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Sedative Agents and Prophylaxis in ICU Delirium

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Abstract Delirium is a form of acute brain dysfunction in the critically ill that is associated with significant morbidity and mortality in addition to increases in healthcare costs. Important risk factors for delirium include a patient's underlying illness, metabolic disturbances, sedative and psychoactive medications, and underlying cognitive impairment. Vigilant monitoring and recognition are the first step in reducing the burden of delirium. The Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (IDCSC) are the validated methods of diagnosing delirium in the intensive care unit. Definitive evidence of treatments to reduce the incidence or duration of delirium in the intensive care unit is limited. Protocolized care to ensure minimization of sedation and appropriate sedative selection, early ventilator liberation, adequate treatment of pain, early mobility, and proper sleep hygiene offer the best hope of reducing the incidence of delirium and its burden on healthcare and society.

Keywords Delirium · Intensive care unit · Risk factors · Prevention · Treatment

This article is part of the Topical Collection on *Perioperative Delirium*.

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Introduction

Delirium is a syndrome of acute brain dysfunction that is becoming increasingly recognized as an important contributor to both in-hospital and post-discharge morbidity and mortality. Delirium manifests as fluctuations in mental status and may present with a wide spectrum of symptoms. Cardinal symptoms are inattention, disorganized thinking, disorientation, and/or altered levels of consciousness, and additional symptoms can include sleep disturbance, acute psychosis, emotional disturbance, and increased or decreased psychomotor activity [1–3]. In addition, patients may manifest symptoms on a wide spectrum from hypoactivity to hyperactivity and may fluctuate between the two (mixed delirium). The most common form, hypoactive delirium, can also prove to be the most difficult to diagnose [1].

Delirium that develops during an intensive care unit (ICU) stay has been shown to increase the length of stay in the ICU, as well as total hospital length of stay, and increase healthcare costs. Prior estimates have placed the healthcare costs associated with delirium at $164 billion per year in the USA and €140 billion per year in 18 combined European countries [4, 5]. In addition, every day of delirium a patient suffers increases their risk of death by approximately 10 % [6–10]. Similar outcomes are also seen in the operative setting, where patients who develop delirium have increased odds of death both in the hospital and six months after discharge [11•, 12]. Increasing durations of delirium have been shown to be associated with significantly worse cognitive and executive functioning at 3 and 12 months [13••]. This cognitive impairment is independent of severity of illness and age. In addition, postoperative patients who develop delirium have significant declines in physical and social functioning as well as vitality [11•].

Delirium in the ICU is common and likely under recognized. In mixed medical and surgical ICU patients who are mechanically ventilated, 60–80 % develops delirium [14]. This was confirmed in more recent prospective cohort studies of mixed medical and surgical ICU patients, demonstrating 75 % of patients developed delirium during their stay [13••]. Up to a quarter of elderly patients will have delirium upon presentation to the hospital, with an additional third developing it over their stay [15–17]. Given the high incidence of delirium and the tremendous impact delirium has on patient outcomes, clinician education in diagnosis, prevention, and treatment is essential.

Diagnosis of Delirium

The first step toward preventing the deleterious effects of delirium is correctly identifying delirium when it occurs. The cornerstone of diagnosis of delirium is a careful history and physical examination. If a patient is identified as unresponsive (i.e., a Richmond Agitation and Sedation Scale [RASS] of −4 or −5) [18], they are considered to be in coma, and thus cannot be evaluated for delirium. Using the history and examination, providers should seek to identify acute changes and fluctuation in a patient's mental status. Upon identifying this, providers can use one or two validated tools for diagnosis. Both the Confusion Assessment Method for the ICU (CAM-ICU) [19] and the Intensive Care Delirium Screening Checklist (IDCSC) [20] have been validated as tools for diagnosing delirium in the critically ill. The CAM-ICU assesses four clinical features: acute change or fluctuation in mental status, inattention, disorganized thinking, and altered level of consciousness (Fig. 1). The ICDSC uses eight diagnostic features, with four or more positive features diagnosing delirium. Delirium is especially difficult to detect in the presence of underlying dementia, and the symptoms of delirium can be frequently attributed to pre-existing cognitive dysfunction. The diagnosis of delirium in the demented patient is especially important, however, given that 60–89 % of demented hospitalized patients have delirium [21, 22] and that delirium has been shown to accelerate the process of cognitive decline amongst those with dementia [23•]. Current evidence supports the use of the CAM-ICU as the best tool for evaluating delirium in patients with dementia [24].

Risk Factors for Delirium

Identification of patients at highest risk for delirium can help in controlling risk factors and aid in appropriately identifying delirious patients. Risk factors for delirium can be categorized as patient-related factors associated with underlying comorbid disease or iatrogenic risk factors. Patient-related factors can include age, diabetes, heart failure, underlying dementia, electrolyte imbalance, pain, and numerous others [25]. Appropriate management of these chronic underlying conditions is an important facet of preventing delirium. Some iatrogenic factors that can be controlled by clinicians should be considered carefully in the management of the critically ill patient. Sedative medications and sleep hygiene are amongst the two most important.

Studies have consistently shown associations between psychoactive medications, in particular, benzodiazepines, and the development of delirium in the critically ill population. In a cohort of mechanically ventilated medical ICU patients, lorazepam was shown to be an independent risk factor for transition to delirium after controlling for other important patient factors such as age and severity of illness [26]. In medical ICU patients on mechanical ventilation, greater daytime benzodiazepine doses and nighttime increase in benzodiazepine dosing, which occurred in nearly half of patients, were associated with delirium [27•]. Midazolam has also been associated with more delirium among surgical and burn patients [28, 29]. Opioid medications have been shown to decrease delirium when appropriately used to control pain [28, 30, 31]. However, excessive opioid administration has also been associated with increased risk of delirium [31, 32]. In a recent secondary analysis of a prospective observational study, benzodiazepine and/or opioid infusions were strongly associated with transition to delirium in mechanically ventilated ICU patients [33•]. These studies point to the importance of judicious use of sedative medications in the critically ill patients.

Prevention of Delirium

Among ICU patients, several interventions have been shown to have a positive impact in reducing delirium incidence (Table 1). Early mobilization with physical and occupational therapy has been shown to reduce duration of delirium by 50 % and significantly improve functional status at the time of discharge [34]. Improving sleep hygiene by providing ear plugs to patients in the ICU has been shown to reduce the incidence of delirium and improve sleep perception [35]. Choice of sedative agents has also been shown to impact delirium outcomes. Several studies have demonstrated improved delirium endpoints in patients sedated with dexmedetomidine versus benzodiazepines. The Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) study showed that sedation with dexmedetomidine compared to

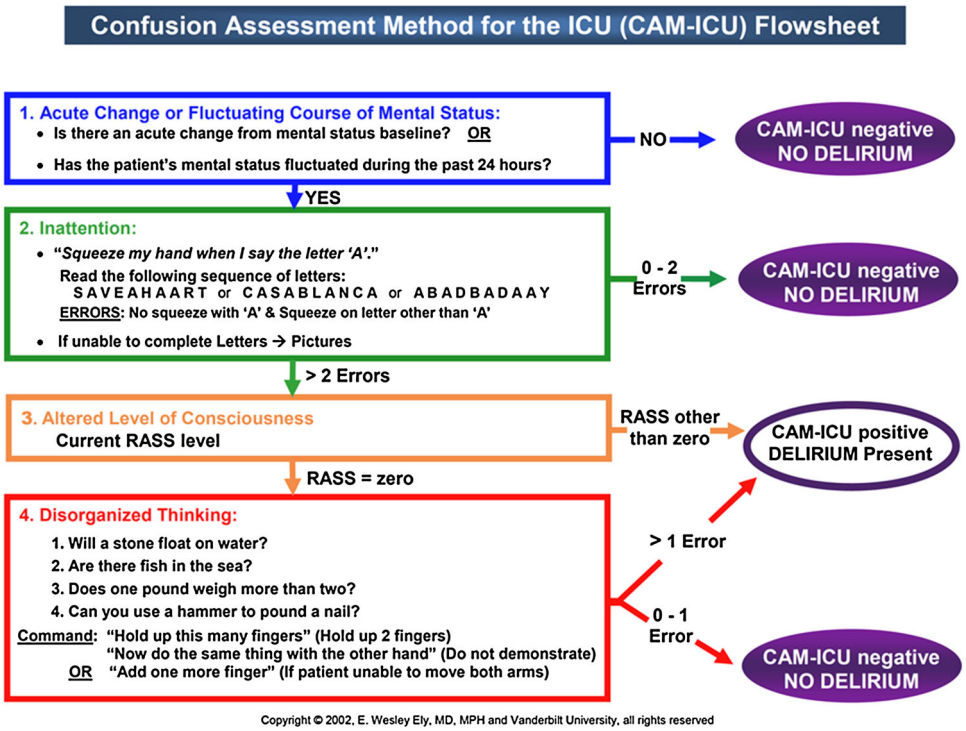

Fig. 1 The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Patients are considered to have delirium if they have a Richmond Agitation–Sedation Scale score of −3 and above, and have features *1* and *2* plus either feature *3* or *4*. Reproduced with permission from Dr. E. Wesley Ely (www.icudelirium.org)

lorazepam decreased duration of delirium, with lower likelihood of delirium on subsequent days [36]. The Safety and Efficacy of Dexmedetomidine Compared with Midazolam (SEDCOM) study showed a reduction in delirium prevalence in those sedated with dexmedetomidine [37]. In another trial, the DEXmedetomidine COmpared to Morphine (DEXCOM) study demonstrated a reduction in the duration of delirium in patients after cardiac surgery sedated with dexmedetomidine compared to morphine but no reduction in delirium incidence [38]. Another study showed improvements in outcomes related to mental status including arousability, communication, and patient cooperation in patients treated with dexmedetomidine compared to midazolam or propofol [39•].

The direct effect of sedation on delirium in the form of "rapidly reversible, sedation-related delirium," defined as delirium that abates shortly after sedative interruption, was recently studied in a prospective cohort study [40••]. It found delirium to be prevalent, with 89 % of patients developing delirium. A small group of patients (12 %) whose delirium abated after sedation interruption had fewer ventilator days, ICU days, and hospital days, and were also more likely to be discharged home. Those with persistent delirium (77 % of patients) had higher 1-year morality [40••]. This has two potentially important implications. First, recent sedative administration should be carefully considered when evaluating for delirium. Second, given consistent findings of higher mortality, impaired functional status, and cognitive impairment in all patients with delirium, and the likelihood that those with rapidly reversible delirium may be "diluting" the negative outcomes, the effect of persistent delirium is likely greater than has been measured in studies to date.

Studies have investigated the effect of antipsychotics in preventing the incidence of delirium with mixed results. In a blinded, placebo-controlled trial in patients undergoing cardiac surgery, a single dose of sublingual risperidone upon regaining consciousness reduced incidence of delirium compared to placebo [41]. A recent before and after study of haloperidol as prophylaxis in patients at high risk for delirium showed significantly less incidence and duration of delirium [42]. The Haloperidol Effectiveness in ICU Delirium (HOPE-ICU) study, on the other hand, showed no difference in days alive and free of delirium or coma between patients prophylactically treated with intravenous haloperidol compared to placebo [43••].

Pointing to potential neuroinflammation as a mechanism in causing delirium, ongoing statin therapy while in the ICU has been shown in two studies to be associated with lower overall risk of delirium, especially in chronic statin users [44•, 45•]. Further, randomized controlled trial evidence is needed to provide conclusive evidence of the effect of statins on incident delirium. Prior evidence of the association between sleep disturbances and delirium has generated interest in melatonin as an agent to prevent delirium. A recent double-blind randomized controlled trial of melatonin versus placebo in patients with hip fracture

Table 1 Studies of delirium prevention in the ICU

Study	Design	Intervention	Control	Patients	Delirium outcome
Non-pharmacologic measures					
Schweickert [34]	Randomized controlled trial	Physical and occupational therapy	Usual care	104 general ICU	Reduced delirium duration (2 vs. 4 days, $p = 0.02$)
Van Rompaey [35]	Randomized controlled trial	Earplugs at night	Usual care	136 general ICU	Decreased risk of delirium or confusion (HR 0.47, $p = 0.006$)
Sedative medications					
Pandharipande [1]	Randomized controlled trial	Dexmedetomidine	Lorazepam	106 medical and surgical	Increased days alive without delirium or coma (median 7.0 vs. 3.0 days, $p = 0.01$)
Riker [37]	Randomized controlled trial	Dexmedetomidine	Midazolam	375 medical and surgical	Decreased delirium prevalence (54 vs. 76.6 %, $p \leq 0.001$)
Shehabi [38]	Randomized controlled trial	Dexmedetomidine + open label propofol	Morphine + open label propofol	306 post cardiac surgery	Reduced delirium duration (2 vs. 5 days, $p = 0.03$) but not incidence ($p = 0.09$)
Jakob [39•]	Randomized controlled trial	Dexmedetomidine	Midazolam	500 general ICU	No difference in neuro adverse events; improved communication ($p \leq 0.001$)
Jakob [39•]	Randomized controlled trial	Dexmedetomidine	Propofol	498 general ICU	Less neuro adverse events ($p = 0.008$); improved communication ($p \leq 0.001$)
Antipsychotic medications					
Prakanrattana [41]	Randomized controlled trial	Risperidone	Placebo	126 cardiac surgery with bypass	Decreased postoperative delirium incidence (RR 0.35, $p = 0.009$)
van den Boogaard [42]	Prospective before–after study	Haloperidol	Usual care	177 general ICU with "high risk" for delirium	Decreased delirium incidence ($p = 0.01$); increased delirium-free days (20 vs. 13, $p = 0.003$)
Page [43••]	Randomized controlled trial	Haloperidol	Placebo	142 general ICU	No difference in days alive without delirium or coma ($p = 0.53$)
Other medications					
de Jonghe [46]	Randomized controlled trial	Melatonin	Placebo	378 elderly hip surgery	No difference in delirium incidence (29.6 vs. 25.5 %, CI 0.05–13.1)
Page [44•]	Prospective cohort study	Statin administration prior evening	No statin prior evening	470 medical and surgical	Increased odds of being free of delirium (OR 2.28, $p = 0.05$)
Morandi [45•]	Prospective cohort study	Pre-hospital or in-ICU statin use	No pre-hospital or in-ICU statin use	763 medical and surgical	In-ICU statin use reduced delirium ($p < 0.01$); holding home statin increased odds of delirium ($p < 0.001$)
Protocol implementation					
Dale [47]	Prospective before–after study	RASS, CAM-ICU, protocolized sedation	Usual care	1,483 trauma and surgical	Decreased odds of delirium (OR 0.67, $p = 0.01$)
Balas [48••]	Prospective before–after study	Implementation of ABCDE bundle	Usual care	296 medical and surgical	Decreased odds of delirium (OR 0.55, $p = 0.03$)

Table 2 Studies of delirium treatment in the ICU

Study	Design	Intervention	Control	Patients	Delirium outcome
Antipsychotic medications					
Skrobik [50]	Randomized controlled trial	Olanzapine	Haloperidol	73 medical and surgical	No difference in decrease in delirium indices
Devlin [52]	Randomized controlled trial	Quetiapine + PRN haloperidol	Placebo + PRN haloperidol	36 medical and surgical	Shorter time to delirium resolution ($p = 0.001$); reduced delirium duration ($p = 0.006$)
Girard [51]	Randomized controlled trial	Haloperidol or ziprasidone	Placebo	101 medical and surgical	No differences in days alive without delirium or coma
Other medications					
Reade [54]	Randomized parallel pilot trial	Dexmedetomidine	Haloperidol	20 general ICU with delirium preventing extubation	Reduced time to extubation ($p = 0.016$), ICU length of stay ($p = 0.004$), tracheostomy requirement
van Eijk [53]	Randomized controlled trial	Rivastigmine + haloperidol	Placebo + haloperidol	104 general ICU	Increased delirium duration (5 vs. 3 days, $p = 0.06$) and increased mortality ($p = 0.07$)

did not demonstrate a difference in incidence of delirium [46].

Taken together, this body of literature supports a systematic approach to sedation during critical illness focusing on the ABCDEs—(A) Awakening and (B) Breathing trials, (C) Choice of sedation, (D) Delirium monitoring and management, and (E) early Exercise—in order to improve patient outcomes, including delirium. For example, measurement of RASS and CAM-ICU paired with protocolized de-escalation of sedation reduced mean hourly benzodiazepine dose, duration of mechanical ventilation, ICU length of stay, hospital length of stay, and resulted in a 33 % reduction in odds of delirium [47]. Additionally, a study of the implementation of an ABCDE protocol demonstrated a 3-day increase in ventilator free days, an increased rate of mobilization, and a 45 % reduction in delirium [48••].

Management of Delirium

The cornerstone of delirium management is prevention and correction of underlying processes contributing to brain dysfunction. Large randomized controlled trials do not exist for any pharmacologic treatments for delirium. Numerous smaller studies and reports suggest that antipsychotic medications may be a treatment for delirium, but there are an equal number of studies suggesting no effect (Table 2) [49]. An early study showed that haloperidol and olanzapine were equally efficacious at reducing symptoms of delirium in critically ill patients with olanzapine having fewer extrapyramidal side effects [50]; however, the lack of a control group makes it impossible to draw definitive conclusions on the efficacy of antipsychotics versus spontaneous resolution. The Modifying the Incidence of Delirium (MIND) study compared ziprasidone, haloperidol, and placebo in mechanically ventilated patients with delirium and found no difference in the number of days alive and free of coma or delirium between the three groups [51]. In patients already ordered to receive as needed haloperidol, another study showed that quetiapine was more effective than placebo in time to resolution of first episode of delirium [52]. Based on evidence that impaired cholinergic neurotransmission may play an important role in the development of delirium, rivastigmine was studied as an adjunct treatment to haloperidol versus a combination of placebo and haloperidol [53]. There was no decrease in duration of delirium, and there was a trend toward increased mortality in the rivastigmine group [53]. In delirious mechanically ventilated patients, dexmedetomidine was shown to reduce time to extubation, incidence of tracheostomy, and ICU length of stay compared to haloperidol [54]. Taken together, the body of literature does not support a single pharmacologic approach to treatment of delirium. In general, we recommend treating only when non-pharmacologic measures such as reorientation and mobilization have not succeeded and using the smallest dose of psychoactive agents for the shortest possible duration.

Conclusion

Acute brain dysfunction in the form of delirium is a common problem in the critically ill population, and associated with increased healthcare costs and significant increases in morbidity and mortality both in the hospital

and after discharge. With a combination of efforts through implementation of best practices, however, we can reduce the burden of delirium. Overall, we recommend an integrated approach to delirium management that involves attention to the ABCDEs—(A) Awakening and (B) Breathing trials, (C) Choice of sedation, (D) Delirium monitoring and management, and (E) early Exercise. In addition, ongoing clinical trials are investigating pharmacologic therapies for delirium and may offer hope for better evidenced-based treatment in the future.

Compliance with Ethics Guidelines

Conflict of Interest Brett C. Norman declares that he has no conflict of interest. Christopher G. Hughes has received compensation from Orion Pharma for service as a consultant.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Recently published papers of particular interest have been highlighted as:
- • Of importance
- •• Of major importance

1. Pandharipande P, Cotton BA, Shintani A, Thompson J, Costabile S, Pun BT, Dittus R, Ely EW. Motoric subtypes of delirium in mechanically ventilated surgical and trauma intensive care unit patients. Intensive Care Med. 2007;33(10):1726–31.
2. Watson P. Sleep in the ICU: where dreams go to die. Minerva Anestesiol. 2011;77(6):568–70.
3. Watson PL, Ceriana P, Fanfulla F. Delirium: is sleep important? Best Pract Res Clin Anaesthesiol. 2012;26(3):355–66.
4. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014;383(9920):911–22.
5. Milbrandt EB, Deppen S, Harrison PL, Shintani AK, Speroff T, Stiles RA, Truman B, Bernard GR, Dittus RS, Ely EW. Costs associated with delirium in mechanically ventilated patients. Crit Care Med. 2004;32(4):955–62.
6. Ely EW, Gautam S, Margolin R, Francis J, May L, Speroff T, Truman B, Dittus R, Bernard R, Inouye SK. The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med. 2001;27(12):1892–900.
7. Lin SM, Liu CY, Wang CH, Lin HC, Huang CD, Huang PY, Fang YF, Shieh MH, Kuo HP. The impact of delirium on the survival of mechanically ventilated patients. Crit Care Med. 2004;32(11):2254–9.
8. Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, Inouye SK, Bernard GR, Dittus RS. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. J Am Med Assoc. 2004;291(14):1753–62.
9. Shehabi Y, Riker RR, Bokesch PM, Wisemandle W, Shintani A, Ely EW, Group SS. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. Crit Care Med. 2010;38(12):2311–8.
10. Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. Am J Respir Crit Care Med. 2009;180(11):1092–7.
11. • Abelha FJ, Luis C, Veiga D, Parente D, Fernandes V, Santos P, Botelho M, Santos A, Santos C. Outcome and quality of life in patients with postoperative delirium during an ICU stay following major surgery. Crit care. 2013;17(5):R257. *This prospective study demonstrated that surgical ICU patients who experienced postoperative delirium had increased mortality in the hospital and at 6 months and had a greater decline in physical function, vitality, and social function.*
12. Bellelli G, Mazzola P, Morandi A, Bruni A, Carnevali L, Corsi M, Zatti G, Zambon A, Corrao G, Olofsson B, et al. Duration of postoperative delirium is an independent predictor of 6-month mortality in older adults after hip fracture. J Am Geriatr Soc. 2014;62(7):1335–40.
13. •• Pandharipande PP, Girard TD, Jackson JC, Morandi A, Thompson JL, Pun BT, Brummel NE, Hughes CG, Vasilevskis EE, Shintani AK, et al. Long-term cognitive impairment after critical illness. N Engl J Med. 2013;369(14):1306–1316. *This landmark study of over 800 medical and surgical ICU patients found that cognitive and executive dysfunction were common in survivors at 3 and 12 months. Delirium during the hospitalization was one of the strongest predictors of cognitive and executive dysfunction.*
14. McNicoll L, Pisani MA, Zhang Y, Ely EW, Siegel MD, Inouye SK. Delirium in the intensive care unit: occurrence and clinical course in older patients. J Am Geriatr Soc. 2003;51(5):591–8.
15. Pompei P, Foreman M, Cassel CK, Alessi C, Cox D. Detecting delirium among hospitalized older patients. Arch Intern Med. 1995;155(3):301–7.
16. Levkoff SE, Evans DA, Liptzin B, Cleary PD, Lipsitz LA, Wetle TT, Reilly CH, Pilgrim DM, Schor J, Rowe J. Delirium: the occurrence and persistence of symptoms among elderly hospitalized patients. Arch Intern Med. 1992;152(2):334–40.
17. Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. J Am Med Assoc. 1990;263(8):1097–101.
18. Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK. The Richmond Agitation–Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002;166(10):1338–44.
19. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, Speroff T, Gautam S, Bernard GR, Inouye SK. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med. 2001;29(7):1370–9.
20. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Med. 2001;27(5):859–64.
21. Fick DM, Kolanowski AM, Waller JL, Inouye SK. Delirium superimposed on dementia in a community-dwelling managed care population: a 3-year retrospective study of occurrence, costs, and utilization. J Gerontol A. 2005;60(6):748–53.
22. Fick DM, Hodo DM, Lawrence F, Inouye SK. Recognizing delirium superimposed on dementia: assessing nurses' knowledge using case vignettes. J Gerontol Nurs. 2007;33(2):40–7.
23. • Gross AL, Jones RN, Habtemariam DA, Fong TG, Tommet D, Quach MS, Shmitt E, Yap L, Inouye SK. Delirium and long-term cognitive trajectory among persons with dementia. Arch Intern Med. 2012; 172(17):E1–E8. *This nested cohort study of hospitalized patients with Alzheimer's Disease found that delirium was prevalent during the hospital stay and associated with increased rate of cognitive decline for up to 5 years.*
24. Morandi A, McCurley J, Vasilevskis EE, Fick DM, Bellelli G, Lee P, Jackson JC, Shenkin SD, Marcotrabucchi NV, Schnelle J,

et al. Tools to detect delirium superimposed on dementia: a systematic review. J Am Geriatr Soc. 2012;60(11):2005–13.
25. Girard TD, Ely EW. Delirium in the ICU. In: Rehm CG, Fuhrman TM, editors. 12th critical care refresher—Society of Critical Care Medicine. 12th ed. Mount Prospect: Society of Critical Care Medicine; 2008. p. 101–7.
26. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, Bernard GR, Ely EW. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology. 2006;104(1):21–6.
27. • Seymour CW, Pandharipande PP, Koestner T, Hudson LD, Thompson JL, Shintani AK, Ely EW, Girard TD. Diurnal sedative changes during intensive care: impact on liberation from mechanical ventilation and delirium. Crit Care Med. 2012;40(10):2788–96. *This prospective cohort study of medical ICU patients on mechanical ventilation found that greater daytime benzodiazepine doses and nighttime increase in benzodiazepine dosing, which occurred in nearly half of patients, were associated with failed spontaneous breathing trials, coma, and delirium.*
28. Agarwal V, O'Neill PJ, Cotton BA, Pun BT, Haney S, Thompson J, Kassebaum N, Shintani A, Guy J, Ely EW, et al. Prevalence and risk factors for development of delirium in burn intensive care unit patients. J Burn Care Res. 2010;31(5):706–15.
29. Pandharipande P, Cotton BA, Shintani A, Thompson J, Pun BT, Morris JA Jr, Dittus R, Ely EW. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. J Trauma. 2008;65(1):34–41.
30. Morrison RS, Magaziner J, Gilbert M, Koval KJ, McLaughlin MA, Orosz G, Strauss E, Siu AL. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. J Gerontol A. 2003;58(1):76–81.
31. Marcantonio ER, Goldman L, Orav EJ, Cook EF, Lee TH. The association of intraoperative factors with the development of postoperative delirium. Am J Med. 1998;105(5):380–4.
32. Dubois MJ, Bergeron N, Dumont M, Dial S, Skrobik Y. Delirium in an intensive care unit: a study of risk factors. Intensive Care Med. 2001;27(8):1297–304.
33. • Kamdar BB, Niessen T, Colantuoni E, King LM, Neufeld KJ, Bienvenu OJ, Rowden AM, Collop NA, Needham DM. Delirium transitions in the medical ICU: exploring the role of sleep quality and other factors. Crit Care Med. 2014. doi:10.1097/CCM.0000000000000610. *This secondary analysis of a prospective observational study of mechanically ventilated ICU patients found that infusion of benzodiazepine and/or opioid medications was associated with transition to delirium.*
34. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet. 2009;373(9678):1874–82.
35. Van Rompaey B, Elseviers MM, Van Drom W, Fromont V, Jorens PG. The effect of earplugs during the night on the onset of delirium and sleep perception: a randomized controlled trial in intensive care patients. Crit Care. 2012;16(3):R73.
36. Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, Shintani AK, Thompson JL, Jackson JC, Deppen SA, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. J Am Med Assoc. 2007;298(22):2644–53.
37. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, Whitten P, Margolis BD, Byrne DW, Ely EW, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. J Am Med Assoc. 2009;301(5):489–99.
38. Shehabi Y, Grant P, Wolfenden H, Hammond N, Bass F, Campbell M, Chen J. Prevalence of delirium with dexmedetomidine compared with morphine based therapy after cardiac surgery: a randomized controlled trial (DEXmedetomidine COmpared to Morphine-DEXCOM Study). Anesthesiology. 2009;111(5):1075–84.
39. • Jakob SM, Ruokonen E, Grounds RM, Sarapohja T, Garratt C, Pocock SJ, Bratty JR, Takala J. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. J Am Med Assoc. 2012;307(11):1151–60. *These randomized controlled trials found that patients sedated with dexmedetomidine vs. midazolam or propofol had inreased arousability, ability to communicate, and cooperation.*
40. •• Patel SB, Poston JT, Pohlman A, Hall JB, Kress JP. Rapidly reversible, sedation-related delirium versus persistent delirium in the intensive care unit. Am J Respir Crit Care Med. 2014;189(6):658–65. *This prospective cohort study of medical ICU patients found 89 % of patients developed delirium, of which a small group of patients (12 %) had delirium that abated after sedation interruption. Those with "rapidly reversible sedation-related" delirium had fewer ventilator days, ICU days, and hospital days and were also more likely to be discharged home. Those with "persistent" delirium (77 % of patients) had higher 1-year morality.*
41. Prakanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. Anaesth Intensive Care. 2007;35(5):714–9.
42. Van den Boogaard M, Schoonhoven L, van Achterberg T, van der Hoeven JG, Pickkers P. Haloperidol prophylaxis in critically ill patients with a high risk for delirium. Crit care. 2013;17(1):R9.
43. •• Page VJ, Ely EW, Gates S, Zhao XB, Alce T, Shintani A, Jackson J, Perkins GD, McAuley DF. Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients (Hope-ICU): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med. 2013;1(7):515–523. *This randomized controlled trial found no difference in days alive and free of delirium or coma between patients prophylactically treated with intravenous haloperidol compared to placebo.*
44. • Page VJ, Davis D, Zhao XB, Norton S, Casarin A, Brown T, Ely EW, McAuley DF. Statin use and risk of delirium in the critically ill. Am J Respir Crit Care Med. 2014;189(6):666–73. *This prospective cohort analysis of mixed medical and surgical critically ill patients found that ongoing statin therapy was associated with a lower daily risk of delirium.*
45. • Morandi A, Hughes CG, Thompson JL, Pandharipande PP, Shintani AK, Vasilevskis EE, Han JH, Jackson JC, Laskowitz DT, Bernard GR, et al. Statins and delirium during critical illness: a multicenter, prospective cohort study. Crit Care Med. 2014;42(8):1899–1909. *This multicenter prospective cohort study found that ICU statin use was associated with reduced delirium, especially early during sepsis and that discontinuation of a previously used statin was associated with increased delirium.*
46. de Jonghe A, van Munster BC, Goslings JC, Kloen P, van Rees C, Wolvius R, van Velde R, Levi M, de Haan RJ, de Rooij SE et al. Effect of melatonin on incidence of delirium among patients with hip fracture: a multicentre, double-blind randomized controlled trial. Can Med Assoc J. 2014 Sep 2 (Epub).
47. Dale CR, Kannas DA, Fan VS, Daniel SL, Deem S, Yanez ND 3rd, Hough CL, Dellit TH, Treggiari MM. Improved analgesia, sedation, and delirium protocol associated with decreased duration of delirium and mechanical ventilation. Ann Am Thorac Soc. 2014;11(3):367–74.
48. •• Balas MC, Vasilevskis EE, Olsen KM, Schmid KK, Shostrom V, Cohen MZ, Peitz G, Gannon DE, Sisson J, Sullivan J, et al. Effectiveness and safety of the awakening and breathing

coordination, delirium monitoring/management, and early exercise/mobility bundle. Crit Care Med. 2014;42(5):1024–36. *This prospective before-after study found that critically ill patients managed with the ABCDE bundle experienced less delirium and had an increase in days breathing without assistance*.

49. Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41(1):263–306.
50. Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting. Intensive Care Med. 2004;30(3):444–9.
51. Girard TD, Pandharipande PP, Carson SS, Schmidt GA, Wright PE, Canonico AE, Pun BT, Thompson JL, Shintani AK, Meltzer HY, et al. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. Crit Care Med. 2010;38(2):428–37.
52. Devlin JW, Roberts RJ, Fong JJ, Skrobik Y, Riker RR, Hill NS, Robbins T, Garpestad E. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. Crit Care Med. 2010;38(2):419–27.
53. van Eijk MM, Roes KC, Honing ML, Kuiper MA, Karakus A, van der Jagt M, Spronk PE, van Gool WA, van der Mast RC, Kesecioglu J, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. Lancet. 2010;376(9755):1829–37.
54. Reade MC, O'Sullivan K, Bates S, Goldsmith D, Ainslie WR, Bellomo R. Dexmedetomidine versus haloperidol in delirious, agitated, intubated patients: a randomised open-label trial. Crit care. 2009;13(3):R75.