

How can delirium best be prevented and managed in older patients in hospital?

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The case

You are asked to conduct a preoperative assessment of an 86-year-old woman recently admitted to hospital with a fractured right hip. She reports having fallen while getting out of her bathtub but denies any prior history of falls. She has no other injuries. She lives alone at home and was functioning independently before admission. Her medical history includes osteoporosis, mild cognitive impairment and cataracts. She has no history of cardiac or respiratory disease and no known cardiac risk factors. Her medications on admission include calcium carbonate, vitamin D and etidronate. She does not drink alcohol. Her physical examination is remarkable for visual impairment, a fractured right hip and a Mini-Mental Status Examination score of 23/30. Results of her preoperative tests, including measurement of electrolytes, blood glucose, creatinine and complete blood count as well as an electrocardiogram, are unremarkable. Given her age and her history of mild cognitive impairment and visual impairment, you are concerned that she is at increased risk of postoperative delirium. What is the best way to prevent delirium? How should you manage the patient if she does become delirious?

Delirium occurs in 25%–65% of patients admitted to hospital because of hip fracture.^{1,2} The prevalence of delirium is as high as 74% among surgical patients³ and 11%–42% among general medical in-patients.⁴ Delirium is defined as an acute disturbance of consciousness accompanied by a change in cognition or by development of a perceptual disturbance.⁵ It develops over a short period (hours to days), and its course tends to fluctuate. Delirium may be caused by a general medical condition, substance intoxication, substance withdrawal or multiple causes.⁵ In this article, we systematically review the evidence regarding the prevention and management of delirium among older patients in hospital.

Patients in whom delirium develops while in hospital have significantly worse outcomes than those who do not become delirious. Developing delirium in hospital has been associated with an increased risk of death, longer hospital stays, an increased risk of hospital-acquired complications, persistent cognitive deficits and increased rates of discharge to long-term care facilities.^{6–9} Delirium is also predictive of poor postoperative recovery of functional status and mobility among patients with hip fracture.^{7,10} Because sicker patients are more

Key points

- Multicomponent interventions that combine a comprehensive assessment and strategies targeting risk factors for delirium appear to be effective in preventing delirium in older in-patients.
- There is insufficient evidence to support pharmacologic interventions for the prevention or management of delirium in older in-patients.
- Multicomponent interventions aimed at managing delirium have not been found to decrease mortality or length of hospital stay.

likely to become delirious than those with fewer comorbidities, delirium may not be the only factor contributing to these adverse outcomes.

What are the risk factors for delirium?

Based on evidence from a prospective cohort of over 1300 surgical patients and a subsequent systematic review, there are preoperative factors that are associated with an increased risk of delirium after noncardiac surgery^{11,12} (Box 1). Similar independent risk factors were found among 281 medical patients 70 years of age or older at the time of hospital admission; these included visual impairment (relative risk [RR] 3.5, 95% confidence interval [CI] 1.2–10.7), severe illness (RR 3.5, 95% CI 1.5–8.2), pre-existing cognitive impairment (RR 2.8, 95% CI 1.2–6.7) and dehydration (high urea-to-creatinine ratio; RR 2.0, 95% CI 0.9–4.6).¹³ Prospective data from 508 medical patients 70 years of age or older identified several hospital-related risk factors; these included the use of physical restraints (RR 4.4, 95% CI 2.5–7.9), malnutrition (RR 4.0, 95% CI 2.2–7.4), the use of a bladder catheter (RR 2.4, 95% CI 1.2–4.7), the addition of more than 3 new medications (RR 2.9, 95% CI 1.6–5.4) and any iatrogenic event (RR 1.9, 95% CI 1.1–3.2).¹⁴ The cause of delirium was rarely isolated to just 1 factor; instead multiple precipitating factors contributed to the condition.¹⁴

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Box 1: Risk factors for delirium after noncardiac surgery*^{11,12}

- Age \geq 70 years (OR 3.3, 95% CI 1.9–5.9)
- Existing cognitive impairment (OR 4.2, 95% CI 2.4–7.3)
- Functional impairment (OR 2.5, 95% CI 1.2–5.2)
- Alcohol abuse (OR 3.3, 95% CI 1.4–8.3)
- Abnormal preoperative level of sodium, potassium or glucose (OR 3.4, 95% CI 1.3–8.7)
- Preoperative psychotropic drug use (OR not available)
- Depression (OR not available)
- Increased comorbidity (OR not available)
- Living in a long-term care facility (OR not available)
- Visual or hearing impairment (OR not available)

*Odds ratios (ORs) and 95% confidence intervals (CIs) are provided where available.

Literature review

Given the prevalence of delirium and its association with adverse health outcomes, it is important to prevent delirium among older patients admitted to hospital and to initiate appropriate management strategies when it does occur. We searched MEDLINE (using Ovid) from 1950 to October 2007 and EMBASE from 1980 to October 2007 to identify relevant studies. The search strategy included the terms “delirium,” “confusion,” “aged 65 or older,” “hospitalization” and “in-patient,” using the Cochrane randomized controlled trial filter and a systematic review filter. We also searched the Cochrane Database of Systematic Reviews and reviewed the references included in relevant systematic reviews. We identified English-language articles that addressed the prevention or management of delirium among adults aged 65 years or older in hospital. We accepted the definition for delirium used in the studies as long as one was described. We identified additional studies by searching the bibliographies of retrieved articles. Articles in languages other than English were excluded for logistic reasons. Additional details on the search methods are available in Appendix 1 (available at www.cmaj.ca/cgi/content/full/cmaj.080519/DC1).

The search yielded 408 citations (92 from MEDLINE and 316 from EMBASE). We excluded 30 non-English studies (7% of the citations). We retrieved the full-text articles of 56 citations that met the initial inclusion criteria. A further 14 articles were identified through review of references cited in retrieved articles and Cochrane systematic reviews (Appendix 2, available at www.cmaj.ca/cgi/content/full/cmaj.080519/DC1). After assessing the 70 articles, we excluded 59 for the following reasons: the article was a review article or editorial (24 studies), the study was not a randomized controlled trial (19), there were no relevant outcome data (10), the article described the protocol only (1), the article was a practice guideline (1), or the study population did not consist primarily of in-patients aged 65 years or older (4). The remaining 11 articles, published between 1987 and 2007, were included in our systematic review (Table 1).^{15–25}

How can delirium be prevented?

We identified 8 trials that studied methods to prevent delirium in older patients in hospital (Table 1). Three trials involved multicomponent interventions ($n = 646$) among hip fracture patients. Five trials involved pharmacological interventions.

Multicomponent interventions

All 3 trials of multicomponent interventions for the prevention of delirium involved specialists in geriatrics and multicomponent strategies to target risk factors for delirium (Table 2). Two of the 3 studies conducted intention-to-treat analyses. The outcome assessors in all 3 trials were blinded. Two trials used the Confusion Assessment Method²⁶ to diagnosis delirium; the third trial used a modified version of the Organic Brain Syndrome Scale.²⁷ The Confusion Assessment Method is a tool designed for diagnosing delirium. It can be completed in less than 5 minutes, includes 4 criteria (acute onset and fluctuating course, inattention, disorganized thinking, and altered level of consciousness), is very accurate (sensitivity 94%, specificity 90%) and has high interobserver reliability ($\kappa > 0.8$).²⁶ The Organic Brain Syndrome Scale was designed to detect and monitor confusion. It consists of 2 parts (disorientation subscale and confusion subscale) and has excellent agreement with the Confusion Assessment Method.²⁷

The multicomponent interventions appeared to be effective in preventing delirium among patients admitted to hospital with hip fracture (summary RR 0.75, 95% CI 0.64–0.88; p for heterogeneity = 0.58). The number needed to treat to prevent 1 case of delirium was 7 (95% CI 4–20). In one of the trials, there were nonsignificant ($p > 0.1$) differences in baseline characteristics, including prefracture dementia and impairment in activities of daily living.²³ In multivariable analyses to adjust for these differences, they found similar effect sizes, but the results were no longer significant.

In only 1 of the 3 studies did the intervention have a significant effect on postoperative length of hospital stay (28 days in the intervention group v. 38 days in the control group; $p = 0.03$).²² However, the intervention in this study also involved extensive staff education and teamwork around other issues such as the prevention of osteoporosis, rehabilitation goals and discharge planning. There was no difference in discharge location between the intervention and control groups in the 2 studies reporting this outcome.^{22,23}

Two studies reported on mortality.^{22,25} Only one trial found a significant decrease in hospital mortality (0.6% [1/155] in the intervention group v. 5.5% [9/164] in the control group; $p = 0.03$).²⁵ The intervention in this trial primarily involved a geriatric team comprising a geriatrician, a rehabilitation specialist and a social worker that helped the usual-care group of surgeons and orthopedic nurses coordinate and provide care. However, the details around the care provided by this team were not well documented. As for other secondary outcomes, the multicomponent interventions appeared to reduce the incidence of medical complications, including pressure ulcers,^{22,25} urinary tract infections,²² sleeping problems,²² nutritional complications²² and falls.²² Despite the limitations of these trials, there appears to be a role for multicomponent interventions to

prevent delirium. There is further evidence in support of this from an earlier study involving 852 medical in-patients (RR 0.66, 95% CI 0.46–0.95).²⁸ In this trial, the intervention was clearly outlined and involved many of the same preventive strategies used in the 3 trials we included in our review. Although it is one of the largest and best known trials of the prevention of delirium, we did not include it because patient assignment was done using prospective matching instead of randomization.

Recent practice guidelines developed by the British Geriatrics Society in conjunction with the Royal College of Physicians of London recommend that patients at high risk of delirium be identified at the time of hospital admission and that prevention strategies be incorporated into their care plan (grade A evidence).²⁹ Clinical practice guidelines for the management of delirium in older people in Australia also agree

that only hospital-based multicomponent preventive strategies currently have good evidence to support their use.³⁰

Pharmacologic interventions

There were 5 trials of pharmacologic interventions, 4 of which enrolled fewer than 100 patients (Table 1). Since no 2 trials used the same drug, we were unable to combine data for analysis, and thus each trial is described individually.

In a trial involving 57 patients with hip fracture, rates of delirium were examined between patients who received epidural anesthesia with prilocaine and epinephrine with or without bupivacaine ($n = 28$) and patients who received general anesthesia with thiopental, succinylcholine, atropine and halothane ($n = 29$).¹⁷ Delirium was assessed using the Organic Brain Syndrome Scale. The method of randomization was not described. Outcome assessors were blinded and intention-to-

Table 1: Details of randomized controlled trials included in the systematic review of interventions for the prevention and management of delirium among older patients* in hospital

Study	N	Randomization method	Treatment allocation concealed	Blinding	Withdrawal, no. of patients	Intention-to-treat analysis	Method used to identify delirium
Prevention							
<i>Multicomponent intervention</i>							
Marcantonio et al., 2001 ²³	126	Random-number tables	Yes	Outcome assessor	0	Yes	CAM
Vidan et al., 2005 ²⁵	321	Stratified randomization	NR	Outcome assessor	2	No	CAM
Lundstrom et al., 2007 ²²	199	Stratified randomization	Yes	Outcome assessor	39	Yes	Modified OBS
<i>Pharmacologic intervention</i>							
Berggren et al., 1987 ¹⁷ (anesthesia)	57	NR	NR	Outcome assessor	0	Yes	OBS
Beaussier et al., 2006 ¹⁶ (pain medications)	59	Computer generated	Yes	Health care providers	7	No	CAM
Kalisvaart et al., 2005 ²⁰ (haloperidol)	430	Computer generated	Yes	Study participants, health care providers and outcome assessor	48	Yes	DSM-IV criteria and CAM
Liptzin et al., 2005 ²¹ (donepezil)	90	Randomization by the research pharmacist	NR	Study participants, health care providers and outcome assessor	10	No	DSM-IV criteria, Delirium Symptom Interview and CAM
Aizawa et al., 2002 ¹⁵ (drug-induced sleep)	42	NR	NR	Outcome assessor	2	No	DSM-IV criteria
Management							
<i>Multicomponent intervention</i>							
Cole et al., 1994 ¹⁹	88	NR	NR	Outcome assessor	17	Yes	CAM
Pitkala et al., 2006 ²⁴	174	Computer generated	Yes	Unclear	4	Yes	CAM
Cole et al., 2002 ¹⁸	227	Computer generated	Yes	Outcome assessor	9	Yes	CAM

Note: CAM = Confusion Assessment Method, NR = not reported, OBS = Organic Brain Syndrome Scale.

*Age 65 years or more.

treat analysis was completed. No significant difference in the rates of delirium were observed between the 2 study groups (50% [14/28] in the epidural group v. 38% [11/29] in the general anesthetic group).

One trial examined postoperative rates of delirium among 59 older patients undergoing surgical resection of colon or rectal cancers.¹⁶ The intervention group received preoperative intrathecal morphine at L4–L5 ($n = 29$); the control group received a preoperative subcutaneous injection of saline at L4–L5 ($n = 30$). Postoperatively both groups received propacetamol intravenously and patient-controlled morphine intravenously for breakthrough pain. Delirium was assessed using the Confusion Assessment Method. Randomization was computer generated; treatment allocation was concealed. The physicians in charge of the patients during the intraoperative

and postoperative periods were blinded to group assignment. Three patients were excluded in the intervention group: 1 each because of a major deviation in surgery, early postoperative abdominal sepsis, and aspiration pneumonia requiring intubation. Four patients were excluded in the control group: 2 because of a major deviation in surgery, 1 because of early postoperative abdominal sepsis and 1 because of death from pulmonary embolism. Of those remaining in the study, 9 patients in the intervention group and 10 in the control group had postoperative delirium.

The largest of the pharmacologic trials compared prophylactic haloperidol (0.5 mg 3 times daily starting on admission and continued for 3 days postoperatively) and placebo in 430 patients with hip fracture at moderate or high risk of delirium.²⁰ Computer-generated randomization was conducted;

treatment allocation was concealed. The research team and study patients were blinded to treatment allocation. Delirium was diagnosed on the basis of the DSM-IV criteria and the Confusion Assessment Method. Once delirium was diagnosed, patients were given haloperidol or lorazepam, or both. Twenty of the 212 patients in the intervention group and 28 of the 218 in the control group dropped out. Among those who dropped out, data were missing for 35 patients (11 in the intervention group and 24 in the control group). The rates of delirium did not differ significantly between the 2 groups (15.1% [32/212] in the haloperidol group v. 16.5% [36/218] in the placebo group; RR 0.91, 95% CI 0.59–1.44). However, among the patients in whom delirium developed, those originally assigned to the haloperidol group had a shorter duration of delirium (5.4 days v. 11.8 days in the placebo group; $p < 0.001$) and a shorter hospital stay (17.1 days v. 22.6 days in the placebo group; $p < 0.001$). There were no reports of drug-related extrapyramidal symptoms or sedation.

Donepezil (5 mg/d for 14 days preoperatively and 14 days postoperatively), a cholinesterase inhibitor most commonly used in the treatment of dementia, was compared with placebo in a trial involving 90 patients undergoing elective total knee or hip replacement.²¹ Randomization was done by the research pharmacist. Study patients, health care providers and the outcome assessor were blinded to treatment allocation. Delirium was diagnosed on the basis of the DSM-IV criteria, the Delirium Symptom Interview³¹ and the Confusion Assessment Method. The rate of delirium did not differ significantly between the study

Table 2: Examples of strategies that targeted risk factors in multicomponent interventions for the prevention of delirium^{22,23,28,29}

Targeted risk factor	Strategy
Cognitive impairment	<ul style="list-style-type: none"> • Orientation protocols • Provision of clocks and calendars
Functional impairment	<ul style="list-style-type: none"> • Early mobilization, including getting patient out of bed regularly and as tolerated starting on postoperative day 1 • Daily physiotherapy with occupational therapy as needed
Fluid and electrolyte imbalances	<ul style="list-style-type: none"> • Restoration of serum sodium, potassium and glucose levels to normal limits • Detection and treatment of dehydration or fluid overload
High-risk medications	<ul style="list-style-type: none"> • Discontinuation or minimization of use of benzodiazepines, anticholinergics, antihistamines and meperidine • Modification of dosage or discontinuation of drugs to minimize drug interactions and adverse effects
Pain	<ul style="list-style-type: none"> • Standing orders for acetaminophen use rather than use as needed • Treatment of breakthrough pain starting with low-dose narcotics; avoidance of meperidine
Impaired vision and hearing	<ul style="list-style-type: none"> • Appropriate use of glasses, hearing aids and adaptive equipment
Malnutrition	<ul style="list-style-type: none"> • Ensurance of proper use of dentures, proper positioning, assistance with eating if required and use of supplements if required
Iatrogenic complications	<ul style="list-style-type: none"> • Removal of urinary catheter by postoperative day 2, with screening for urinary retention and incontinence • Implementation of a skin-care program • Bowel regimen to ensure bowel movements by postoperative day 2 then every 48 hours • Chest physiotherapy and supplemental oxygen if indicated • Appropriate anticoagulation therapy • Screening and treatment of urinary tract infection
Sleep deprivation	<ul style="list-style-type: none"> • Unit-wide strategies to reduce noise • Scheduling of medications and procedures to allow for proper sleep • Use of nonpharmacologic measures to promote sleep

groups (20.5% [8/39] in the donepezil group v. 17.1% [7/41] in the placebo group; $p = 0.69$). The mean length of hospital stay did not differ either (4.4 days in the donepezil group v. 4.2 days in the placebo group; $p = 0.09$).

A small trial involving 42 older patients undergoing surgical resection of gastric or colon cancer examined the use of intramuscular diazepam combined with a continuous intravenous infusion of flunitrazepam and pethidine administered from 8 pm until 4 am each night for 3 nights postoperatively.¹⁵ The investigators hypothesized that sleep disorders are a critical factor in the development of postoperative delirium and designed this protocol in an attempt to control disturbances in the sleep-wake cycle. The protocol was compared with usual care. The method of randomization was not documented. Delirium was diagnosed on the basis of the DSM-IV criteria by a psychiatrist who was blinded to group assignment. Two patients in the intervention group were excluded from analysis because of incomplete administration of the protocol. The rate of postoperative delirium was lower in the intervention group (5% [1/20] v. 35% [7/20] in the control group; $p = 0.02$). However, there was no statistically significant difference in length of hospital stay (25.6 days in the intervention group v. 29.9 days in the control group; $p = 0.74$). The intervention led to morning lethargy in 8 patients.

Overall, there is currently insufficient evidence to support the use of any pharmacologic intervention for the prevention or management of delirium. However, further study into the role of antipsychotic agents in reducing the duration of delirium appears indicated.

How should delirium be managed?

We identified 3 trials (total 489 patients) that studied methods to manage delirium in medical in-patients (Table 1). All 3 trials involved a comprehensive geriatric assessment and multicomponent interventions targeted at precipitants of delirium. There were no pharmacologic trials identified.

The multicomponent interventions varied somewhat between studies but included strategies such as optimizing sensory input, orientation protocols, provision of familiar items and family presence, avoidance of restraints, encouragement of self-care, use of atypical antipsychotic agents for hyperactive and psychotic symptoms, use of nutritional supplements where indicated, screening for potentially treatable causes of cognitive impairment and comprehensive discharge planning. In 2 of the studies a geriatrician or geriatric psychiatrist assessed the patient;^{18,19} it is unclear who conducted the assessment in the third trial.²⁴ All 3 trials conducted intention-to-treat analysis; the outcome assessors were blinded in 2 trials. In 2 trials, computer-generated randomization and concealed treatment allocation were used. The third trial did not describe the method of randomization. All 3 studies used the Confusion Assessment Method to diagnose delirium.

The multicomponent interventions for the management of delirium did not decrease mortality (summary RR 1.08, 95% CI 0.81–1.44; p for heterogeneity = 0.77). There was no effect on length of hospital stay (summary weighted mean difference 3.25 days, 95% CI –2.85 to 9.34 days; p for hetero-

geneity = 0.12).^{18,24} There was no impact on postdischarge dependency,^{18,19} function²⁴ or the need for institutional care.²⁴

Gaps in knowledge

Effectiveness studies are needed to determine whether multicomponent interventions for the prevention of delirium are feasible and cost-effective in everyday practice. There is insufficient evidence to support the use of any pharmacologic intervention for the prevention or management of delirium. Further study into the role of antipsychotic agents in reducing the duration of delirium would be useful.

The case revisited

After completing a comprehensive assessment, the physician elects to initiate a multicomponent preventive strategy that is targeted at the patient's risk factors for delirium, keeping in mind that not all the evidence around preventive strategies involved patients with hip fracture (Table 2). The physician chooses this option because the number needed to treat is only 7, which indicates that this type of strategy has an excellent chance of reducing the risk of delirium in the patient.

High-risk medications such as benzodiazepines and anticholinergic agents are avoided. The patient receives a standing order for acetaminophen postoperatively, with low-dose narcotics (codeine 15–30 mg every 6 hours) as needed for breakthrough pain. A bowel regimen and appropriate anticoagulation are initiated following surgery. The patient's medication schedule is timed so as not to disturb her sleep through the night. The patient is oriented to place and time each morning. On postoperative day 1, her urinary catheter is removed and she is helped out of bed. She receives daily physiotherapy starting 24 hours after surgery. Her oral intake is monitored, and her electrolytes and renal function are measured every 3 days. Appropriate strategies are used to compensate for her visual impairment, including ensuring that she wears her glasses. The patient is monitored closely for postoperative confusion using the Confusion Assessment Method on day 2 and 4. Delirium does not develop. After a short course of rehabilitation, she is discharged to her own home.

Conclusion

Although limited, the evidence currently available from randomized controlled trials of the prevention and management of delirium supports the implementation of multicomponent preventive strategies. In addition, the importance of consistently adhering to the various preventive strategies in these multicomponent interventions should be highlighted and considered when trying to implement these strategies into everyday clinical practice.

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