

Patient Safety Tip of the Week

June 16, 2015 Updates on Delirium

A recent systematic review and meta-analysis of 42 studies on **delirium in ICU patients** ([Salluh 2015](#)) reinforces much of which we have already discussed about delirium. The authors found that about a third (31.8%) of ICU patients develop delirium, most studies using the CAM-ICU tool for diagnosis of delirium. The overall risk of death in patients with delirium was about double that of patients without delirium, and remained high even after adjustment for age and severity of illness (as measured by APACHE II scores). Patients with delirium had longer mean length of stay in the ICU (1.38 days longer), mean hospital length of stay (0.97 days longer), and mean duration of mechanical ventilation (1.79 days longer). Studies on longer term mortality (6 months to 1 year) were conflicting, with some showing considerable relationship between delirium and mortality but at least one sizable study showing no relationship after adjustment for multiple variables. Delirium was associated with worse function on a variety of cognitive outcome measures in multiple studies.

The incidence of **postoperative delirium** in the elderly tends to be even higher, particularly in certain types of surgery. A new study ([Zywiell 2015](#)) looked at hip fracture patients aged 65 and older in Canada over a 2 year period. They found that 48% developed delirium before, during or after surgery. Those with delirium were older and had higher ASA scores but even after adjustment for these factors they had an average 7.4 day longer hospital stay and costs that were 50% higher than those without delirium.

A recent systematic review of risk factors for delirium in the ICU found somewhat surprising results ([Zaal 2015](#)). The authors looked only for those risk factors having high or moderate strength of evidence. They identified 33 studies of acceptable quality to review. They found that only 11 putative risk factors for delirium are supported by either strong or moderate level of evidence. There was strong evidence that age, dementia, hypertension, pre-ICU emergency surgery or trauma, APACHE II score, mechanical ventilation, metabolic acidosis, delirium on the prior day, and coma are risk factors for delirium and moderate evidence that multiple organ failure is a risk factor for delirium. Evidence was strong that gender is not associated with delirium. They found strong evidence that use of dexmedetomidine is associated with a lower delirium prevalence.

Most striking in the Zaal review is that they found the evidence inconclusive for benzodiazepines, analgesedatives, and opiates as risk factors for delirium. That is disturbing, since those are among the few truly modifiable risk factors traditionally noted for preventing delirium. Multiple previous studies have demonstrated benzodiazepines, sedatives and opioids as factors contributing to the development of delirium. Another recent study found a strong association between infusion of benzodiazepines and/or

opioids and transition to delirium in mechanically ventilated ICU patients ([Kamdar 2015](#)).

However, we concur with the view of the editorial accompanying the Zaal study that the considerable heterogeneity of the studies makes it very difficult to truly assess risk factors. Brown and Dowdy ([Brown 2015](#)) point out that even those studies in the Zaal review using the same tool (the CAM-ICU) found the incidence of delirium in the ICU ranged from 22% to 78%. So the original intent of Zaal and colleagues to use pooled data to assess delirium risk factors was largely precluded by the heterogeneity. Brown and Dowdy conclude that the Zaal results likely reflect preferential collection of certain data as much as any underlying causal link.

The systematic review by Zaal and colleagues ([Zaal 2015](#)) found strong evidence that use of dexmedetomidine is associated with a lower delirium prevalence. We don't concur with that conclusion. Two of the studies they note as showing strong evidence of this beneficial association we discussed in our February 10, 2009 Patient Safety Tip of the Week "[Sedation in the ICU: The Dexmedetomidine Study](#)". We pointed out several methodological and other problems with those studies. We think that the jury is still out on whether use of dexmedetomidine is associated with a lower delirium prevalence.

There are **no proven pharmacologic agents for preventing or treating delirium**. One that has had some mixed results in past studies is haloperidol. Now a new study even questions whether haloperidol may actually increase the risk of delirium ([Pisani 2015](#)). Among nonintubated patients, and after adjustment for time-dependent confounding and important covariates, each additional cumulative milligram of haloperidol was associated with 5% higher odds of next-day delirium.

Another recent systematic review and meta-analysis looked at pharmacologic agents for the prevention and treatment of delirium in patients undergoing cardiac surgery ([Mu 2015](#)). It somewhat surprisingly concluded that moderate to high-quality evidence supports the use of pharmacologic agents for the prevention of delirium but those results are based largely on one randomized controlled trial. That trial showed a beneficial effect of intraoperative dexamethasone ([Dieleman 2012](#)). They also note their funnel plot indicated that there is likely publication bias. They go on to state that the evidence for treating post-cardiac surgery delirium is inconclusive. The accompanying editorial concurs that there is "no magic bullet" at this time ([Bruder 2015](#)). We'll also note that a substudy of the above mentioned large study showing less delirium with dexamethasone showed no beneficial effect of dexamethasone on postoperative cognitive dysfunction at one or twelve months after cardiac surgery ([Ottens 2014](#)).

Of the nonpharmacologic means of preventing and treating delirium, **promoting more normal sleep-waking and day-night cycles** has been a focus. One study done in a medical ICU employed multifaceted sleep-promoting interventions implemented with the aid of daily reminder checklists for ICU staff ([Kamdar 2013](#)). Though improvements in overall sleep quality ratings did not reach statistical significance, there were significant improvements in the incidence of delirium/coma (odds ratio: 0.46) and daily

delirium/coma-free status (odds ratio: 1.64). In a subsequent secondary analysis from that study Kamdar and colleagues ([Kamdar 2015](#)) found that there was no association between daily perceived sleep quality ratings (by patients or their nurses) and transition to delirium. However, as mentioned above, that study showed a strong association between infusion of benzodiazepines and/or opioids and transition to delirium in mechanically ventilated patients. Interestingly, it also showed that patients reporting use of sleep aids at home were less likely to transition to delirium.

Speaking of the relationship between sleep and delirium we had previously noted it was only a matter of time until someone looked at manipulation of melatonin in patients with delirium (see our March 25, 2014 Patient Safety Tip of the Week “[Melatonin and Delirium](#)”). In that column we noted 3 studies that had shown a beneficial effect of melatonin or the melatonin agonist ramelteon in preventing or treating delirium. But we expressed our skepticism about these studies because of small numbers, methodological concerns, and “too good to be true” results. A more recent randomized controlled study of almost 400 patients age 65 and older who were scheduled for acute hip surgery found that melatonin treatment did not reduce the risk of delirium ([de Jonghe 2014](#)).

The mainstay of delirium prevention has been **multicomponent nonpharmacological interventions** such as HELP, the Hospital Elder Life Program (see our October 21, 2008 Patient Safety Tip of the Week “[Preventing Delirium](#)”). Inouye et al ([Inouye 1999](#)) showed in a landmark study of 852 medical patients aged 70 and older that management of 6 risk factors was able to reduce the incidence of delirium from 15% to 9.9%. The number of days with delirium and the number of episodes of delirium was also reduced by the intervention. The intervention targeted cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration. This was strong evidence that a multicomponent intervention could be of benefit in reducing delirium.

A meta-analysis of multicomponent nonpharmacological interventions for delirium prevention was recently published ([Hshieh 2015](#)). It confirmed that multicomponent nonpharmacological interventions are effective in decreasing delirium incidence and preventing falls. It estimates that potential savings in the US from such programs might be more than \$16 billion annually. The meta-analysis included over 4000 patients from 14 studies. Most used HELP or a modified HELP program. Some used volunteers, family, or nurses in their interventions. Overall, the **odds of delirium were 53% lower in patients receiving these interventions** and the NNT (number needed to treat) was 14.3. In addition, the **odds of falling were 62% lower** among patients with such interventions (delirium is a risk factor for falls). While there were trends favoring those in the intervention group for length of stay, rate of institutionalization, and changes in functional or cognitive status, these trends did not reach statistical significance.

Multicomponent nonpharmacological interventions may also be used for management of patients who already have delirium. A good example of team-delivered multicomponent nonpharmacological interventions for delirium was recently presented at the American Association of Critical-Care Nurses (AACN) 2015 National Teaching Institute and Critical Care Exposition ([Haseeb 2015](#)). A nurse-led team consisted of a critical care

nurse, physician, pharmacist, and an exercise physiologist. Patients in a med/surg ICU were randomized in a 2:1 fashion after screening positive for delirium with the CAM-ICU tool. Patients managed by the team had a statistically significant reduction in mean duration of delirium (4.96 vs 9.00 days). There were also statistically significant reductions in duration of therapy for benzodiazepines and opiates.

With the evidence now accumulating for the effectiveness and cost-effectiveness of multicomponent nonpharmacological interventions for delirium prevention and treatment it makes sense for any hospital with a sizable ICU population or significant surgical volume to consider putting together a team to deliver such interventions.

We also refer you back to our December 2014 What's New in the Patient Safety World column "[American Geriatrics Society Guideline on Postoperative Delirium in Older Adults](#)". The American Geriatrics Society has just published a best practice statement for Postoperative Delirium in Older Adults ([AGS Expert Panel 2014](#)). It's a guideline that really only recommends evidence-based best practices. Though it is for patients with postoperative delirium most of the principle recommendations also apply to delirium in general. And we also refer you back to our many previous columns on delirium prevention and management noted below.

Some of our prior columns on delirium assessment and management:

- October 21, 2008 "[Preventing Delirium](#)"
- October 14, 2009 "[Managing Delirium](#)"
- February 10, 2009 "[Sedation in the ICU: The Dexmedetomidine Study](#)"
- March 31, 2009 "[Screening Patients for Risk of Delirium](#)"
- June 23, 2009 "[More on Delirium in the ICU](#)"
- January 26, 2010 "[Preventing Postoperative Delirium](#)"
- August 31, 2010 "[Postoperative Delirium](#)"
- September 2011 "[Modified HELP Helps Outcomes in Elderly Undergoing Abdominal Surgery](#)"
- December 2010 "[The ABCDE Bundle](#)"
- February 28, 2012 "[AACN Practice Alert on Delirium in Critical Care](#)"
- April 3, 2012 "[New Risk for Postoperative Delirium: Obstructive Sleep Apnea](#)"
- August 7, 2012 "[Cognition, Post-Op Delirium, and Post-Op Outcomes](#)"
- September 2013 "[Disappointing Results in Delirium](#)"
- October 29, 2013 "[PAD: The Pain, Agitation, and Delirium Care Bundle](#)"
- February 2014 "[New Studies on Delirium](#)"
- March 25, 2014 "[Melatonin and Delirium](#)"
- May 2014 "[New Delirium Severity Score](#)"
- August 2014 "[A New Rapid Screen for Delirium in the Elderly](#)"
- August 2014 "[Delirium in Pediatrics](#)"

- November 2014 “[The 3D-CAM for Delirium](#)”
- December 2014 “[American Geriatrics Society Guideline on Postoperative Delirium in Older Adults](#)”

References:

Salluh JIF, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. *BMJ* 2015; 350: h2538 (published online June 3, 2015)

<http://www.bmj.com/content/350/bmj.h2538>

Zywiol MG, Hurley R, Perruccio A, et al. The Health Economic Implications of Perioperative Delirium in Older Patients with Low-energy Hip Fractures. American Academy of Orthopaedic Surgeons 2015 Annual Meeting. Paper 038 (abstract).

<http://www.abstractsonline.com/Plan/ViewAbstract.aspx?sKey=71e61e06-a9c2-4301-abbc-d0b186276c3a&cKey=a017cd4b-4ffd-4323-a0ac-5b9234f15179&mKey={31EB97E9-7ED4-4166-ACFC-DBE541BE7D75}>

Zaal IJ, Devlin JW, Peelen LM, Slooter AJC. A Systematic Review of Risk Factors for Delirium in the ICU. *Critical Care Medicine* 2015; 43(1): 40-47

http://journals.lww.com/ccmjournal/Abstract/2015/01000/A_Systematic_Review_of_Risk_Factors_for_Delirium.6.aspx

Kamdar BB, Niessen T, Colantuoni E, et al. Delirium Transitions in the Medical ICU: Exploring the Role of Sleep Quality and Other Factors. *Critical Care Medicine* 2015; 43(1): 135-141

http://journals.lww.com/ccmjournal/Abstract/2015/01000/Delirium_Transitions_in_the_Medical_ICU_.16.aspx

Brown CH, Dowdy D. Risk Factors for Delirium: Are Systematic Reviews Enough? *Critical Care Medicine* 2015; 43(1): 232-233

http://journals.lww.com/ccmjournal/Citation/2015/01000/Risk_Factors_for_Delirium_Are_Systematic_Reviews.28.aspx

Pisani MA, Araujo KLB, Murphy TE. Association of Cumulative Dose of Haloperidol with Next-Day Delirium in Older Medical ICU Patients. *Crit Care Med* 2015; 43(5): 996-1002

http://journals.lww.com/ccmjjournal/Abstract/2015/05000/Association_of_Cumulative_Dose_of_Haloperidol_With.10.aspx

Mu JL, Lee A, Joynt G. Pharmacologic Agents for the Prevention and Treatment of Delirium in Patients Undergoing Cardiac Surgery: Systematic Review and Metaanalysis. *Critical Care Medicine* 2015; 43(1): 194-204

http://journals.lww.com/ccmjjournal/Abstract/2015/01000/Pharmacologic_Agents_for_the_Prevention_and.23.aspx

Dieleman JM, Nierich AP, Rosseel PM, et al. for the Dexamethasone for Cardiac Surgery (DECS) Study Group. Intraoperative High-Dose Dexamethasone for Cardiac Surgery: A Randomized Controlled Trial. *JAMA* 2012; 308(17): 1761-1767

<http://jama.jamanetwork.com/article.aspx?articleid=1389612&resultClick=3>

Bruder NJ, Velly L. Pharmacologic Approach for Delirium after Cardiac Surgery: There Is No Magic Bullet. *Critical Care Medicine* 2015; 43(1): 256-257

http://journals.lww.com/ccmjjournal/Citation/2015/01000/Pharmacologic_Approach_for_Delirium_After_Cardiac.43.aspx

Ottens TH, Dieleman JM, Sauër AC, et al. Effects of Dexamethasone on Cognitive Decline after Cardiac Surgery: A Randomized Clinical Trial. *Anesthesiology* 2014; 121: 492-500

<http://anesthesiology.pubs.asahq.org/Article.aspx?articleid=1921499>

Kamdar BB, King LM, Collop NA, et al. The Effect of a Quality Improvement Intervention on Perceived Sleep Quality and Cognition in a Medical ICU. *Critical Care Medicine* 2013; 41(3): 800-809

http://journals.lww.com/ccmjjournal/Abstract/2013/03000/The_Effect_of_a_Quality_Improvement_Intervention.12.aspx

de Jonghe A, van Munster BC, Goslings JC, et al. on behalf of the Amsterdam Delirium Study Group. Effect of melatonin on incidence of delirium among patients with hip fracture: a multicentre, double-blind randomized controlled trial. *CMAJ* 2014; published ahead of print September 2, 2014

<http://www.cmaj.ca/content/early/2014/09/02/cmaj.140495.full.pdf+html?sid=fdeac61a-a88d-4c1e-b6d2-cc2b27c32ba1>

Inouye SK, Bogardus ST, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, Cooney LM. A Multicomponent Intervention to Prevent Delirium in Hospitalized Older Patients. N Engl J Med 1999; 340: 669-676

<http://content.nejm.org/cgi/reprint/340/9/669.pdf>

Hshieh TT, Yue J, Oh E, et al. Effectiveness of Multicomponent Nonpharmacological Delirium Interventions: A Meta-analysis. JAMA Intern Med 2015; 175(4): 512-520

<http://archinte.jamanetwork.com/article.aspx?articleid=2107611&resultClick=3>

Haseeb C, Prado I, Moscoso-Stafford G, Grami P. Delirium Causing Havoc in Health Care: A Multidisciplinary Approach to Delirium Assessment and Management in the Intensive Care Unit. American Association of Critical-Care Nurses (AACN) 2015 National Teaching Institute and Critical Care Exposition. Abstract RS2. Presented May 19, 2015

<http://ajcc.aacnjournals.org/content/24/3/e28.short>

The American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. Postoperative Delirium in Older Adults: Best Practice Statement from the American Geriatrics Society. Journal of the American College of Surgeons 2014; Published Online: November 14, 2014

<http://www.journalacs.org/article/S1072-7515%2814%2901793-1/fulltext>



Healthcare Consulting

www.patientsafetysolutions.com

<http://www.patientsafetysolutions.com/>

[Home](#)

[Tip of the Week Archive](#)

[What's New in the Patient Safety World Archive](#)