to use this computer programme in different countries that do not have similar computer systems.

Quality of the evidence

There is very low-quality evidence on the effectiveness of hydration interventions for reducing the incidence of delirium in older people in LTC. It is therefore not possible to draw firm conclusions.

There is moderate-quality evidence that a computerised medication search programme and pharmacist review may reduce the incidence of delirium in older people in LTC.

There is no clear evidence that a computerised medication search programme and pharmacist review reduces hospitalisation, mortality or falls for older people in LTC.

As this review only found a very small number of research studies, we have recommended that further research should be conducted testing different ways of preventing delirium for older people living in LTC. This may help improve the quality of care for this vulnerable group.

External funding

There was no source of external funding for this review.

Conflicts of interest

NS is chief investigator for a National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB) grant to investigate the effects of a delirium prevention intervention for older people in long term care.

JY is a co-applicant for a National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB) grant to investigate the effects of a delirium prevention intervention for older people in long term care.

AC, RH and AH declare that they have no known conflicts of interest.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Single-component medication monitoring and adjustment intervention versus control for preventing delirium in older people in institutional long term care

Patient or population: People at risk of delirium in institutional long term care
Settings: Long term care institutions
Intervention: Single-component medication monitoring and adjustment intervention versus control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of resident months (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Single-component medication monitoring and adjustment intervention versus control				
Incidence of delirium[1] NH CAM Follow-up: mean 12 months	**Study population**		**HR 0.42** (0.34 to 0.51)	7311 (1 study)[2]	⊕⊕⊕◯ **moderate**[3,4,5]	
	104 per 1000	**45 per 1000** (37 to 54)				
	Medium risk population					
	99 per 1000	**43 per 1000** (35 to 52)				
Unplanned hospitalisation[1] Admissions to hospital Follow-up: mean 12 months	**Study population**		**HR 0.89** (0.72 to 1.10)	7599 (1 study)[2]	⊕⊕⊕◯ **moderate**[3,4,5]	
	55 per 1000	**49 per 1000** (40 to 60)				
	Medium risk population					
	57 per 1000	**51 per 1000** (41 to 63)				

Mortality[1] Mortality Follow-up: months	mean	12	**Study population**		**HR 0.88** (0.66 to 1.17)	9412 (1 study)[2]	⊕⊕⊕○ **moderate**[3,4,5]
			25 per 1000	**22 per 1000** (17 to 29)			
			Medium risk population				
			25 per 1000	**22 per 1000** (17 to 29)			
Falls[1] Fall events Follow-up: months	mean	12	**Study population**		**RR 1.03** (0.92 to 1.15)	2275 (1 study)[2]	⊕⊕⊕○ **moderate**[3,4,5]
			523 per 1000	**539 per 1000** (481 to 601)			
			Medium risk population				
			523 per 1000	**539 per 1000** (481 to 601)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **HR:** Hazard ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Assumed risk based on control group risk in included study.
[2]Number of participants is number of resident months, defined as number of days from first assessment to the first outcome occurrence, the last date in the nursing home, the death date, or December 31 2004.
[3]The trial was assessed at high risk of methodological bias for blinding of participants and personnel.
[4]Only one trial therefore unable to assess consistency.
[5]Large effect size observed but only one trial therefore not eligible for upgrade.

BACKGROUND

Delirium is a distressing complication of a range of stressor events, including infection, new medications and dehydration, and is often experienced by older people with frailty and dementia. Although a single event can precipitate delirium, it is more common for multiple factors to interact and a multifactorial model of delirium has been established to help illustrate how delirium is precipitated in people at risk (Inouye 1996). Using this model, a seemingly small insult such as a minor infection or new medication in those at high risk can lead to delirium.

Delirium is associated with increased morbidity, functional decline, risk of developing or worsening dementia and death (Inouye 2006; Witlox 2010). It is common throughout the health and social care system and has substantial health and socioeconomic costs (Inouye 2006; Leslie 2008). The majority of delirium research has focused on hospitalised people, but long-term care (LTC) residents are also at high risk, with the point prevalence of delirium at around 15% in these settings (Siddiqi 2009). The multifactorial model of delirium has been validated in the LTC setting (Voyer 2010) and LTC residents with moderate to severe cognitive impairment are at particularly high risk (McCusker 2011). The development of delirium in older people in LTC is associated with increases in risk of admission to hospital, rates of re-admission and mortality (Siddiqi 2009). Notably, the duration of delirium in LTC residents is typically increased, compared to delirium in hospitalised people (Cole 2012). Although it is possible to prevent delirium in the hospital setting by providing multicomponent delirium prevention interventions (Inouye 1999; Marcantonio 2001), it is currently unclear whether interventions to prevent delirium in LTC are effective.

LTC facilities have expanded over recent decades in response to the ageing population. In the UK, 4.5% of people aged over 65 live in LTC, rising to 20% of people aged over 85 (Soule 2005). The environment and systems of care in LTC share features with hospitals that are likely to increase the risk of delirium. As age over 65 and presence of cognitive impairment or dementia are important risk factors for delirium, the high point prevalence of delirium is likely to be a reflection of clustering of these risk factors in LTC.

LTC facilities are considered to be the 'usual place of residence', which distinguishes them from other more temporary facilities, including respite care, intermediate care and post-acute care. LTC is the broad umbrella term for facilities including residential homes, which provide personal care, supervision with medications and some help with activities of daily living, and nursing homes, which provide 24-hour nursing care by staff with specialist skills in management of physical and mental health conditions (Ames 2005).

Description of the condition

Delirium is characterised by the rapid onset of fluctuating confusion, disturbed awareness and inattention. The diagnostic criteria for delirium have been operationalised in the *Diagnostic and Statistical Manual of Mental Disorders* Volumes III, III-revised, IV and 5 (APA 1980; APA 1987; APA 1994; APA 2013) and the *International Classification of Diseases* Volume 10 (WHO 1992). A key feature of delirium is change and fluctuation in a range of key symptoms and behaviours including:

1. Cognitive function (e.g. worsened concentration, slow responses, confusion);
2. Perception (e.g. visual or auditory hallucinations);
3. Physical function (e.g. reduced mobility, reduced movement, restlessness, agitation, changes in appetite, sleep disturbance);
4. Social behaviour (e.g. lack of co-operation, withdrawal, or alterations in communication, mood or attitude or both (NICE 2010)).

Delirium is triggered when a susceptible individual is exposed to often multiple precipitating factors, including infection, medications, pain and dehydration (Inouye 1998). These multiple factors are considered to interact in a cumulative manner; the greater the number of factors, the greater the risk of delirium. The pathophysiology of delirium is incompletely understood, but a complex interaction between acetylcholine and multiple neurotransmitters including dopamine, noradrenaline, glutamate and gamma-amino hydroxybutyric acid (GABA) is considered important (Alagiakrishnan 2004; Hshieh 2008; Clegg 2011).

Description of the intervention

This review examines the effectiveness of single- and multicomponent non-pharmacological and pharmacological interventions for preventing delirium in older people in LTC.

Non-pharmacological interventions target the important precipitating factors for delirium and usually incorporate a multicomponent approach to address the multiple potential factors, including: actively looking for and treating infection; avoiding unnecessary urinary catheterisation; undertaking a medication review to identify medications associated with increased risk of delirium; assessing for pain and initiating treatment where appropriate; addressing sensory impairment by providing visual and hearing aids (NICE 2010). Multicomponent delirium prevention interventions incorporating such strategies have been demonstrated to be effective at reducing delirium in hospitalised people (Inouye 1999; Marcantonio 2001; NICE 2010). Introduction of protocols, staff education or systems redesign are methods that have been used to introduce these interventions (Inouye 1999; Rockwood 1999). As many of the reported risk factors for delirium are similar in both hospitalised people and LTC residents (Siddiqi 2009), non-pharmacological interventions that have been shown to be effective in hospitals by targeting these risk factors may have a role in reducing the incidence of delirium in LTC, with appropriate

modification to account for differences in environmental factors and care processes (McCusker 2013).
Although it is biologically plausible that pharmacological agents could prevent delirium by acting on neurotransmitter pathways, a small number of trials of pharmacological interventions for preventing delirium in hospitalised people have demonstrated limited effectiveness (Kalisvaart 2005; Siddiqi 2007; Tabet 2009) and require further investigation (NICE 2010).

How the intervention might work

Non-pharmacological interventions target the multiple potential precipitating factors for delirium to reduce their cumulative effect. Pharmacological interventions target the important neurotransmitter pathways that have been implicated in the complex pathophysiology of delirium.

Why it is important to do this review

This review examines evidence from randomised controlled trials (RCTs) and cluster-randomised controlled trials (cluster-RCTs) for the clinical and cost effectiveness of non-pharmacological and pharmacological interventions to prevent delirium in older people in LTC. This evidence will help inform the development and future commissioning of evidence-based services to improve the health and well-being of this vulnerable group. It will also help improve knowledge about delirium in LTC, inform the development of LTC staff education programmes and help stimulate future research into prevention of delirium in LTC residents.

OBJECTIVES

To assess the effectiveness of interventions for preventing delirium in older people in LTC.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs) and cluster-randomised controlled trials (cluster-RCTs) for this review.

Types of participants

For this review, LTC is defined as an institution that is the permanent residence of an individual, providing accommodation together with personal or nursing care.

Inclusion criteria

Trials investigating interventions for preventing delirium in older people in LTC were eligible for inclusion. It is possible that any general health intervention for older people in LTC will have the effect of reducing delirium. However, we only considered trials that used a validated method of delirium diagnosis, such as DSM-III, DSM-III-R, DSM-IV and ICD-10 (APA 1980; APA 1987; APA 1994; WHO 1992), or a diagnostic tool validated against these, e.g. confusion assessment method (CAM) (Inouye 1990), delirium rating scale (DRS) (Trzepacz 1988).
Trials in which the mean age of participants was 65 years or older.

Exclusion criteria

Trials of hospitalised people.
Trials taking place in a setting that was not the permanent residence of study participants (e.g. post-acute care, intermediate care, continuing care).
Trials taking place in a palliative care setting.
Non-randomised intervention trials, observational studies.

Types of interventions

We considered interventions designed to prevent delirium, including non-pharmacological and pharmacological single- and multicomponent interventions which included a control group for comparison.

Types of outcome measures

We identified the primary, secondary and adverse outcome measures that are important both for older people in LTC and for health and social care systems.

Primary outcomes

Prevalence and incidence of delirium, using a validated diagnostic method (see Types of studies).
Severity of delirium, using a validated diagnostic method (e.g. delirium rating scale (Trzepacz 1988)).

Secondary outcomes

Length of delirium episode.
Proportion of time spent with delirium (total number of days of delirium/length of follow-up period).
Total number of delirium episodes.
Cognitive function, using any validated continuous scale.

New diagnosis of dementia.
Worsening severity of dementia, using a validated diagnostic method e.g. clinical dementia rating (CDR) scale (Morris 1993), dementia severity rating scale (DSRS) (Clark 1996).
Quality of life.
Direct costs of intervention.
Health utility change and cost effectiveness of intervention.
Activities of daily living.
Adverse outcomes (adverse medication outcomes, falls, new pressure ulcers, unplanned hospitalisation, mortality).
We will include the following outcomes in the final 'Summary of findings' tables:
Prevalence of delirium.
Incidence of delirium.
Severity of delirium.
Length of delirium episode.
Cognitive function, using any validated continuous scale.
Cost effectiveness of intervention.
Adverse outcomes.

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois) - the Cochrane Dementia and Cognitive Improvement Group's Specialised Register - on 23 April 2013. The search was as sensitive as possible to identify all studies on ALOIS relating to delirium.
ALOIS is maintained by the Trials Search Co-ordinator of the Cochrane Dementia and Cognitive Improvement Group and contains dementia and cognitive improvement studies identified from:

1. Monthly searches of a number of major healthcare databases: MEDLINE, EMBASE, PsycINFO, CINAHL, and LILACS.
2. Monthly searches of a number of trial registers: meta Register of Controlled Trials; Umin Japan Trial Register; WHO portal (which covers ClinicalTrials.gov; ISRCTN; Chinese Clinical trials Register; German Clinical trials register; Iranian Registry of Clinical trials; Netherlands National Trials Register, plus others).
3. Quarterly search of the Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library.*
4. Monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses.

To view a list of all sources searched for ALOIS see About ALOIS on the ALOIS website.
We ran additional separate searches in Medline (OVID SP), EMBASE (OVID SP), PschInfo (OVID SP), CINAHL (EBSCO host), Web of Science and conference proceedings (Web of Knowledge), LILACS (BIREME), CENTRAL (*The Cochrane Library*), Clinicaltrials.gov (www.clinicaltrials.gov) and ICTRP Search Portal (apps.who.int/trialsearch) to ensure that the search was as comprehensive as possible. All search strategies and the number of hits retrieved can be viewed in Appendix 1.

Searching other resources

We checked the reference lists of all papers of included studies for further potentially eligible studies.

Data collection and analysis

Selection of studies

Two independent review authors (AC and AH) examined the titles and abstracts of citations identified by the search for eligibility, with any disagreements settled by consensus. We retrieved full-text copies and two review authors (AC and AH) independently assessed them for inclusion on the basis of the stated eligibility criteria. We settled any disagreements by consensus.

Data extraction and management

Two review authors (AC and AH) independently extracted data from included trials using a piloted data extraction form, and settled any disagreements by consensus. We created Characteristics of included studies tables and Summary of findings for the main comparison and Summary of findings 2 using GRADEpro and Review Manager 5 software (RevMan 2012).

Assessment of risk of bias in included studies

Two review authors (AC and AH) independently assessed risks of bias using Cochrane criteria as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Cochrane 2011). We assessed included trials for adequacy of sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other potential sources of bias. For each domain, we made a judgement of low risk, high risk or unclear risk of bias. We settled any disagreements by consensus. We generated 'Risk of bias' summary figures using Review Manager 5 (RevMan) software (RevMan 2012).

Measures of treatment effect

We used risk ratios (RR) as measures of treatment effect for dichotomous outcomes. We used hazard ratios (HR) when time to event data were reported.

Unit of analysis issues

Both included trials were cluster-randomised. Where the authors reported analyses which had adjusted for the effects of clustering, we extracted the adjusted effect measures (RR, HR) and their 95% confidence intervals (CIs) directly. If unadjusted analyses had been performed, we sought to calculate approximately correct analyses by extracting data on number of clusters, mean size of each cluster, primary outcome data and estimates of the intra-cluster correlation coefficient (ICC). If an approximately correct analysis was not possible, then we extracted primary data and calculated risk ratios with 95% CIs.

Dealing with missing data

Where data were missing due to loss of participants or clusters from follow-up, we recorded this with reasons where possible. We preferred Intention-to-treat data. If these were not available, we recorded per protocol data.

Assessment of heterogeneity

We anticipated that national and international models of LTC may lead to clinical heterogeneity. For example, in the UK residential homes and nursing homes comprise residents who have different levels of dependence and associated care needs. Furthermore, different interventions for preventing delirium in older people in long term care were likely to lead to methodological and statistical heterogeneity. For example, there may be heterogeneity between strategies targeting LTC residents or LTC facilities, or heterogeneity due to timing of the delirium prevention intervention.
We planned separate categorisation and analysis of non-pharmacological/pharmacological single/multicomponent interventions to help address trial heterogeneity. Due to clear clinical heterogeneity (see Included studies), we did not conduct any meta-analysis of the included trials.

Assessment of reporting biases

We sought clinical trial registration databases and trial protocols to assess potential reporting biases, and documented the funding source for all trials to assist the assessment.

Data synthesis

Where adjusted hazard ratios were presented, we analysed data using generic inverse variance methods, deploying natural logarithms of hazard ratios and associated standard errors. We did not perform a meta-analysis because of clinical and methodological differences between the trials.

Subgroup analysis and investigation of heterogeneity

See Differences between protocol and review.

Sensitivity analysis

See Differences between protocol and review.

RESULTS

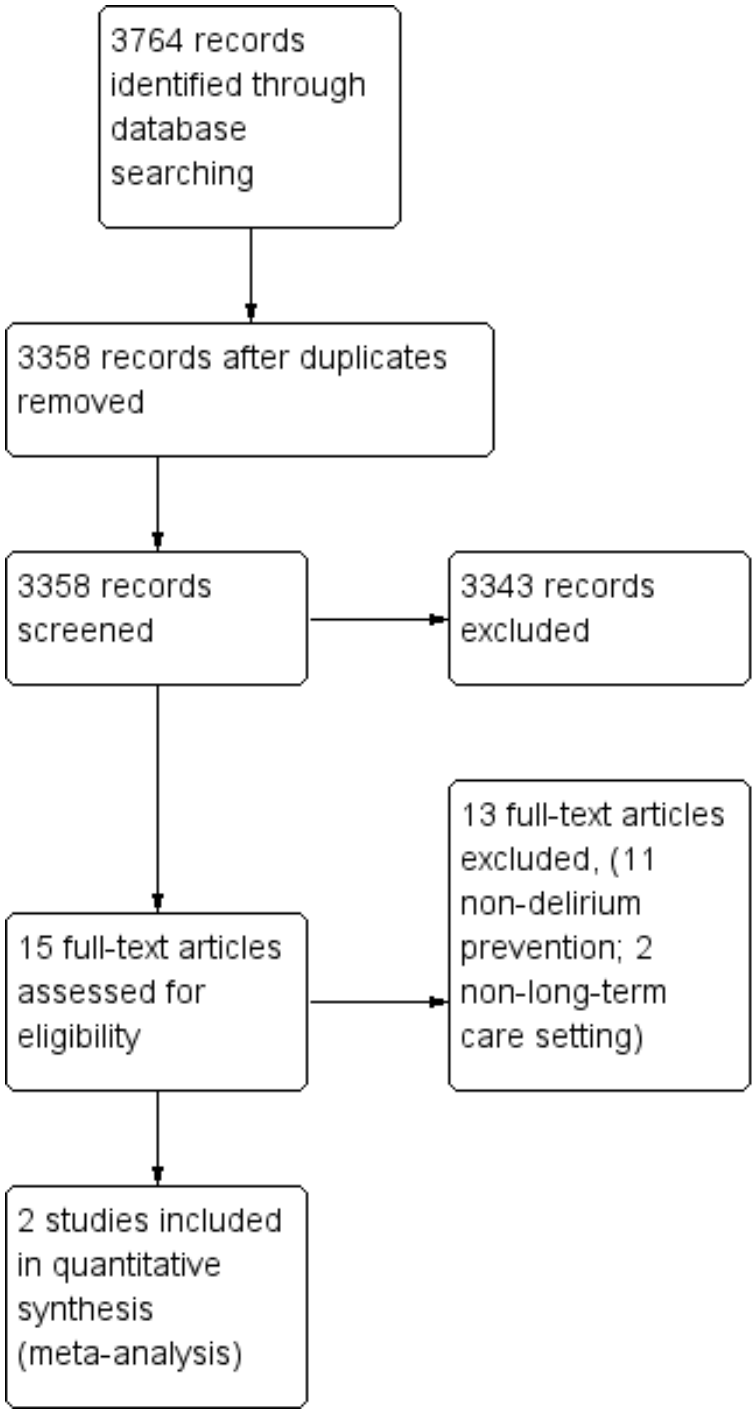
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

The results of the search are outlined in a PRISMA diagram (Figure 1). We retrieved 15 full-text studies, 13 of which we excluded (see Excluded studies), leaving two eligible for inclusion (see Included studies). One potentially eligible trial is ongoing (see Ongoing studies).

Figure 1. Study flow diagram.



Included studies

We include two trials that recruited 3636 participants (Culp 2003; Lapane 2011). Both trials were complex single-component non-pharmacological delirium prevention interventions.

The first trial (Culp 2003) was a cluster-RCT of a four-week hydration management intervention that recruited 98 residents across seven nursing homes in the United States. All residents were considered eligible for inclusion; those with acute confusion at baseline, terminal illness, uncontrolled diabetes, nasogastric or gastrostomy tube, severe renal failure, severe congestive heart failure, current urinary tract infection or serum sodium < 135 mEq/L were excluded. The intervention was a hydration management programme whereby an individual fluid intake goal was calculated according to participant body weight. Seventy-five per cent of the fluid intake goal was delivered with meals, and the remaining 25% during non-meal times. Nursing staff were instructed on the treatment regimen. A research assistant calculated the fluid goal and measured fluid intake randomly to ensure protocol compliance. No individual fluid intake goal was calculated for control arm participants. Follow-up was at four weeks post-randomisation.

The second trial (Lapane 2011) was a cluster-RCT of the Geriatric Risk Assessment MedGuide (GRAM) software programme that included 3538 residents across 25 care homes in the United States. Medicare- and Medicaid-certified nursing homes with contracts with Omnicare pharmacies, 50 or more geriatric beds and few short-stay residents were considered for inclusion. All residents were considered eligible; individual resident consent was assessed as not required on the basis that the intervention involved a wholesale change in clinical and administrative practices at the nursing home. The GRAM was used to identify medications that may contribute to delirium and falls risk for individual residents. Pharmacy automatically generated a GRAM report within 24 hours of nursing home admission. For those identified as being on medication contributing to risk of delirium or falls, an automatic report was sent to the pharmacist to coincide with a monthly visit to the nursing home. A medication review was then undertaken at the visit and a proactive monitoring plan was initiated by the care-home staff to assess for medication side effects. Control nursing homes did not receive the triggered pharmacist visit or proactive monitoring plan. All outcomes were recorded electronically by participating care-home staff over a 12-month period. The trial used resident months rather than individuals as its unit of outcome measurement. Results apply only to new admissions during 2004.

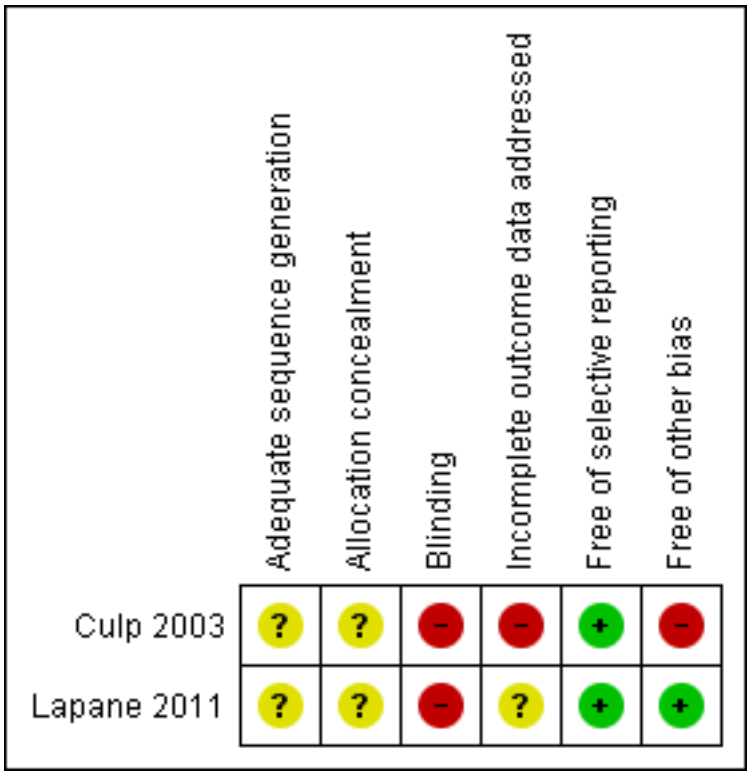
Excluded studies

We excluded 13 trials: 11 were not delirium prevention trials (Greendyke 1986; Hofferberth 1989; Mittal 2004; Moretti 2004; Ushijima 2008; Kim 2010; Overshott 2010; Pellfolk 2010; Tahir 2010; Grover 2011; Yoon 2011), with the focus either on delirium treatment or on health conditions other than delirium; two were not conducted in a long term care setting (Isaia 2009; Marcantonio 2010).

Risk of bias in included studies

Our assessment of risk of bias in the two included trials is presented in the 'Characteristics of included studies' table and is summarised here in the text and in Figure 2. Neither trial was assessed as being at low risk of methodological bias across all domains. Notably, there was no evidence of blinding of trial participants or assessors in either trial. Risk of bias for many domains was unclear because insufficient information was reported.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Neither trial reported sufficient information on sequence generation or allocation concealment, so risk of selection bias was assessed as unclear.

Blinding

There was no evidence of participant or assessor blinding in either trial, so both were assessed as being at high risk of bias. Culp 2003 reported that the study was not blinded and members of the research team who were not blind to allocation completed outcome assessments. Similarly, Lapane 2011 reported that participants and personnel were aware of allocated intervention. The minimum data set (MDS) was used for outcome data and was completed by care staff with knowledge of allocation.

Incomplete outcome data

Culp 2003 did not report information on losses to follow-up and did not perform an intention-to-treat analysis, so was assessed as being at high risk of attrition bias. Lapane 2011 did not report an intention-to-treat analysis, so risk of attrition bias was assessed as unclear.

Selective reporting

There was no evidence of selective outcome reporting in either trial, so both were assessed as being at low risk of reporting bias.

Other potential sources of bias

Culp 2003 reported that staff alerted researchers to change in cognition, so identification of delirium was partly dependent on staff knowledge. The nursing facility director recommended which unit should be used in the study, which may have introduced further potential for bias. There was a significantly higher baseline blood urea nitrogen (BUN):creatinine ratio in the intervention group, indicating that this group were more dehydrated at baseline and results were not adjusted to account for this. No adjustments were made for the potential effects of clustering. There may have been potential for between-cluster contamination of the relatively simple hydration-based intervention, and measures to prevent this

were not reported by the investigators. On the basis of these additional considerations, Culp 2003 was assessed as being at high risk of bias in this domain.

Lapane 2011 reported that only one cluster was lost and Poisson regression was used to account for the cluster design. This trial was therefore assessed as being at low risk of bias for this domain.

Effects of interventions

See: **Summary of findings for the main comparison** Single-component medication monitoring and adjustment intervention versus control for preventing delirium in older people in institutional long term care; **Summary of findings 2** Single-component hydration intervention versus control for preventing delirium in older people in institutional long term care

Primary outcomes

Both trials reported data on one of the primary outcome measures, incidence of delirium. Culp 2003 reported no effect of a hydration-based intervention on delirium incidence (risk ratio (RR) 0.85, 95% confidence interval (CI) 0.18 to 4.00). No adjustment was made for the effects of clustering and it was not possible to calculate an approximately correct analysis due to limitations in data reporting.

Lapane 2011 reported that the introduction of the intervention (GRAM report, pharmacist-led medication review and subsequent proactive monitoring plan) was associated with a significant reduction in delirium incidence, compared to control (12-month hazard ratio (HR) 0.42, CI 0.34 to 0.51). Adjustments were made for the effects of clustering. No data were reported on the other primary outcomes.

Secondary outcomes

Culp 2003 did not report data for any of the secondary outcomes.

Lapane 2011 reported adjusted analyses for additional outcomes of unplanned hospitalisation, mortality and falls. There was no clear evidence of reduction in unplanned hospitalisation (HR 0.89, CI 0.72 to 1.10), in mortality (HR 0.88, CI 0.66 to 1.17) or in falls (HR 1.03, CI 0.92 to 1.15). Neither study reported data on direct costs or cost effectiveness of the interventions.

Clear intervention heterogeneity precluded synthesis of data for meta-analysis. Limitations of data reporting precluded subgroup analysis for participants with and without dementia.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Single-component hydration intervention versus control for preventing delirium in older people in institutional long term care

Patient or population: People at risk of delirium in institutional long term care
Settings: Long term care institutions
Intervention: Single-component hydration intervention versus control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Single-component hydration intervention versus control				
Incidence of delirium[1] NEECHAM confusion scale Follow-up: mean 4 weeks	**Study population**		**RR 0.85** (0.18 to 4.0)	98 (1 study)	⊕◯◯◯ **very low**[2,3,4]	
	67 per 1000	**57 per 1000** (12 to 268)				
	Medium risk population					
	67 per 1000	**57 per 1000** (12 to 268)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Assumed risk based on control group risk in included study.

[2]Assessed as at high risk of methodological bias for blinding, outcome data and other bias.
[3]One trial only so not possible to assess for consistency.
[4]Very low rate of delirium events. Wide confidence limits indicate uncertainty.

DISCUSSION

Summary of main results

Our review has identified two randomised controlled trials (RCTs) of delirium prevention interventions for older people in institutional long term care, recruiting 3636 participants. One small cluster-RCT (n = 98) of a hydration-based intervention reported no reduction in delirium incidence in the intervention group compared to control. Results were imprecise, not adjusted for the effects of clustering and with serious limitations evident in trial design. Importantly, the investigators reported that both intervention and control groups were consuming approximately the same volume of fluids over the follow-up period, but only 51% of intervention participants had 90% or greater compliance with the fluid goal. Previous research has identified that many LTC residents do not consume adequate fluid (Armstrong-Esther 1996) and this result may indicate that achieving target fluid intake in care-home residents is challenging, even in the context of a clinical trial.

One large cluster-RCT (n = 3538) of a computerised system to identify medications that may contribute to delirium risk and trigger a pharmacist-led medication review reported a large reduction in delirium incidence but no clear evidence of reductions in hospital admissions, mortality or falls. Although the analysis was adjusted for the effects of clustering, there were limitations evident in trial design, notably an absence of either participant or assessor blinding.

Overall completeness and applicability of evidence

The very small number of included trials identify a limited body of evidence on the effectiveness of interventions for preventing delirium in older people in institutionalised long term care. We identified only two single-component non-pharmacological interventions with methodological limitations. We did not find any multicomponent non-pharmacological delirium prevention interventions or pharmacological delirium prevention interventions for this population. Both trials were conducted in the United States and international differences in the organisation of long term care mean that the results may not be directly applicable to other settings.

Quality of the evidence

We used GRADEpro software to inform the generation of evidence quality statements.

On the basis of one large RCT there is moderate-quality evidence that a single component medication monitoring and adjustment intervention may reduce the incidence of delirium in older people in institutional LTC (see Summary of findings for the main comparison). Notably, personnel, participants and outcome assessors were not blinded in this trial.

On the basis of one large RCT there is moderate-quality evidence that a single component medication monitoring and adjustment intervention does not appear to be associated with reduced hospitalisation, mortality or falls for older people in institutional LTC (Summary of findings for the main comparison). Notably, personnel, participants and outcome assessors were not blinded in this trial.

On the basis of a single RCT with serious limitations in trial design and very imprecise results, there is very low-quality evidence on the effectiveness of hydration-based interventions for reducing the incidence of delirium in older people in institutional LTC. It is therefore not possible to draw firm conclusions about this intervention (Summary of findings 2).

Potential biases in the review process

This review has followed Cochrane procedures and there were only a small number of minor amendments to the review protocol following initial publication. The very small number of included trials precluded an accurate assessment of consistency of results or a statistical assessment of reporting bias.

Agreements and disagreements with other studies or reviews

To our knowledge there are no previous systematic reviews on the effectiveness of delirium prevention interventions for older people in institutional long term care.

AUTHORS' CONCLUSIONS

Implications for practice

Introduction of a software-based intervention to identify medications that could contribute to delirium risk so that a pharmacist-led medication review and monitoring plan can be initiated may reduce the incidence of delirium for older people in institutional LTC. This is based on one large RCT in the United States and may not be practical in other countries which do not have comparable information technology services available in care homes. There was no clear evidence of reduction in hospital admissions, mortality or falls. One small RCT of a weight-based hydration intervention for older people in nursing homes had serious methodological limitations and it is not possible to use the results from this trial to support the use of this intervention.

Implications for research

There is very limited evidence on the effectiveness of interventions for preventing delirium in older people in institutional LTC. Adequately powered trials are justified of computerised medication management interventions for delirium prevention in LTC residents that incorporate blinding of outcome assessors. These trials should be supported by research investigating methods of implementation across different care systems. There is evidence for the effectiveness of multicomponent non-pharmacological interventions to prevent delirium in hospitalised older people and trials to test these interventions in LTC residents are indicated. There have been no trials of pharmacological agents for preventing delirium in LTC residents and future trials should be considered.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Culp 2003

Methods	Cluster-randomised controlled trial with nursing home as the unit of randomisation
Participants	98 residents of 7 care homes in Iowa, USA. Mean age 84.5 (SD 9.3) years in intervention group; 83.8 (SD 8.1) years in control group 54.7% women in intervention group; 53.3% female in control group
Interventions	A 4-week weight-based hydration management intervention for nursing-home residents. Individual fluid intake goal was calculated according to body weight. 75% of the fluid intake goal was delivered with meals, the remaining 25% during non-meal times. Nursing staff were instructed on the treatment regimen. A research assistant calculated the fluid goal and measured fluid intake randomly to ensure protocol compliance No individual fluid intake goal calculated for control arm participants
Outcomes	Incidence of delirium, measured using the Neelon & Champagne (NEECHAM) confusion scale (Neelon 1996). Outcomes recorded at 4 weeks post-randomisation.
Notes	Funding source: National Institute for Nursing Research

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation	Unclear risk	No information provided on generation of allocation sequence
Allocation concealment	Unclear risk	Cluster randomised trial. Unclear if all care homes recruited prior to randomisation
Blinding All outcomes	High risk	No. Stated not double-blind and research team conducted all assessments. Assessments conducted weekly or if acute change in mental status was noted by either the research team or care-home staff
Incomplete outcome data addressed All outcomes	High risk	No information on loss to follow-up. No intention-to-treat analysis
Free of selective reporting	Low risk	No evidence of selective outcome reporting.

Culp 2003 (*Continued*)

Free of other bias	High risk	Staff alerted researchers to change in cognition so dependent on staff knowledge. Nursing facility director recommended which unit should be used in the study. A higher blood urea nitrogen (BUN):creatinine ratio in the intervention group, indicating that this group were more dehydrated at baseline. No adjustment made for effects of clustering. Potential for between-cluster contamination of the relatively simple hydration-based intervention, and measures to prevent this were not reported by the investigators

Lapane 2011

Methods	Cluster-randomised controlled trial with nursing home as the unit of randomisation
Participants	3538 residents of 25 nursing homes in Virginia, USA, recruited between 2003 and 2004 Medicare- and Medicaid-certified nursing homes with contracts with Omnicare pharmacies, 50 or more geriatric beds and few short-stay residents were considered for inclusion 73.9% women. 39.0% aged > 85.
Interventions	Geriatric Risk Assessment MedGuide (GRAM) software used to identify resident-specific medications that may contribute to delirium and falls risk. Pharmacy automatically generated GRAM report within 24 hours of nursing-home admission. For those who triggered GRAM resident assessment protocols (RAPS) for delirium or falls risk, an automatic report was sent to the pharmacist to coincide with a monthly visit to the nursing home. A medication review was then undertaken at the visit and a proactive monitoring plan was initiated by the care home staff to assess for medication side effects Control nursing homes did not receive the triggered pharmacist visit or proactive monitoring plan
Outcomes	Incidence of delirium, measured using the Nursing Home Confusion Assessment Method (NH-CAM) (Dosa 2007). Fall events, measured using MDS records. Hospital admissions, measured using MDS records. Mortality, measured using MDS records. The trial used resident months (defined as the number of days from date of first assessment to the first outcome occurrence, the last date in the nursing home, the death date, or December 31, 2004), rather than individuals as its unit of outcome measurement Results apply only to new admissions during 2004. All outcomes were recorded electronically by participating care-home staff over a 12-month period
Notes	Funding source: Agency for Healthcare Research and Quality

Lapane 2011 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation	Unclear risk	Method of allocation sequence generation not provided.
Allocation concealment	Unclear risk	Unclear if all care homes recruited prior to randomisation.
Blinding All outcomes	High risk	Participants and personnel aware of allocated intervention. MDS used for outcome data and completed by care staff with knowledge of allocation
Incomplete outcome data addressed All outcomes	Unclear risk	No information on intention-to-treat analysis.
Free of selective reporting	Low risk	No evidence of selective outcome reporting.
Free of other bias	Low risk	Only one cluster was lost. Poisson regression accounting for the cluster design was used

MDS: minimum data set

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Greendyke 1986	Not a delirium prevention trial.
Grover 2011	Not a delirium prevention trial.
Hofferberth 1989	Not a delirium prevention trial.
Isaia 2009	Trial not conducted in a long term care setting.
Kim 2010	Not a delirium prevention trial.
Marcantonio 2010	Trial not conducted in a long term care setting.
Mittal 2004	Not a delirium prevention trial.

(*Continued*)

Moretti 2004	Not a delirium prevention trial.
Overshott 2010	Not a delirium prevention trial.
Pellfolk 2010	Not a delirium prevention trial.
Tahir 2010	Not a delirium prevention trial.
Ushijima 2008	Not a delirium prevention trial.
Yoon 2011	Not a delirium prevention trial.

Characteristics of ongoing studies *[ordered by study ID]*

Siddiqi 2012

Trial name or title	A cluster-randomised controlled pilot trial of 'Stop Delirium!' a complex intervention to prevent delirium in care homes for older people
Methods	Cluster-randomised controlled trial.
Participants	288 care home residents.
Interventions	STOP delirium! intervention.
Outcomes	Incidence of delirium, severity of delirium.
Starting date	26th March 2012
Contact information	Dr Najma Siddiqi, Leeds Insitute of Health Sciences, University of Leeds, LS2 9JT
Notes	

DATA AND ANALYSES

Comparison 1. Single component hydration intervention versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of delirium	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Comparison 2. Single component medication monitoring and adjustment intervention versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Incidence of delirium	1		Hazard Ratio (Random, 95% CI)	Subtotals only
2 Unplanned hospitalisation	1		Hazard Ratio (Random, 95% CI)	Subtotals only
3 Mortality	1		Hazard Ratio (Random, 95% CI)	Subtotals only
4 Falls	1		Hazard Ratio (Random, 95% CI)	Subtotals only

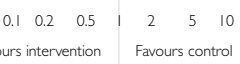
Analysis 1.1. Comparison 1 Single component hydration intervention versus control, Outcome 1 Incidence of delirium.

Review: Interventions for preventing delirium in older people in institutional long-term care

Comparison: 1 Single component hydration intervention versus control

Outcome: 1 Incidence of delirium

Study or subgroup	Intervention n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Culp 2003	3/53	3/45		0.85 [0.18, 4.00]
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 3 (Intervention), 3 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Not applicable				



Analysis 2.1. Comparison 2 Single component medication monitoring and adjustment intervention versus control, Outcome 1 Incidence of delirium.

Review: Interventions for preventing delirium in older people in institutional long-term care

Comparison: 2 Single component medication monitoring and adjustment intervention versus control

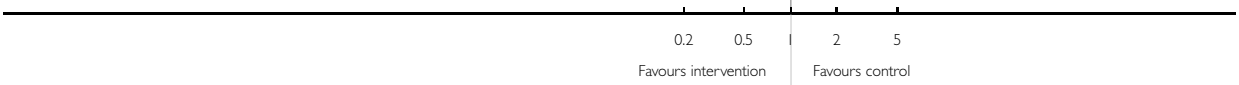
Outcome: 1 Incidence of delirium

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Hazard Ratio IV,Random,95% CI
Lapane 2011	-0.8675006 (0.101)		0.42 [0.34, 0.51]
Subtotal (95% CI)			**0.0 [0.0, 0.0]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Single component medication monitoring and adjustment intervention versus control, Outcome 2 Unplanned hospitalisation.

Review: Interventions for preventing delirium in older people in institutional long-term care

Comparison: 2 Single component medication monitoring and adjustment intervention versus control

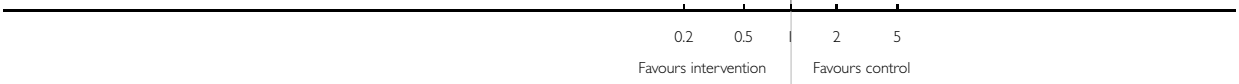
Outcome: 2 Unplanned hospitalisation

Study or subgroup	log [Hazard Ratio] (SE)	Hazard Ratio IV,Random,95% CI	Hazard Ratio IV,Random,95% CI
Lapane 2011	-0.1165338 (0.106)		0.89 [0.72, 1.10]
Subtotal (95% CI)			**0.0 [0.0, 0.0]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Test for subgroup differences: Not applicable

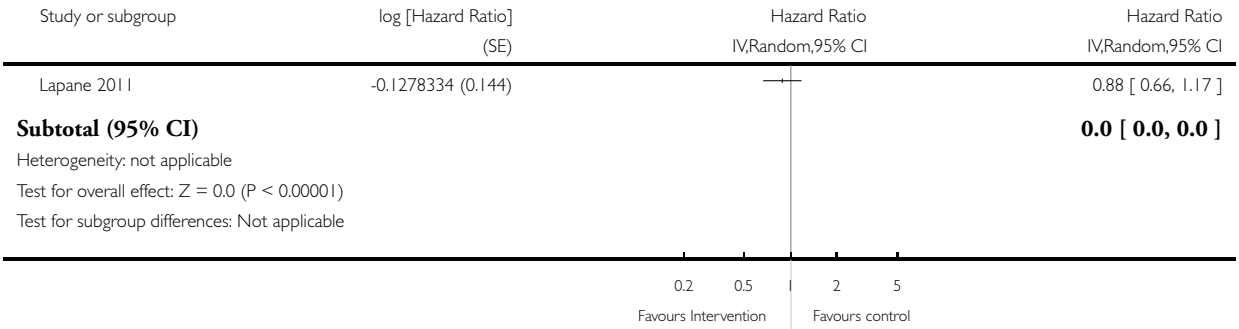


Analysis 2.3. Comparison 2 Single component medication monitoring and adjustment intervention versus control, Outcome 3 Mortality.

Review: Interventions for preventing delirium in older people in institutional long-term care

Comparison: 2 Single component medication monitoring and adjustment intervention versus control

Outcome: 3 Mortality

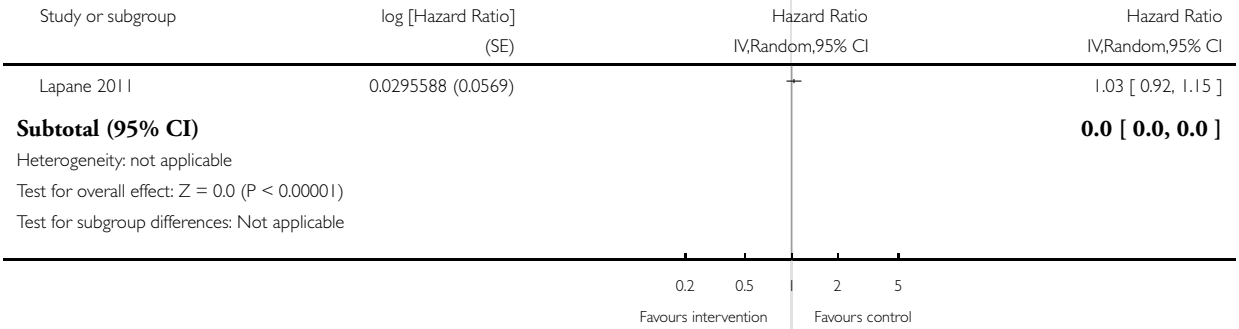


Analysis 2.4. Comparison 2 Single component medication monitoring and adjustment intervention versus control, Outcome 4 Falls.

Review: Interventions for preventing delirium in older people in institutional long-term care

Comparison: 2 Single component medication monitoring and adjustment intervention versus control

Outcome: 4 Falls



APPENDICES

Appendix 1. Update and pre-publication searches: July 2012 and April 2013

Source	Search strategy	Hits retrieved
1. ALOIS (www.medicine.ox.ac.uk/alois)	delirium	Jul 2012: 96 Apr 2013: 9
2. MEDLINE In-process and other non-indexed citations and MEDLINE 1950 - present (Ovid SP)	1. Delirium/ 2. deliri*.mp. 3. "acute confusion*".ti,ab. 4. "acute organic psychosyndrome".ti,ab. 5. "acute brain syndrome".ti,ab. 6. "metabolic encephalopathy".ti,ab. 7. "acute psycho-organic syndrome".ti,ab. 8. "clouded state".ti,ab. 9. "clouding of consciousness".ti,ab. 10. "exogenous psychosis".ti,ab. 11. "toxic psychosis".ti,ab. 12. "toxic confusion".ti,ab. 13. Delirium, Dementia, Amnestic, Cognitive Disorders/su [Surgery] 14. obnubilat*.ti,ab. 15. or/1-14 16. Primary Prevention/ 17. prevent*.mp. 18. reduc*.ti,ab. 19. stop*.ti,ab. 20. taper*.ti,ab. 21. avoid*.ti,ab. 22. "cut* down".ti,ab. 23. or/16-22 24. 15 and 23 25. randomized controlled trial.pt. 26. controlled clinical trial.pt. 27. randomi?ed.ab. 28. placebo.ab. 29. drug therapy.fs. 30. randomly.ab. 31. trial.ab. 32. groups.ab. 33. or/25-32 34. (animals not (humans and animals)).sh. 35. 33 not 34 36. 24 and 35	Jul 2012: 821 Apr 2013: 118

(*Continued*)

3. EMBASE 1980 - 2012 week 30 (Ovid SP)	1. Delirium/ 2. deliri*.mp. 3. "acute confusion*".ti,ab. 4. "acute organic psychosyndrome".ti,ab. 5. "acute brain syndrome".ti,ab. 6. "metabolic encephalopathy".ti,ab. 7. "acute psycho-organic syndrome".ti,ab. 8. "clouded state".ti,ab. 9. "clouding of consciousness".ti,ab. 10. "exogenous psychosis".ti,ab. 11. "toxic psychosis".ti,ab. 12. "toxic confusion".ti,ab. 13. Delirium, Dementia, Amnestic, Cognitive Disorders/su [Surgery] 14. obnubilat*.ti,ab. 15. or/1-14 16. primary prevention/ 17. prevent*.mp. 18. reduc*.ti,ab. 19. stop*.ti,ab. 20. taper*.ti,ab. 21. avoid*.ti,ab. 22. "cut* down".ti,ab. 23. or/16-22 24. 15 and 23 25. randomized controlled trial/ 26. random*.ti,ab. 27. placebo.ti,ab. 28. trial.mp. 29. controlled clinical trial/ 30. or/25-29 31. 24 and 30	Jul 2012: 835 Apr 2013: 161
4. PsycINFO 1806 - July week 4 2012 (Ovid SP)	1. Delirium/ 2. deliri*.mp. 3. "acute confusion*".ti,ab. 4. "acute organic psychosyndrome".ti,ab. 5. "acute brain syndrome".ti,ab. 6. "metabolic encephalopathy".ti,ab. 7. "acute psycho-organic syndrome".ti,ab. 8. "clouded state".ti,ab. 9. "clouding of consciousness".ti,ab. 10. "exogenous psychosis".ti,ab. 11. "toxic psychosis".ti,ab. 12. "toxic confusion".ti,ab. 13. obnubilat*.ti,ab. 14. or/1-13 15. Prevention/ 16. prevent*.mp.	Jul 2012: 163 Apr 2013: 19

(*Continued*)

	17. reduc*.ti,ab. 18. stop*.ti,ab. 19. taper*.ti,ab. 20. avoid*.ti,ab. 21. "cut* down".ti,ab. 22. or/15-21 23. 14 and 22 24. random*.mp. 25. trial.mp. 26. placebo*.mp. 27. group.ab. 28. or/24-27 29. 23 and 28	
5. CINAHL (EBSCO host)	S1 (MH "Delirium") OR (MH "Delirium Management (Iowa NIC)") OR (MH "Delirium, Dementia, Amnestic, Cognitive Disorders/SU") S2 TX deliri* S3 TX "acute confusion*" S4 TX "acute organic psychosyndrome" S5 TX "acute brain syndrome" S6 TX "metabolic encephalopathy" S7 TX "acute psycho-organic syndrome" S8 TX "clouded state" S9 TX "clouding of consciousness" S10 TX "exogenous psychosis" S11 TX "toxic psychosis" S12 TX "toxic confusion" S13 TX obnubilat* S14 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 S15 (MH "Preventive Trials") OR (MH "Preventive Health Care") S16 TX prevent* S17 TX reduc* S18 TX stop* S19 TX taper* S20 TX avoid* S21 TX "cut* down" S22 S15 or S16 or S17 or S18 or S19 or S20 or S21 S23 S14 and S22 S24 TX random* S25 TX placebo S26 TX trial S27 (MH "Clinical Trials") OR (MH "Intervention Trials") S28 S24 or S25 or S26 or S27 S29 S23 and S28	Jul 2012: 189 Apr 2013: 0

(*Continued*)

6. Web of Science and conference proceedings (Web of Knowledge)	Topic=(deliri* OR "acute confusion*" OR "acute organic psychosyndrome" OR "acute brain syndrome" OR "metabolic encephalopathy" OR "acute psycho-organic syndrome" OR "clouded state" OR "clouding of consciousness" OR "exogenous psychosis" OR "toxic psychosis" OR "toxic confusion" OR obnubilat*) AND Topic=(prevent* OR reduc* OR stop* OR taper* OR avoid* OR "cut* down") AND Topic=(random* or placebo or "double-blind" or trial OR groups OR "controlled study" OR "time series" OR "Comparative Study" OR "Pretest-Posttest Design") Timespan=All Years. Databases=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH Lemmatization=On	Jul 2012: 654 Apr 2013: 163
7. LILACS (BIREME)	randomly OR randomised OR randomized OR trial OR ensaio clínico OR control OR controlled [Words] and delirium OR delious OR deliria OR delirio OR loucura [Words]	Jul 2012: 47 Apr 2013: 1
8. CENTRAL (*The Cochrane Library*) (Issue 2 of 4, 2012)	#1 MeSH descriptor Delirium, this term only #2 deliri* #3 "acute confusion*" #4 "acute organic psychosyndrome" #5 "acute brain syndrome" #6 "metabolic encephalopathy" #7 "acute psycho-organic syndrome" #8 "clouded state" #9 "clouding of consciousness" #10 "exogenous psychosis" #11 "toxic psychosis" #12 "toxic confusion" #13 obnubilat* #14 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13) #15 MeSH descriptor Primary Prevention, this term only #16 prevent* #17 reduc* #18 stop* #19 taper* #20 avoid*	Jul 2012: 230 Apr 2013: 7

(*Continued*)

	#21 "cut* down" #22 (#15 OR #16 OR #17 OR #18 OR # 19 OR #20 OR #21) #23 (#14 AND #22), trials	
9. Clinicaltrials.gov (www.clinicaltrials.gov)	care home OR institutionalised OR institutionalized OR long term care OR home | Interventional Studies | delirium OR toxic psychosis OR toxic confusion OR metabolic encephalopathy OR clouded state OR exogenous psychosis | Senior	Jul 2012: 156 Apr 2013: 23
10. ICTRP Search Portal (apps.who.int/trialsearch) [includes: Australian New Zealand Clinical Trials Registry; ClinicalTrials.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry - India; Clinical Research Information Service - Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register]	care home OR institutionalised OR institutionalized OR long term care OR home | Interventional Studies | delirium OR toxic psychosis OR toxic confusion OR metabolic encephalopathy OR clouded state OR exogenous psychosis	Jul 2012: 72 Apr 2013: 0
TOTAL before de-duplication		July 2012: 3263 April 2013: 501
TOTAL after de-duplication and first assessment		July 2012: 120 April 2013: 15

CONTRIBUTIONS OF AUTHORS

AC, NS, RH and JY all contributed to the writing of the protocol for this review. AC and AH completed the handsearch and extracted data for all studies. AC completed 'Summary of findings' tables and generated GRADE Evidence Profiles. All authors contributed to the writing of the review.

DECLARATIONS OF INTEREST

NS is chief investigator for a National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB) grant to investigate the effects of a delirium prevention intervention for older people in long term care.

JY is a co-applicant for a National Institute for Health Research (NIHR) Research for Patient Benefit (RfPB) grant to investigate the effects of a delirium prevention intervention for older people in long term care.

AC, RH and AH declare that they have no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- University of Leeds, UK.

Salary support for AC and JY.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

An additional co-author (Anne Heaven) was added to the review between the protocol and review stage. Following publication of the protocol, amendments were made to Measures of treatment effect and Data synthesis to incorporate the analysis of adjusted data from cluster-randomised trials using generic inverse variance methods. A post hoc decision was made to include the adverse outcome of falls in the 'Summary of findings' tables. We planned participant-level subgroup analyses for those with and without dementia, but we were unable to conduct these analyses because of limitations in reporting. We planned sensitivity analyses for trials at low risk of methodological bias, but these were not possible because of the very small number of included trials.