Published in final edited form as:

J Geriatr Oncol. 2015 January ; 6(1): 60–69. doi:10.1016/j.jgo.2014.10.002.

Prevention of Post-operative Delirium in Older Cancer Patients Undergoing Surgery

Beatriz Korc-Grodzicki, MD, PhD,

Geriatrics Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, 1275 York Avenue Box 205, New York NY 10065, Phone: 646 888 3659, Fax: 646 888 3181, korcgrob@mskcc.org

James C. Root, PhD, and

Department of Psychiatry and Behavioral Science, Memorial Sloan Kettering Cancer Center, New York, NY, rootj@mskcc.org

Yesne Alici, MD

Department of Psychiatry and Behavioral Science, Memorial Sloan Kettering Cancer Center, New York, NY, aliciy@mskcc.org

Abstract

Post-operative delirium (POD) occurs in as much as 50% of all surgical cancer patients, with older patients being particularly at risk. (1–3) Population aging is a real concern for the surgical oncologists (4) who are treating patients who would not have been considered for surgery in the past. There is a strong association between increasing age, a cancer diagnosis, and the need for surgical intervention. Therefore the identification of pre-surgical risk factors and those patients at higher risk of POD as well as indentifying prophylactic measures aimed at reducing POD emergence, and targeted therapies for POD are especially important. Prevention has been shown to be the most effective strategy for minimizing the occurrence of delirium as well as delirium-associated complications. (5) Therefore prevention of delirium in older adults undergoing surgery is a top research priority given the extent of the problem in this patient population. In this review, we will describe the POD syndrome, previously identified risk factors that predict POD in surgical cancer patients, long-term outcomes of POD and both non-pharmacologic and pharmacologic therapies aimed at preventing POD.

Keywords

Delirium; Cancer; Surgery

Correspondence to: Beatriz Korc-Grodzicki.

Conflicts of Interest/Disclosure Statements: The authors have no relationships with organizations or industry that could be viewed as potential conflicts of interest, including personal, academic, or financial..

Post-operative Delirium Defined

With the introduction of the Diagnostic and Statistical Manual of Mental Disorders – 5th Edition (DSM-5), delirium is included in the broader category of Neurocognitive Disorders, which includes syndromes in which acquired cognitive dysfunction is the principal symptom. DSM-5 criteria for delirium consist of a fluctuating disturbance in attention and awareness that represents a decline from baseline status, accompanied by cognitive dysfunction (in orientation, memory, language function, etc.), and may have multiple possible causes (i.e. intoxication, withdrawal, surgical intervention, infection). Delirium is additionally sub-typed as either: *hyperactive*, characterized by increased psychomotor activity, agitation, and mood lability; *hypoactive*, characterized by reduced psychomotor activity and lethargy; or *mixed*, characterized by fluctuating psychomotor activity between hyper- and hypoactive states or, more rarely, normal psychomotor activity with disordered attention and awareness. POD is distinguished from the syndrome of emergence delirium, (6) which is characterized by behavioral disorganization and disorientation in the immediate period following emergence and recovery from anesthetic exposure and more common in pediatric surgical patients. While emergence delirium may in some cases precede POD, the latter generally refers to cases in which symptoms emerge within the first three days of the post-operative course.

While most of the work on POD has focused on general and cardiac surgical cohorts, POD in patients undergoing surgery for resection of primary cancers has received less attention. Despite this, the nature of cancer diagnosis and treatment prior to surgery may confer an even greater risk for POD following surgery, and this area continues to be understudied. Indeed, POD occurs in as much as 50% of all surgical cancer patients, with older patients being particularly at risk. (1, 3, 7, 8) Radiation therapies that may precede surgery, presence of induction (or neo-adjuvant) chemotherapy treatment, suboptimal nutrition and hydration, pain medications, stress of diagnosis and treatment, primary CNS cancer pathology, inflammatory dysregulation, pharmacologic interactions, and the possibility for multiple surgical interventions in the presence of recurrence all may lead to higher rates of POD in a cancer cohort.

Post-operative Delirium Outcomes

A growing body of research strongly suggests that post-operative delirium is associated with an increased risk of long-term decreased functional independence, cognitive decline, dementia risk, and shortened survival time. (9, 10) Evidence for cognitive decline following resolved delirium appears early in the course of recovery (3–6 months) as indicated by decreased Mini-Mental State Exam (MMSE) scores (11) and decreased performance on neuropsychological measures compared to unaffected individuals. (12) Most significantly, evidence of chronic long term decline is demonstrated at two to five year follow-up; following a delirium episode, affected individuals exhibit decreased MMSE performance, (13, 14) a higher incidence of diagnosed mild cognitive impairment and dementia (15–18) and increased mortality. (19–21) In addition to increased burdens and risks to the affected patient, POD is associated with increased caretaker burden, increased health care costs largely due to lengthened hospital stays, additional staff required for the patient's care, and

extensive medical and supervision needs following discharge to home or institutional care. (22–24)

Risk Factors

Several risk factors that may predispose surgical patients to POD have been identified in both general and cardiac surgical groups, and, most recently, in patients undergoing surgical resection for primary cancers (Table 1). (25, 26) For cardiac surgical patients, preoperative comorbidities including cardiovascular disease, intraoperative procedures that influence blood pressure and perfusion, as well as potential for CNS emboli, suggest specific risk factors and interventions that may not be representative of patients undergoing surgical intervention for primary cancers. In non-cardiac surgical patients (emergent and elective orthopedic, thoracic, and peripheral vascular procedures), which may be more representative of risk factors for POD in surgical cancer patients, several factors have been identified with some regularity. (26) The general concept of “frailty” (27) in patients has been used to aggregate a collection of specific factors that are associated with treatment outcomes in general, and following surgical intervention specifically. (28) Age represents a strong risk factor for POD, likely due to the accumulation of medical and other comorbidities together with decreasing reserve throughout later life. A study in ICU patients monitored for delirium found that, starting at 65, the probability of transitioning to delirium increased by 2% with each additional year. (29) Medical conditions and cognitive dysfunction (mild cognitive impairment, dementia) associated with advanced age have also been found to be significant risk factors. (26) Bladder cancer patients 65 years undergoing radical cystectomy had an incidence of postoperative delirium of 29% which was significantly associated with older age and a lower Mini Mental Status Examination score before surgery.(30) In addition to pre-operative cognitive dysfunction, increased medical comorbidities and decreased functional independence have been found to increase risk for delirium following surgery. Pain and pain management have also been found to significantly influence risk of POD, (31) with pre-surgical resting pain, increased pain following surgery, and method of pain control (oral versus patient controlled IV treatment) all found to be independently associated with POD risk. Recent work from our group confirms the importance of frailty more generally and similar individual risk factors more specifically in patients undergoing surgery for primary cancers (25); similar to the work described above in non-cancer surgical procedures, in cancer patients 75 years and older, increased comorbidities, history of recent falls, dependence in instrumental activities of daily living, and cognitive dysfunction were all found to be independent predictors of POD (POD rate = 20%; n = 416).

Significantly, with regard to cognitive, functional and behavioral risk factors, pre-operative brain pathology may be an important link underlying their association with POD. Recent work from our group and others has demonstrated significant associations specifically of idiopathic white matter hyperintensities with risk and duration of POD in cardiac patients and in patients undergoing resection for non-small cell lung cancer. (32, 33) How white matter hyperintensities lead to an increased vulnerability for POD remains unclear, although the inflammatory response associated with surgery together with decreased brain reserve associated with aging may be one possible mechanism. (34) The “inflammatory response syndrome” (35) associated with surgical intervention refers to the stimulation of

macrophages with resultant release of inflammatory mediators including TNF-alpha, IL-6, and IL-1. These inflammatory mediators may then cross the blood brain barrier and in turn lead to microglial activation, neuroinflammation, and oxidative stress. As a result, dysregulation of neuronal function and direct neuronal injury in CNS may occur. Brain reserve refers to functional resilience to CNS insult on the basis of the relative structural and functional integrity of the brain (36) and may be understood as a more recent addition to the concept of frailty in the elderly. A brain reserve model of POD would predict that, given equivalent stressors, the extent or proportion of existing brain pathology will be a key determinant in whether POD is exhibited. Surgical effects might interact both at the level of structural pathology, e.g. by increased blood-brain barrier permeability, or at the level of functional connectivity, e.g., already diminished connectivity between brain regions that are crucial for a given cognitive task or behavior is further disrupted by surgical effects.

Prevention of Delirium: Non-Pharmacological Interventions

Although a common, serious and sometimes fatal disorder, particularly in older hospitalized patients, delirium is often under-recognized and under-diagnosed. It is preventable in 30–40% of cases, and prevention has been shown to be the most effective strategy for minimizing the occurrence of delirium as well as delirium-associated complications. (5, 37–39) Patients with high baseline vulnerability can develop delirium even in response to minor precipitants. Models of pathogenesis emphasize ‘delirium readiness’ (40) where the interaction of a range of predisposing factors with acute precipitants results in the emergence of delirium. The most consistently studied model is that of Inouye and Charpentier (41) who identified four main predisposing factors: cognitive impairment, severe illness, visual impairment and dehydration and five main precipitating factors: polypharmacy, catheterization, use of restraints, malnutrition and any iatrogenic event. These factors predicted a 17-fold variation in the relative risk of older medical inpatients developing delirium. Subsequent work has validated this model in older patients undergoing hip surgery. (42)

The incidence of delirium can be reduced by interventions that minimize exposure to known risk factors. (43) Moreover, delirium is less severe and of shorter duration when it occurs in the setting of active management of delirium proneness. Prevention strategies are typically based on identifying high-risk patients, and addressing modifiable risk factors. (44) Most of the current studies have taken a multi-factorial approach, attempting to prevent several risk factors by protocols, education, or systems redesign, rather than focusing on one risk factor in isolation. (45, 46) Interventions include programs of education for hospital nursing staff, (47) non-pharmacological intervention protocols implemented by a trained interdisciplinary team, (5) review of medications that may contribute to risk for POD, increased patient mobilization, and alteration of the patient’s environment (reduced sleep disruption, orientation reminders, increased daily social interaction etc.). (48) Delirium preventive interventions have generally been found to be cost-effective. (49)

Several delirium risk scales have been validated for risk stratification and resource allocation. (50) These include scales developed for the Intensive Care Unit (PRE-DELIRIC), (51) cardiothoracic (52) and vascular surgery units. (53) Several overlapping delirium

prevention programs focused on non-pharmacological measures have been tested. (5, 37, 54, 55) The most widely disseminated approach is the Hospital Elder Life Program (HELP), (5, 56, 57) a multi-component intervention strategy with proven effectiveness in the prevention of delirium and functional decline. The interventions implemented by an interdisciplinary team include reorientation, therapeutic activities, reduced use and doses of psychoactive drugs, early mobilization, promotion of sleep, maintenance of adequate hydration and nutrition, and provision of vision and hearing adaptations. HELP is now implemented in more than 200 hospitals worldwide, but adaptations and alternatives may be necessary in some settings because of resource constraints or poor availability of skilled interdisciplinary geriatric medicine professionals. (57, 58)

In 2011 the National Clinical Guideline Center published guidelines for the prevention of delirium in hospitalized adults. (38) Eight studies were included in the analysis and all of them took place in a hospital setting. Four studies recruited patients undergoing surgery, either for hip fracture or for elective joint replacements, and four studies included persons with short-term medical illness. The guideline development group made thirteen specific recommendations that addressed the stability of the care environment (both the care team and location) and the provision of a multi-component intervention package tailored for persons at risk for delirium (Table 2). It is important to highlight the need to review patient's medication list taking into account both the type and number of medications in order to prevent adverse drug events and interactions. Medications with increased risk of CNS side effects (e.g. antihistamines, anticholinergics) should be avoided as possible. (59) Future work should target alignment between specific interventions and the needs of individual patients. Opportunities for earlier intervention exist for cancer patients who are entering periods of increased risk for delirium by virtue of elective medical and surgical interventions. 'Prehabilitation,' an intervention that enhances functional capacity in anticipation of a forthcoming physiological stressor, involves risk factor reduction to optimize preparedness for non-emergency procedures. (60) Bjorkelund et al. (61) significantly reduced delirium incidence (from 34% to 22%) in patients undergoing hip fracture surgery with an intervention addressing hydration, oxygenation, analgesia, polypharmacy and optimizing care environment routines that commenced during the pre-hospital period.

Prevention of Delirium: Pharmacological Interventions

Pharmacologic prevention of delirium in older adults undergoing surgery is a top research priority given the extent of the problem in this patient population. Antipsychotics, cholinesterase inhibitors, dexmedetomidine, and melatonin are the main pharmacologic interventions studied in the prevention of delirium in a variety of settings and in mixed age-groups. (43, 62–74)

The U.S. Food and Drug Administration has not approved any pharmacologic agent for use in the prevention of delirium. A 2014 systematic review of prevention interventions in older people in long term care settings failed to show any evidence for the use of pharmacological agents to prevent delirium due to lack of studies in this patient population. (75) Likewise, a 2007 systematic review of delirium prevention studies in mixed patient populations in

inpatient settings failed to make any recommendations regarding the use of pharmacologic interventions as the evidence was sparse. (43) Since then, there have been several delirium prevention trials with pharmacological agents in ICU and postoperative settings. It is important to note that none of the pharmacologic agents were studied specifically in oncology settings; therefore, no recommendations could be made regarding use of these medications in the prevention of delirium in cancer patients. The following sections will provide a review of the current evidence for use of pharmacological interventions in prevention of delirium among older adults.

Antipsychotics

Antipsychotics are a class of psychotropic medications primarily used in schizophrenia, bipolar disorder, as adjunct treatment for depression, and in a number of disorders presenting with psychotic symptoms. Typical antipsychotics such as haloperidol or chlorpromazine exert their effects by blocking the dopamine 2 (D2) receptors in the mesolimbic area of the brain. The newer, or atypical, antipsychotics such as risperidone, olanzapine, aripiprazole, quetiapine show lower affinity for and faster dissociation rate from the D2 receptors. They additionally have serotonin 2A (5HT2A) receptor blocking activities. The main clinical implication of the difference between typical and atypical antipsychotics is the lower rates of extrapyramidal side effects associated with the use of atypical antipsychotics. There does not appear to be a difference in the efficacy of these medications in treatment of psychotic spectrum disorders or delirium. (76)

Antipsychotics have been used to treat symptoms of delirium due to their effects on agitation and psychotic symptoms. Increased dopamine levels is one of the well-established pathophysiological mechanisms in patients with delirium. (34) Therefore, many clinicians may use antipsychotics medications in treatment of patients with delirium even in the absence of psychotic symptoms and agitation. The putative mechanism for use of antipsychotics in prevention of delirium is the dopamine blockade that protects the brain from dopamine excess, hence delirium. In Table 3 we provide a list of the placebo-controlled randomized antipsychotic medication trials for prevention of delirium. A 2013 meta-analysis of antipsychotic medication trials showed a 50% reduction in relative risk of postoperative delirium compared to placebo based on a pooled relative risk analysis of five antipsychotic prevention studies in older adults undergoing elective surgery [RR (95%CI): 0.51 (0.33–0.79; heterogeneity, $p < 0.01$, random effects model)]. (71)

It is important to note that antipsychotics have complex mechanisms of action, mostly affecting multiple neurotransmitter systems that can lead to unwanted side effects in older adults. The benefits of initiating antipsychotics for the prevention of delirium should be weighed against risks associated with their use. The risk of extrapyramidal side effects, sedation, anticholinergic side effects, cardiac arrhythmias, and possible drug-drug interactions should be taken into consideration when initiating antipsychotics. There is an FDA warning on the risk of QTc prolongation and torsades de pointes with the use of intravenous haloperidol. Therefore monitoring QTc intervals at least daily among medically ill patients receiving intravenous haloperidol is the standard clinical practice. The FDA has issued a “black box” warning of increased risk of death when antipsychotics are used to treat

elderly patients with dementia-related psychoses. The initial warning for atypical antipsychotics was prompted by a meta-analysis by Schneider et al. of 17 placebo-controlled trials involving patients with dementia. (77) The risk of death in patients treated with atypical antipsychotic agents was 1.6 to 1.7 times greater than in those who received placebo. Most deaths were associated with cardiovascular disease or infection. A second, retrospective study of nearly 23,000 older patients found higher mortality rates associated with typical compared with atypical antipsychotics--whether or not they had dementia. (78) This finding has led to an extension of the FDA warning to typical antipsychotics. A retrospective, case-control analysis of 326 elderly hospitalized patients with delirium at an acute care community hospital comparing risk of mortality among patients who received an antipsychotic versus those who did not found that of the 111 patients who received an antipsychotic a total of 16 patients died during that hospitalization. The odds ratio of association between antipsychotic use and death was 1.53 (95% C.I, 0.83–2.80) in univariate and 1.61 (95% C.I, 0.88–2.96) in multivariate analysis. The researchers concluded that among elderly medical inpatients with delirium, administration of antipsychotics was not associated with a statistically significant increased risk of mortality. (79) However larger studies are needed to validate this conclusion.

Cholinesterase inhibitors

Cholinesterase inhibitors are indicated for use in patients with Alzheimer's dementia. They act by inhibiting acetylcholinesterase, the enzyme that breaks down acetylcholine, thereby increasing the levels of acetylcholine in the central nervous system. Acetylcholine deficiency has been identified as one of the main pathophysiologic mechanisms underlying delirium. (34) Therefore, the use of cholinesterase inhibitors has been hypothesized to be beneficial in preventing delirium. Four placebo-controlled delirium prevention trials with donepezil (two studies) and rivastigmine (two studies) failed to show efficacy of either of those medications in reducing delirium incidence or severity. (62, 63, 68, 70)

Melatonin

Melatonin and melatonin agonists have been suggested to play a role in the treatment of delirium through direct antioxidant and anti-inflammatory activity, in addition to their effects on the sleep-wake cycle. A randomized, double-blind, placebo-controlled study with melatonin among older adults in an acute care unit was found to be effective in reducing the incidence of delirium. (64) A randomized controlled trial with ramelteon, a melatonin agonist, among a mixed group of older adults have similarly shown a reduced incidence of delirium. (74)

Alpha-2 agonists

Dexmedetomidine is a selective alpha-2 adrenergic agonist that is used for sedation of mechanically ventilated adult patients in ICU settings. (69) Dexmedetomidine has been proposed to decrease incidence of delirium through its alpha-2 agonist effects and associated reduction of noradrenaline levels. A recent meta-analysis of randomized controlled trials involving the use of dexmedetomidine in ICU patients has shown that the incidence of delirium was significantly reduced compared with propofol administration based on three studies including a total of 658 patients, although these did not specifically include older

adults (relative risk 0.40; confidence interval 0.22–0.74). (69) It should be noted that none of the dexmedetomidine trials conducted to date have included a placebo arm.

Conclusion

A significant proportion of all surgical cancer patients develop POD with older patients being particularly at risk. Delirium is potentially preventable and treatable, but major barriers, including under-recognition of the syndrome and poor understanding of the underlying pathophysiology, have hampered the development of successful therapies. Prevention strategies are typically based on identifying high risk patients, and addressing modifiable risk factors in these patients. Non-pharmacological interventions have shown to be effective and a very limited number of delirium prevention studies among postoperative older adults are supportive of the use of antipsychotic drugs and melatonin to reduce incidence of delirium. Opportunities for earlier intervention exist for cancer patients who are entering periods of increased risk for delirium by virtue of elective medical and surgical interventions.

Given these observations, we recommend hospital wide screening for POD risk in older patients, and implementation of preventative measures in patients deemed to be at high risk for POD prior to surgery as well as in the immediate period following surgery. We also recommend increased monitoring and routine assessment for POD following surgery in order to improve recognition of the syndrome in this vulnerable group of patients. Prevention of delirium in older cancer patients undergoing surgery is a top research priority given the extent of the problem in this patient population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Takeuchi M, Takeuchi H, Fujisawa D, Miyajima K, Yoshimura K, Hashiguchi S, et al. Incidence and risk factors of postoperative delirium in patients with esophageal cancer. *Annals of surgical oncology*. 2012; 19(12):3963–70. Epub 2012/06/16. [PubMed: 22699802]
2. Tei M, Ikeda M, Haraguchi N, Takemasa I, Mizushima T, Ishii H, et al. Risk factors for postoperative delirium in elderly patients with colorectal cancer. *Surgical endoscopy*. 2010; 24(9): 2135–9. Epub 2010/02/24. [PubMed: 20177939]
3. Yamagata K, Onizawa K, Yusa H, Wakatsuki T, Yanagawa T, Yoshida H. Risk factors for postoperative delirium in patients undergoing head and neck cancer surgery. *Int J Oral Maxillofac Surg*. 2005; 34(1):33–6. Epub 2004/12/25. [PubMed: 15617964]
4. Administration on Aging (AoA) USDoHaHS. A Profile of Older Americans: 2007. 2007. Available from: <http://www.aoa.gov/PROF/Statistics/profile/2005/2005profile.pdf>
5. Inouye SK, Bogardus ST Jr, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *The New England journal of medicine*. 1999; 340(9):669–76. Epub 1999/03/04. [PubMed: 10053175]
6. Munk L, Andersen LP, Gogenur I. Emergence delirium. *Journal of perioperative practice*. 2013; 23(11):251–4. Epub 2013/12/10. [PubMed: 24312995]
7. Hempenius L, Slaets JP, van Asselt D, de Bock GH, Wiggers T, van Leeuwen BL. Outcomes of a Geriatric Liaison Intervention to Prevent the Development of Postoperative Delirium in Frail

- Elderly Cancer Patients: Report on a Multicentre, Randomized, Controlled Trial. *PLoS One*. 2013; 8(6):e64834. Epub 2013/07/11. [PubMed: 23840308]
8. Gallagher TK, McErlean S, O'Farrell A, Hoti E, Maguire D, Traynor OJ, et al. Incidence and risk factors of delirium in patients post pancreaticoduodenectomy. *HPB : the official journal of the International Hepato Pancreato Biliary Association*. 2014 Epub 2014/04/23.
  9. MacLulich AM, Beaglehole A, Hall RJ, Meagher DJ. Delirium and long-term cognitive impairment. *Int Rev Psychiatry*. 2009; 21(1):30–42. [PubMed: 19219711]
  10. Jackson JC, Gordon SM, Hart RP, Hopkins RO, Ely EW. The association between delirium and cognitive decline: a review of the empirical literature. *Neuropsychol Rev*. 2004; 14(2):87–98. [PubMed: 15264710]
  11. Duppils GS, Wikblad K. Cognitive function and health-related quality of life after delirium in connection with hip surgery. A six-month follow-up. *Orthop Nurs*. 2004; 23(3):195–203. [PubMed: 15211901]
  12. Benoit AG, Campbell BI, Tanner JR, Staley JD, Wallbridge HR, Biehl DR, et al. Risk factors and prevalence of perioperative cognitive dysfunction in abdominal aneurysm patients. *J Vasc Surg*. 2005; 42(5):884–90. [PubMed: 16275442]
  13. Bickel H, Gradingner R, Kochs E, Forstl H. High risk of cognitive and functional decline after postoperative delirium. A three-year prospective study. *Dement Geriatr Cogn Disord*. 2008; 26(1):26–31. [PubMed: 18577850]
  14. Dolan MM, Hawkes WG, Zimmerman SI, Morrison RS, Gruber-Baldini AL, Hebel JR, et al. Delirium on hospital admission in aged hip fracture patients: prediction of mortality and 2-year functional outcomes. *J Gerontol A Biol Sci Med Sci*. 2000; 55(9):M527–34. [PubMed: 10995051]
  15. Lundstrom M, Edlund A, Bucht G, Karlsson S, Gustafson Y. Dementia after delirium in patients with femoral neck fractures. *J Am Geriatr Soc*. 2003; 51(7):1002–6. [PubMed: 12834522]
  16. Rockwood K, Cosway S, Carver D, Jarrett P, Stadnyk K, Fisk J. The risk of dementia and death after delirium. *Age Ageing*. 1999; 28(6):551–6. [PubMed: 10604507]
  17. Kat MG, Vreeswijk R, de Jonghe JF, van der Ploeg T, van Gool WA, Eikelenboom P, et al. Long-term cognitive outcome of delirium in elderly hip surgery patients. A prospective matched controlled study over two and a half years. *Dement Geriatr Cogn Disord*. 2008; 26(1):1–8. [PubMed: 18562793]
  18. Rahkonen T, Eloniemi-Sulkava U, Halonen P, Verkkoniemi A, Niinisto L, Notkola IL, et al. Delirium in the non-demented oldest old in the general population: risk factors and prognosis. *Int J Geriatr Psychiatry*. 2001; 16(4):415–21. [PubMed: 11333430]
  19. McCusker J, Cole M, Abrahamowicz M, Primeau F, Belzile E. Delirium predicts 12-month mortality. *Arch Intern Med*. 2002; 162(4):457–63. [PubMed: 11863480]
  20. Cole MG, You Y, McCusker J, Ciampi A, Belzile E. The 6 and 12 month outcomes of older medical inpatients who recover from delirium. *Int J Geriatr Psychiatry*. 2008; 23(3):301–7. [PubMed: 17668420]
  21. Bellelli G, Frisoni GB, Turco R, Lucchi E, Magnifico F, Trabucchi M. Delirium superimposed on dementia predicts 12-month survival in elderly patients discharged from a postacute rehabilitation facility. *J Gerontol A Biol Sci Med Sci*. 2007; 62(11):1306–9. Epub 2007/11/15. [PubMed: 18000153]
  22. Leslie DL, Inouye SK. The importance of delirium: economic and societal costs. *J Am Geriatr Soc*. 2011; 59(Suppl 2):S241–3. Epub 2011/12/07. [PubMed: 22091567]
  23. Barton CD, DePaulo JR. The unrecognized costs of delirium. *Nat Clin Pract Neurol*. 2008; 4(5):233. [PubMed: 18454132]
  24. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. *Arch Intern Med*. 2008; 168(1):27–32. Epub 2008/01/16. [PubMed: 18195192]
  25. Korc-Grodzicki B, Sun SW, Zhou Q, Iasonos A, Lu B, Root JC, et al. Geriatric Assessment as a Predictor of Delirium and Other Outcomes in Elderly Patients With Cancer. *Annals of surgery*. 2014 Epub 2014/06/03.

26. Dasgupta M, Dumbrell AC. Preoperative risk assessment for delirium after noncardiac surgery: a systematic review. *Journal of the American Geriatrics Society*. 2006; 54(10):1578–89. Epub 2006/10/14. [PubMed: 17038078]
27. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001; 56(3):M146–56. Epub 2001/03/17. [PubMed: 11253156]
28. Hubbard RE, Story DA. Patient frailty: the elephant in the operating room. *Anaesthesia*. 2014; 69(Suppl 1):26–34. Epub 2013/12/16. [PubMed: 24303858]
29. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology*. 2006; 104(1):21–6. Epub 2006/01/06. [PubMed: 16394685]
30. Large MC, Reichard C, Williams JT, Chang C, Prasad S, Leung Y, et al. Incidence, risk factors, and complications of postoperative delirium in elderly patients undergoing radical cystectomy. *Urology*. 2013; 81(1):123–8. Epub 2012/11/17. [PubMed: 23153950]
31. Vaurio LE, Sands LP, Wang Y, Mullen EA, Leung JM. Postoperative delirium: the importance of pain and pain management. *Anesth Analg*. 2006; 102(4):1267–73. Epub 2006/03/23. [PubMed: 16551935]
32. Morandi A, Rogers BP, Gunther ML, Merkle K, Pandharipande P, Girard TD, et al. The relationship between delirium duration, white matter integrity, and cognitive impairment in intensive care unit survivors as determined by diffusion tensor imaging: the VISIONS prospective cohort magnetic resonance imaging study*. *Crit Care Med*. 2012; 40(7):2182–9. Epub 2012/05/16. [PubMed: 22584766]
33. Root JC, Pryor KO, Downey R, Alici Y, Davis ML, Holodny A, et al. Association of pre-operative brain pathology with post-operative delirium in a cohort of non-small cell lung cancer patients undergoing surgical resection. *Psycho-oncology*. 2013 Epub 2013/03/05.
34. Maldonado JR. Neuropathogenesis of Delirium: Review of Current Etiologic Theories and Common Pathways. *Am J Geriatr Psychiatry*. 2013; 21(12):1190–222. Epub 2013/11/12. [PubMed: 24206937]
35. Fricchione GL, Nejad SH, Esses JA, Cummings TJ Jr, Querques J, Cassem NH, et al. Postoperative delirium. *Am J Psychiatry*. 2008; 165(7):803–12. Epub 2008/07/03. [PubMed: 18593786]
36. Satz P, Cole MA, Hardy DJ, Rassovsky Y. Brain and cognitive reserve: mediator(s) and construct validity, a critique. *Journal of clinical and experimental neuropsychology*. 2011; 33(1):121–30. Epub 2010/08/04. [PubMed: 20680883]
37. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *Journal of the American Geriatrics Society*. 2001; 49(5):516–22. Epub 2001/06/15. [PubMed: 11380742]
38. O'Mahony R, Murthy L, Akunne A, Young J. Synopsis of the National Institute for Health and Clinical Excellence guideline for prevention of delirium. *Annals of internal medicine*. 2011; 154(11):746–51. Epub 2011/06/08. [PubMed: 21646557]
39. O'Hanlon S, O'Regan N, MacLulich AM, Cullen W, Dunne C, Exton C, et al. Improving delirium care through early intervention: from bench to bedside to boardroom. *Journal of neurology, neurosurgery, and psychiatry*. 2014; 85(2):207–13. Epub 2013/01/29.
40. Henry WD, Mann AM. Diagnosis and treatment of delirium. *Canadian Medical Association journal*. 1965; 93(22):1156–66. Epub 1965/11/27. [PubMed: 5844423]
41. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA : the journal of the American Medical Association*. 1996; 275(11):852–7. Epub 1996/03/20. [PubMed: 8596223]
42. Kalisvaart KJ, Vreeswijk R, de Jonghe JF, van der Ploeg T, van Gool WA, Eikelenboom P. Risk factors and prediction of postoperative delirium in elderly hip-surgery patients: implementation and validation of a medical risk factor model. *J Am Geriatr Soc*. 2006; 54(5):817–22. [PubMed: 16696749]
43. Siddiqi N, Stockdale R, Britton AM, Holmes J. Interventions for preventing delirium in hospitalised patients. *The Cochrane database of systematic reviews*. 2007; (2):Cd005563. Epub 2007/04/20. [PubMed: 17443600]

44. Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. *Nature reviews Neurology*. 2009; 5(4):210–20. Epub 2009/04/07. [PubMed: 19347026]
45. Cole MG, McCusker J, Bellavance F, Primeau FJ, Bailey RF, Bonnycastle MJ, et al. Systematic detection and multidisciplinary care of delirium in older medical inpatients: a randomized trial. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. 2002; 167(7):753–9. Epub 2002/10/23.
46. Milisen K, Foreman MD, Abraham IL, De Geest S, Godderis J, Vandermeulen E, et al. A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients. *Journal of the American Geriatrics Society*. 2001; 49(5):523–32. Epub 2001/06/15. [PubMed: 11380743]
47. Rockwood K. Educational interventions in delirium. *Dementia and geriatric cognitive disorders*. 1999; 10(5):426–9. Epub 1999/09/04. [PubMed: 10473952]
48. Wanich CK, Sullivan-Marx EM, Gottlieb GL, Johnson JC. Functional status outcomes of a nursing intervention in hospitalized elderly. *Image--the journal of nursing scholarship*. 1992; 24(3):201–7. Epub 1992/01/01. [PubMed: 1521848]
49. Akunne A, Murthy L, Young J. Cost-effectiveness of multi-component interventions to prevent delirium in older people admitted to medical wards. *Age and ageing*. 2012; 41(3):285–91. Epub 2012/01/28. [PubMed: 22282171]
50. MacLulich AM, Anand A, Davis DH, Jackson T, Barugh AJ, Hall RJ, et al. New horizons in the pathogenesis, assessment and management of delirium. *Age and ageing*. 2013; 42(6):667–74. Epub 2013/09/27. [PubMed: 24067500]
51. van den Boogaard M, Pickkers P, Slooter AJ, Kuiper MA, Spronk PE, van der Voort PH, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. *BMJ (Clinical research ed)*. 2012; 344:e420. Epub 2012/02/11.
52. Rudolph JL, Jones RN, Levkoff SE, Rockett C, Inouye SK, Sellke FW, et al. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. *Circulation*. 2009; 119(2):229–36. Epub 2009/01/02. [PubMed: 19118253]
53. Pol RA, van Leeuwen BL, Visser L, Izaks GJ, van den Dungen JJ, Tielliu IF, et al. Standardised frailty indicator as predictor for postoperative delirium after vascular surgery: a prospective cohort study. *European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery*. 2011; 42(6):824–30. Epub 2011/08/04.
54. Lundstrom M, Edlund A, Karlsson S, Brannstrom B, Bucht G, Gustafson Y. A multifactorial intervention program reduces the duration of delirium, length of hospitalization, and mortality in delirious patients. *Journal of the American Geriatrics Society*. 2005; 53(4):622–8. Epub 2005/04/09. [PubMed: 15817008]
55. Siddiqi N, Young J, House AO, Featherstone I, Hopton A, Martin C, et al. Stop Delirium! A complex intervention to prevent delirium in care homes: a mixed-methods feasibility study. *Age and ageing*. 2011; 40(1):90–8. Epub 2010/09/24. [PubMed: 20861087]
56. Inouye SK, Bogardus ST Jr, Baker DI, Leo-Summers L, Cooney LM Jr. The Hospital Elder Life Program: a model of care to prevent cognitive and functional decline in older hospitalized patients. *Hospital Elder Life Program. Journal of the American Geriatrics Society*. 2000; 48(12):1697–706. Epub 2000/12/29. [PubMed: 11129764]
57. Inouye SK, Baker DI, Fugal P, Bradley EH. Dissemination of the hospital elder life program: implementation, adaptation, and successes. *Journal of the American Geriatrics Society*. 2006; 54(10):1492–9. Epub 2006/10/14. [PubMed: 17038065]
58. Chen CC, Lin MT, Tien YW, Yen CJ, Huang GH, Inouye SK. Modified hospital elder life program: effects on abdominal surgery patients. *Journal of the American College of Surgeons*. 2011; 213(2):245–52. Epub 2011/06/07. [PubMed: 21641835]
59. American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2012; 60(4):616–31. Epub 2012/03/02. [PubMed: 22376048]
60. Carli F, Charlebois P, Stein B, Feldman L, Zavorsky G, Kim DJ, et al. Randomized clinical trial of prehabilitation in colorectal surgery. *The British journal of surgery*. 2010; 97(8):1187–97. Epub 2010/07/06. [PubMed: 20602503]

61. Bjorkelund KB, Hommel A, Thorngren KG, Gustafson L, Larsson S, Lundberg D. Reducing delirium in elderly patients with hip fracture: a multi-factorial intervention study. *Acta anaesthesiologica Scandinavica*. 2010; 54(6):678–88. Epub 2010/03/20. [PubMed: 20236093]
62. Liptzin B, Laki A, Garb JL, Fingerth R, Krushell R. Donepezil in the prevention and treatment of post-surgical delirium. *The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry*. 2005; 13(12):1100–6. Epub 2005/12/02. [PubMed: 16319303]
63. Sampson EL, Raven PR, Ndhlovu PN, Vallance A, Garlick N, Watts J, et al. A randomized, double-blind, placebo-controlled trial of donepezil hydrochloride (Aricept) for reducing the incidence of postoperative delirium after elective total hip replacement. *International journal of geriatric psychiatry*. 2007; 22(4):343–9. Epub 2006/09/29. [PubMed: 17006875]
64. Al-Aama T, Brymer C, Gutmanis I, Woolmore-Goodwin SM, Esbaugh J, Dasgupta M. Melatonin decreases delirium in elderly patients: a randomized, placebo-controlled trial. *International journal of geriatric psychiatry*. 2011; 26(7):687–94. Epub 2010/09/17. [PubMed: 20845391]
65. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, Vreeswijk R, Egberts TC, Burger BJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. *Journal of the American Geriatrics Society*. 2005; 53(10):1658–66. Epub 2005/09/27. [PubMed: 16181163]
66. Larsen KA, Kelly SE, Stern TA, Bode RH Jr, Price LL, Hunter DJ, et al. Administration of olanzapine to prevent postoperative delirium in elderly joint-replacement patients: a randomized, controlled trial. *Psychosomatics*. 2010; 51(5):409–18. Epub 2010/09/14. [PubMed: 20833940]
67. Prakanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. *Anaesthesia and intensive care*. 2007; 35(5):714–9. Epub 2007/10/16. [PubMed: 17933157]
68. Gamberini M, Bolliger D, Lurati Buse GA, Burkhart CS, Grapow M, Gagneux A, et al. Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery--a randomized controlled trial. *Critical care medicine*. 2009; 37(5):1762–8. Epub 2009/03/28. [PubMed: 19325490]
69. Xia ZQ, Chen SQ, Yao X, Xie CB, Wen SH, Liu KX. Clinical benefits of dexmedetomidine versus propofol in adult intensive care unit patients: a meta-analysis of randomized clinical trials. *The Journal of surgical research*. 2013; 185(2):833–43. Epub 2013/08/06. [PubMed: 23910886]
70. Zaslavsky A, Haile M, Kline R, Iospa A, Frempong-Boadu A, Bekker A. Rivastigmine in the treatment of postoperative delirium: a pilot clinical trial. *International journal of geriatric psychiatry*. 2012; 27(9):986–8. Epub 2012/08/14. [PubMed: 22886871]
71. Teslyar P, Stock VM, Wilk CM, Camsari U, Ehrenreich MJ, Himelhoch S. Prophylaxis with antipsychotic medication reduces the risk of post-operative delirium in elderly patients: a meta-analysis. *Psychosomatics*. 2013; 54(2):124–31. Epub 2013/02/06. [PubMed: 23380670]
72. Page VJ, Ely EW, Gates S, Zhao XB, Alce T, Shintani A, et al. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. *The lancet Respiratory medicine*. 2013; 1(7):515–23. Epub 2014/01/28. [PubMed: 24461612]
73. Devlin JW, Al-Qadhees NS, Skrobik Y. Pharmacologic prevention and treatment of delirium in critically ill and non-critically ill hospitalised patients: a review of data from prospective, randomised studies. *Best practice & research Clinical anaesthesiology*. 2012; 26(3):289–309. Epub 2012/10/09. [PubMed: 23040282]
74. Hatta K, Kishi Y, Wada K, Takeuchi T, Odawara T, Usui C, et al. Preventive Effects of Ramelteon on Delirium: A Randomized Placebo-Controlled Trial. *JAMA psychiatry*. 2014 Epub 2014/02/21.
75. Clegg A, Siddiqi N, Heaven A, Young J, Holt R. Interventions for preventing delirium in older people in institutional long-term care. *The Cochrane database of systematic reviews*. 2014; 1:CD009537. Epub 2014/02/04.
76. Breitbart W, Alici Y. Evidence-based treatment of delirium in patients with cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2012; 30(11):1206–14. Epub 2012/03/14. [PubMed: 22412123]

77. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA : the journal of the American Medical Association*. 2005; 294(15):1934–43. Epub 2005/10/20. [PubMed: 16234500]
78. Wang PS, Schneeweiss S, Avorn J, Fischer MA, Mogun H, Solomon DH, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. *The New England journal of medicine*. 2005; 353(22):2335–41. Epub 2005/12/02. [PubMed: 16319382]
79. Elie M, Boss K, Cole MG, McCusker J, Belzile E, Ciampi A. A retrospective, exploratory, secondary analysis of the association between antipsychotic use and mortality in elderly patients with delirium. *International psychogeriatrics / IPA*. 2009; 21(3):588–92. Epub 2009/04/17.
80. Wang W, Li HL, Wang DX, Zhu X, Li SL, Yao GQ, et al. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial*. *Critical care medicine*. 2012; 40(3):731–9. Epub 2011/11/10. [PubMed: 22067628]

Table 1

Risk Factors for Delirium

Major Risk Factors (41,42)
Cognitive Impairment
Severity of Illness
Visual Impairment
Dehydration
Minor Risk Factors (41,42)
Polypharmacy
Catheterization
Use of Restraints
Malnutrition
Any Iatrogenic Event
Other Risk Factors for POD
Older Age (26,29,30)
Increased number of comorbidities (25,26)
Increased functional dependency (25,30)
History of falls in the last 6 months (25)
Pre and post surgical pain (31)
Increased White Matter Pathology (33)

Table 2

Guidelines for Non-Pharmacological Prevention of Delirium (38)

1	Ensure that persons at risk for delirium are cared for by a team of health care professionals who are familiar with the patient. Avoid moving persons within and between wards or rooms unless absolutely necessary.
2	Within 24 hours of hospitalization, assess persons at risk for clinical factors contributing to delirium and provide a multi-component intervention tailored to the person's individual needs.
3	The tailored intervention should be delivered by a trained multidisciplinary team.
4	Address cognitive impairment or disorientation. Provide appropriate lighting and clear signage, ensuring that a clock and a calendar are easily visible to the patients. Reorient patients by explaining where they are, who they are, and what your role is; introduce cognitively stimulating activities and facilitating regular visits from family and friends.
5	Avoid dehydration and constipation by ensuring adequate fluid intake
6	Assess for hypoxia and optimize oxygen saturation as clinically appropriate.
7	Look for and treat infection, avoid unnecessary catheterization, and implement infection-control procedures.
8	Address immobility or limited mobility. Encourage persons to mobilize soon after surgery (walking, range of motion).
9	Assess for pain via nonverbal signs, particularly in persons with communication difficulties, and initiate/ review appropriate pain management.
10	Carry out a medication review taking into account both the type and number of medications.
11	Address poor nutrition and provide nutrition support. Ensure that dentures fit properly.
12	Address sensory impairment. Resolve reversible cause of the impairment (i.e. impacted ear wax). Ensure hearing and visual aids are available to and used by persons who need them.
13	Promote good sleep patterns and sleep hygiene. Avoid procedures during sleeping hours, schedule medication rounds to avoid disturbing sleep and reduce noise to a minimum.

Table 3

Randomized placebo-controlled trials with pharmacological agents in prevention of delirium

Study	Study Population	Intervention	Delirium Rate	Comments
<i>Anti-psychotics</i>				
Kalisvaart et al., 2005 (65)	Elective hip surgery patients at moderate to high risk for delirium, n=430, age>70 years of age	Haloperidol 0.5 mg po tid starting day of admission through postoperative day 3.	<i>ns</i>	All patients in the study received nonpharmacologic interventions for prevention of delirium. Patients who developed delirium in the haloperidol group had shorter hospital stays and decreased duration and severity of delirium when compared to the delirious patients in the control group.
Prakanrattana et al., 2007 (67)	Elective cardiac surgery patients with cardiopulmonary bypass, n=126, age>40 years of age (mean age=61)	Risperidone 1mg orally at emergence from anesthesia.	Untreated 20 (31.7%) Treated: 7 (11.1%). p=0.01. NNT=4.85.	Delirium severity was significantly lower among patients in the risperidone group. The length of hospital stay was not significantly different between the two groups. The study was criticized for imprecise reporting of the results in a comprehensive review (69).
Larsen et al., 2010 (66)	Elective hip and knee surgery patients, n=400, age> 65 or age < 65 with a history of delirium	Olanzapine 5 mg before and immediately after surgery, total of two doses.	Untreated: 82 (40.2%) Treated: 28 (14.3%). p<0.0001 NNT=4.	Olanzapine group had longer (p=0.02) and more severe (p=0.02) delirium when compared to those with delirium in the control group. 5 of the patients in the olanzapine group had alcohol withdrawal delirium that might account for the difference in severity and duration of delirium in the drug arm.
Wang et al., 2012 (80)	Noncardiac surgery patients in ICU after surgery, n=457, age>65 years of age	Haloperidol 0.5 mg IV bolus after surgery followed by 12 hours infusion of Haloperidol 0.1mg/hour (total dose of haloperidol 1.7 mg)	Untreated: 53 (23.2%) Treated: 35 (15.3%). p<0.05. NNT=12	The length of ICU stay was shorter in the drug arm. The length of hospitalization was not different between the two groups. No adverse events were identified in either group. Changes in QTc were similar in both groups. There was no difference in the 28 day all cause mortality between the groups. Both groups received nonpharmacologic interventions for prevention of delirium.
Page et al., 2013 (72)	ICU patients with mechanical ventilation, n=142, mean age in the haloperidol group was 67.9; in the placebo group it was 68.7.	Haloperidol 2.5 mg IV every 8 hours for a maximum of 14 days.	<i>ns</i>	Patients in the haloperidol group spent about the same number of days alive, without delirium, and without coma as did patients in the placebo group. No patient had a serious adverse event related to the study drug.
<i>Cholinesterase inhibitors</i>				
Liptzin et al., 2005 (62)	Orthopedic surgery patients, age>50, n=80.	Donepezil 5 mg for 14 days before surgery and 14 days after surgery.	No difference between groups	About 25% of patients dropped out of the study prior to completion (not due to adverse events). There was no difference in discharge to a rehabilitation facility between the two groups.

Study	Study Population	Intervention	Delirium Rate	Comments
Sampson et al., 2007 (63)	Orthopedic surgery patients, n=33.	Donepezil 5 mg a day for 3 days postoperatively	Untreated: (35.7%) Treated: (9.5%). p=0.08	There were no serious adverse events reported in the intervention arm. There was no significant difference in the length of hospital stay.
Gamberini et al., 2009 (68)	Cardiac surgery patients with mechanical ventilation, age>65, n=113	Rivastigmine 1.5 mg q8h for 6 days starting night before surgery.	<i>ns</i>	There was no significant difference in delirium duration, length of hospital stay between the two groups. Nausea was more frequent in the intervention group but not significantly different when compared to the controls.
Zaslavsky et al., 2012 (70)	Elective surgery, age>65, n=28	Rivastigmine transdermal before surgery	<i>ns</i>	The study sample size was too small to report any reliable findings.
<i>Melatonin/Agonists</i>				
Al-Ama et al., 2011 (64)	Hospitalized patients, age>65, n=145.	Melatonin 0.5 mg daily for 14 days.	Untreated: (31%) Treated: (12%). p<0.014	Hallucinations (n=1) and nightmares (n=1) were reported among 2 of the patients on melatonin with symptoms resolving after medication discontinuation.
Hatta et al., 2014 (74)	Intensive care units and general medical wards, age>65, n=77.	Ramelteon 8 mg/day for 7 days.	Untreated: (32%) Treated: (3%). p=0.003	No significant side effects were reported in the drug arm.

N.B. All cited studies were placebo-controlled, randomized designs