

# American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Postoperative Delirium Prevention

Christopher G. Hughes, MD, MS,\* Christina S. Boncyk, MD,\* Deborah J. Culley, MD,† Lee A. Fleisher, MD,‡ Jacqueline M. Leung, MD, MPH,§ David L. McDonagh, MD,|| Tong J. Gan, MD, MHS, FRCA,¶ Matthew D. McEvoy, MD,# and Timothy E. Miller, MB, ChB, FRCA,\*\* for the Perioperative Quality Initiative (POQI) 6 Workgroup

Postoperative delirium is a geriatric syndrome that manifests as changes in cognition, attention, and levels of consciousness after surgery. It occurs in up to 50% of patients after major surgery and is associated with adverse outcomes, including increased hospital length of stay, higher cost of care, higher rates of institutionalization after discharge, and higher rates of readmission. Furthermore, it is associated with functional decline and cognitive impairments after surgery. As the age and medical complexity of our surgical population increases, practitioners need the skills to identify and prevent delirium in this high-risk population. Because delirium is a common and consequential postoperative complication, there has been an abundance of recent research focused on delirium, conducted by clinicians from a variety of specialties. There have also been several reviews and recommendation statements; however, these have not been based on robust evidence. The Sixth Perioperative Quality Initiative (POQI-6) consensus conference brought together a team of multidisciplinary experts to formally survey and evaluate the literature on postoperative delirium prevention and provide evidence-based recommendations using an iterative Delphi process and Grading of Recommendations Assessment, Development and Evaluation (GRADE) Criteria for evaluating biomedical literature. (Anesth Analg XXX:XXX:00–00)

## GLOSSARY

**ADQI** = Acute Dialysis Quality Initiative; **ARDS** = acute respiratory distress syndrome; **ASER** = American Society for Enhanced Recovery; **BIS** = Bispectral Index; **CABG** = coronary artery bypass grafting; **CAM** = Confusion Assessment Method; **CODA** = Cognitive Dysfunction after Anesthesia trial; **COPD** = chronic obstructive pulmonary disease; **CPB** = cardiopulmonary bypass; **Nu-DESC** = Nursing-Delirium Screening Scale; **EEG** = electroencephalogram; **ENGAGES** = Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes Trial; **ERAS** = enhanced recovery after surgery; **GA** = general anesthesia; **GRADE** = Grading of Recommendations Assessment, Development and Evaluation; **ICU** = intensive care unit; **MMSE** = Mini-Mental State Examination; **NAC** = N-acetylcysteine; **PACU** = postanesthesia care unit; **POD** = postoperative delirium; **POQI** = Perioperative Quality Initiative; **QI** = quality improvement; **RCT** = randomized controlled trial; **SA** = spinal anesthesia

Postoperative delirium is a geriatric syndrome occurring after anesthesia and surgery<sup>1</sup> which manifests as acute alterations in mental status, involving changes in cognition, attention, and levels

of consciousness that tend to fluctuate.<sup>2</sup> Patients with delirium can present with different motoric subtypes that include hyperactive, hypoactive, or mixed, and diagnosis can be easily missed if not screened for

From the \*Department of Anesthesiology, Critical Illness, Brain Dysfunction, and Survivorship (CIBS) Center and the Center for Health Services Research, Vanderbilt University Medical Center, Nashville, Tennessee; †Department of Anesthesiology, Perioperative and Pain Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; ‡Department of Anesthesiology & Critical Care, Penn Center for Perioperative Outcomes Research and Transformation, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania; §Department of Anesthesia and Perioperative Care, University of California San Francisco, San Francisco, California; ||Departments of Anesthesiology and Pain Management, Neurological Surgery, and Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas, Texas; ¶Department of Anesthesiology, Stony Brook University Renaissance School of Medicine, Stony Brook, New York; #Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, Tennessee; and \*\*Department of Anesthesiology, Duke University Medical Center; Durham, North Carolina.

Copyright © 2020 International Anesthesia Research Society  
DOI: 10.1213/ANE.00000000000004641

Accepted for publication December 13, 2019.

Funding: The Perioperative Quality Initiative-6 consensus conference was supported by unrestricted educational grants from the American Society for Enhanced Recovery and the Perioperative Quality Initiative, which have received grants from Baxter, Bev MD, Cadence, Cheetah Medical, Edwards, Heron Pharmaceutical, Mallinckrodt, Masimo, Medtronic, Merck, Trevena, and Pacira.

Conflicts of Interest: See Disclosures at the end of the article.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website ([www.anesthesia-analgesia.org](http://www.anesthesia-analgesia.org)).

A full list of contributors can be found at the end of the article.

Reprints will not be available from the authors.

Address correspondence to Timothy E. Miller, MB, ChB, FRCA, Department of Anesthesiology, Duke University Medical Center, DUMC 3094, Durham, NC 27710. Address e-mail to [timothy.miller2@duke.edu](mailto:timothy.miller2@duke.edu).

routinely.<sup>3,4</sup> The incidence of postoperative delirium varies widely depending on the patient population, surgical procedure, and frequency of assessment<sup>5</sup> but is reported to be 10%–50% with the highest rates occurring in older patients undergoing cardiac and major noncardiac surgery.<sup>6</sup> In patients admitted postoperatively to an intensive care unit (ICU), incidence can be as high as 80%.<sup>6</sup>

In addition to being common, postoperative delirium is associated with adverse outcomes, including increased hospital length of stay, higher cost of care, higher rates of institutionalization after discharge, and higher rates of readmission.<sup>7–13</sup> Patients with postoperative delirium are more likely to have functional decline and dependency in activities of daily living after discharge.<sup>14–16</sup> Furthermore, the development of postoperative delirium is one of the strongest predictors of cognitive impairment after surgery,<sup>14,17–23</sup> currently termed delayed neurocognitive recovery or persistent neurocognitive disorder.

As the age, frailty, and comorbidity burden of our surgical population increases, practitioners need to know how to prevent, identify, and potentially treat delirium in high-risk populations. Education of perioperative providers and administrators of hospitals and health systems is central to developing care pathways to limit the occurrence of this geriatric syndrome, as there is great variation among hospitals in delirium rates—and likely detection strategies—in older surgical patients.<sup>24,25</sup> Research in postoperative delirium, however, is occurring rapidly across multiple specialties, making current knowledge difficult to ascertain and creating the need to revisit prior guidelines.<sup>5,26</sup> In addition, several reviews and recommendation statements<sup>27</sup> are published from specific disciplines but often lack formal and robust methodology for literature review and recommendation development. The Perioperative Quality Initiative (POQI) is an international, multidisciplinary nonprofit organization that organizes consensus conferences on clinical topics related to perioperative medicine. Each conference assembles diverse international experts from multiple disciplines to develop consensus-based recommendations in perioperative medicine.<sup>28,29</sup> The goal of the POQI-6 conference and this document is to provide up-to-date, evidence-based consensus statements regarding identification of older surgical patients at high risk for postoperative delirium, potential strategies to decrease the risk, and priority areas for future research that have been developed through a formal iterative process and literature review.

## METHODS

### Expert Group and Process

The POQI-6 consensus conference took place in Dallas, TX, from November 29 to December 1, 2018. The objective was to produce consensus statements

and practice recommendations concerning postoperative delirium prevention and concerning intraoperative neuromonitoring to improve outcomes. Participants in the POQI conference were recruited based on their expertise in these domains, clinical and health services research, and/or guideline development and implementation. Conference participants were divided into 3 work groups: group 1—risk factors for and prevention of postoperative delirium; group 2—electroencephalogram (EEG) and postoperative outcomes; group 3—cerebral oximetry and postoperative outcomes.

The POQI process is based on an established modified Delphi process<sup>30–32</sup> and includes the following iterative steps before (steps 1 and 2) and during (step 3) the conference: (1) building consensus around the most important questions related to the topic, (2) a literature review of the topic raised by each question, (3) sequential steps of content development and refinement until agreement is achieved and a consensus document is produced. See Supplemental Digital Content, Material, <http://links.lww.com/AA/D5>, for further details. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) process is used to rate the strength of recommendations and the level of evidence in the statements (Supplemental Digital Content, Table 1, <http://links.lww.com/AA/D5>).<sup>33–43</sup> In determining the strength of the recommendations, the group weighed the importance, benefits and risks, feasibility, implementation processes, cost, and several other factors in addition to the strength of the reported evidence. In the exceptional circumstance in which a major new study that impacts recommendation statements is published after the conference but before manuscript submission, the group can propose a revised final consensus statement that will be voted on electronically by the workgroup. The revised statement will be accepted if the clear majority supports the revised statement, and dissenting votes and reasons will be recorded. This occurred with the Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES) trial<sup>44</sup> for the POQI-6 conference.

This POQI-6 subgroup sought to develop a consensus document addressing postoperative delirium prevention in high-risk patients. Our target population included older adults undergoing cardiac and noncardiac surgery. This consensus document does not apply to pediatric patients, emergence delirium, delirium in nonsurgical patients, or delirium in the nonsurgical ICU patient, nor does it fully describe the pathophysiology of delirium, outcomes following delirium, or treatment of active delirium.

A priori we addressed the following questions:

1. What are the baseline and precipitating risk factors for postoperative delirium?

2. What are the best screening methods for predicting postoperative delirium?
3. What are the methodologic considerations and best tools for measuring postoperative delirium?
4. If a patient screens positive for high risk of postoperative delirium, what can be done to reduce the risk?
5. What are high priority research questions needing to be addressed regarding postoperative delirium?

**Literature Review**

We complied with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines in conducting a systematic search of available literature pertaining to postoperative delirium. The literature on postoperative delirium is vast; therefore, only studies that evaluated risk factors, screening methods, assessment tools, and interventions aimed at reducing delirium risk were evaluated. For content to be included, we searched PubMed from 1966 to October 2018 using relevant search terms (MeSH Terms, All Fields, and similar wording for each included term) with the filters of “human,” “age 18+,” and “published in English” selected. See Supplemental Digital Content, Material, <http://links.lww.com/AA/D5>, for further details. This literature search was supplemented by relevant references from identified articles and by articles known to members. We excluded case reports, commentaries, letters, editorials, review articles, and articles regarding

treatment of delirium. Results were reviewed at the title and abstract level for inclusion. Included articles relevant to the individual questions and recommendations were then further reviewed to determine the GRADE level of evidence for each recommendation.

**RESULTS**

After review, 163 studies met inclusion criteria across the questions addressed (Supplemental Digital Content, Figure 1, <http://links.lww.com/AA/D5>). The formal consensus recommendations and level of evidence supporting each are listed in Table 1, with voting results in Supplemental Digital Content, Table 2, <http://links.lww.com/AA/D5>. A systematic model for the prevention of postoperative delirium based on the recommendations is displayed in Figure 1. The results and discussion for each topic and consensus statement are discussed, beginning with the recommendation in bold.

**Patients at Risk for Postoperative Delirium**

**We recommend hospitals and health systems develop processes to reduce the incidence and consequences of postoperative delirium through an iterative multidisciplinary quality improvement process (strong recommendation, grade D evidence).** Postoperative delirium is one of the most common postoperative complications in older patients and is associated with adverse patient-centered outcomes.<sup>12</sup> The importance of delirium to patients, health care systems, and payors mandates this strong

<b>Table 1. Consensus Statements and Recommendations</b>		
<b>Statement</b>	<b>Strength<sup>a</sup></b>	<b>LOE<sup>b</sup></b>
We recommend hospitals and health systems develop processes to reduce the incidence and consequences of postoperative delirium through an iterative multidisciplinary quality improvement process.	Strong	D
We recommend that health care providers identify surgical patients at high risk for postoperative delirium.	Strong	C
We recommend that surgical patients identified as high risk for postoperative delirium be informed of their risk.	Weak	D
We recommend hospital and health systems develop a process to assess for postoperative delirium in older high-risk patients.	Strong	C
We recommend the use of multicomponent nonpharmacologic interventions for the prevention of postoperative delirium in older high-risk patients.	Strong	B
We recommend minimization of medications known to be associated with an increased risk of postoperative delirium in older high-risk surgical patients.	Strong	C
There is insufficient evidence to recommend using processed EEG monitoring in older high-risk surgical patients undergoing general anesthesia to reduce the risk of postoperative delirium. <sup>c</sup>	N/A	N/A
There is insufficient evidence to recommend specific anesthetic agents or doses to reduce the risk of postoperative delirium.	N/A	N/A
There is insufficient evidence to recommend regional/neuraxial blockade as the primary anesthetic technique to reduce the risk of postoperative delirium.	N/A	N/A
We recommend optimization of postoperative pain control to reduce the risk of postoperative delirium.	Weak	C
There is insufficient evidence to recommend administration of prophylactic medications to reduce the risk of postoperative delirium.	N/A	N/A
We recommend using ICU protocols that include sedation with dexmedetomidine to reduce the risk of postoperative delirium in patients requiring postoperative mechanical ventilation.	Strong	B

Abbreviations: EEG, electroencephalogram; GRADE, Grading of Recommendations Assessment, Development and Evaluation; ICU, intensive care unit; LOE, level of evidence.

<sup>a</sup>Strength of recommendation per GRADE process.

<sup>b</sup>Level of evidence per GRADE process.

<sup>c</sup>Additional evidence published after consensus conference which led to a change in recommendation statement.

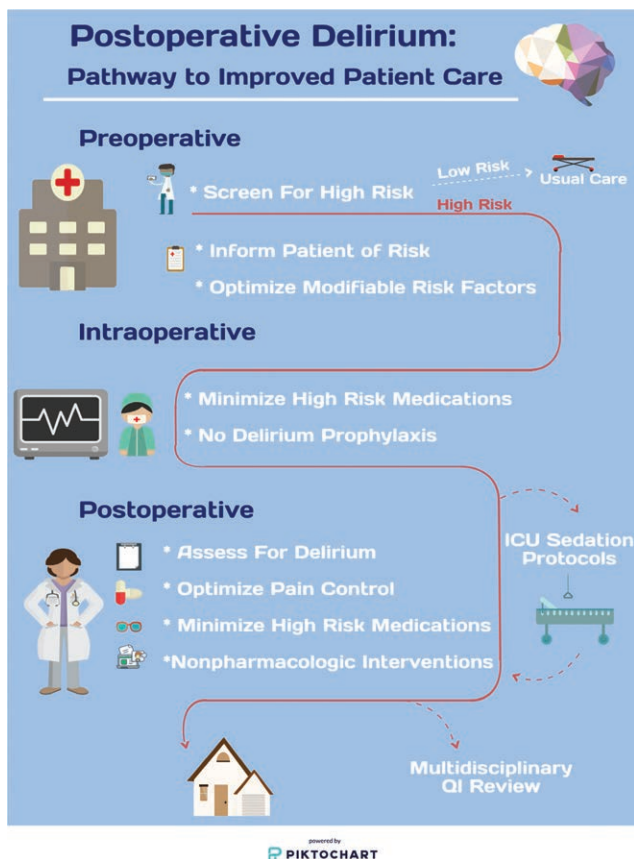
recommendation to develop processes to reduce the incidence of postoperative delirium and its associated outcomes. All perioperative disciplines should be involved in this multidisciplinary quality improvement process to maximize identification of high-risk patients, adoption of patient-centered care pathways, assessment for the presence of postoperative delirium, and continual evaluation of the implemented processes. A reasonable percentage of postoperative delirium (up to 40% in some reports) is thought to

be preventable,<sup>25,45</sup> and delirium reduction protocols across some high risk surgical and ICU patient populations have shown success in reducing incidence and/or duration.<sup>46,47</sup> Thus, implementation and advancement of delirium prevention protocols aimed at the high-risk surgical population have the potential to greatly improve perioperative patient care and thus warrant a coordinated effort.

**We recommend that health care providers identify surgical patients at high risk for postoperative delirium (strong recommendation, grade C evidence).**

Identifying patients at high risk for postoperative delirium is imperative for the development of perioperative care plans and optimal resource allocation. While theoretically all effective delirium prevention strategies could be routinely provided to every older surgical patient throughout their perioperative course, this approach is usually not feasible. The resource constraints at most centers and the lack of these interventions occurring at most centers led to the recommendations to focus on identifying those patients at highest risk and starting attempts at delirium reduction in those patients.

Several systematic reviews and meta-analyses regarding risk factors for postoperative delirium have previously been published.<sup>48-56</sup> Commonly cited predisposing factors are summarized in Table 2. In general, patients with lower cognitive and physical reserve appear to possess decreased capacity to maintain normal brain functioning in response to the stress of the perioperative period, identifying a vulnerable phenotype.<sup>57-62</sup> Although some risk factors are included within current preoperative evaluations, many such as cognitive impairment, functional impairment, frailty, and malnutrition are not routinely and objectively assessed. Formal assessment in these preoperative patients is important to identify those at high risk. Failure to do so can lead to missed opportunities to not only optimize patients but also discuss risk. Identifying this subgroup to target resources is, therefore, important at the patient and systems level, and determination of the optimal predictive tool<sup>63</sup> for patient or surgery



**Figure 1.** A systematic model for prevention of postoperative delirium based on the consensus recommendations. ICU indicates intensive care unit; QI, quality improvement. Figure reused with the permission of the Perioperative Quality Initiative (POQI). For permission requests, contact info@poqi.org.

Table 2. Predisposing Factors Associated With Postoperative Delirium					
Identified Predisposing Factors by System					
General	Neuropsychological	Cardiovascular	Respiratory	Gastrointestinal	Renal/Heme
Increasing age	Cognitive impairment	Hypertension	COPD	Diabetes mellitus	Chronic kidney disease
Multiple comorbidities	Dementia	Heart failure	Obstructive sleep apnea	Malnutrition	Biochemistry abnormalities
Severity of illness	Structural disease	Ischemic heart disease	Smoking status	Low albumin	Preoperative anemia
Alcohol or drug abuse	Prior stroke	...	...	Body mass index	...
Low functional reserve or frailty	Depression	...	...	...	...
Disability	Limited cognitive reserve	...	...	...	...
Living in institution	Previous delirium	...	...	...	...

Abbreviation: COPD, chronic obstructive pulmonary disease.

**Table 3. Precipitating Factors Associated With Postoperative Delirium**

Identified Precipitating Factors		
Intraoperative Aspects	Postoperative Issues	Medication Exposure
Surgical complexity	Anemia	Benzodiazepines
Surgical duration	Pain	Diphenhydramine
Surgical approach	Sleep disturbances	Scopolamine
Cardiopulmonary bypass	Renal insufficiency	Ketamine
Transfusion	Atrial fibrillation	Meperidine
Blood pressure	Infection	Morphine
Glycemic control	Hypoxemia	Zolpidem
Depth of sedation/ burst suppression	Mechanical ventilation	Histamine-receptor antagonists

type is a future research priority to promote risk discussions and management decisions. Modifications of potential risk factors using formalized prehabilitation have primarily focused on nutrition and physical training with improvement in physical outcomes.<sup>64-71</sup> Data on how this could impact postoperative delirium and cognitive outcomes are yet to be reported.

The risk of postoperative delirium is also influenced by the type of surgery and medication exposure. Commonly identified precipitating clinical factors are displayed in Table 3. In general, many of the factors relate to the magnitude of the surgical stress and to the postoperative hospital course. Importantly, for many of these associated precipitating factors, there is no evidence for cause and effect with regard to delirium development. Additional perioperative factors currently not included in the table as they require additional study are fluid status,<sup>72</sup> intraoperative hypotension or hypertension,<sup>73,74</sup> cerebral autoregulation limits,<sup>75</sup> blood glucose control,<sup>76</sup> and intraoperative hyperoxia.<sup>77</sup> Whether these become potential precipitating risks that may be intervenable remains to be seen. Research to date has primarily focused on precipitating risk factors for patients undergoing major surgery with expected hospital admission; studies are now required to identify risk factors for postoperative delirium in the ambulatory setting.<sup>78</sup>

**We recommend that surgical patients identified as high risk for postoperative delirium be informed of their risk (weak recommendation, grade D evidence).**

Identification of patients at high risk for postoperative delirium enables preoperative discussion of risk with the patients and families. This should be considered essential in conforming to legal requirements of the informed consent given the potential long-lasting consequences<sup>79</sup> and aligns with the medical community’s goal for implementation of a shared decision-making model to increase patient involvement in the decision-making process.<sup>80</sup> Hence, this discussion should occur amid discussion of other surgical course risks, and is, therefore, ideally performed by members of the

surgical team before the decision to proceed with surgery.<sup>81</sup> Anesthesia team members should additionally confirm this risk to patients and families as it impacts the expected perioperative course and perioperative management strategies. Discussion of delirium may reduce the distress of patients and families by increasing their understanding and involvement in care plans if it occurs.<sup>82</sup> This communication may be particularly delicate for some high-risk patients and surgeries. Discussion should be tailored to each individual case to confirm levels of risk as well as patient understanding.<sup>80</sup> Furthermore, the discussion with patients, family, and the surgical service will add important information to guide discharge planning given the impact of delirium on postoperative outcomes. The uncertainty in accurate risk stratification currently in practice, the questionable ability to widely implement this into the informed consent process in the surgical realm, and the limited published evidence examining this topic led to the weak recommendation despite strong beliefs in its importance. While this risk discussion could be added for the majority of patients, it would be most prudent and productive to start in patients with the highest risk until the concept and importance gain traction. The impact of implementation on surgical scheduling, patient understanding, and patient/family satisfaction are all areas for future research. Also, of important note, once delirium develops, it presents complexities for the informed consent process for future procedures.<sup>83</sup> This can greatly impact the consent of patients who present with preoperative delirium or who develop postoperative delirium but require repeat surgery.

**Postoperative Delirium Assessment**

**We recommend hospitals and health systems develop a process to assess for postoperative delirium in older high-risk patients (strong recommendation, grade C evidence).**

In patients at high risk for developing postoperative delirium, we recommend hospitals and health systems develop and implement programs that include routine postoperative assessment for delirium on a daily basis using validated assessment tools, as lack of formalized assessment practices results in failure of recognition among care providers.<sup>3,84,85</sup>

For many studies, the gold standard for diagnosing delirium is considered a formal evaluation by a psychiatrist using The Diagnostic and Statistical Manual of Mental Disorders criteria.<sup>2</sup> This is often not feasible owing to resource and time limitations. Delirium assessment tools have been validated for the clinical and research environments. While there is insufficient evidence to recommend a specific tool, examples of delirium assessment tools that have been validated for postoperative delirium are listed in Supplemental Digital Content, Table 3, <http://links.lww.com/AA/D5>.

Due to clinical time constraints, shorter assessment tools may be preferred (eg, Confusion Assessment Method for the ICU [CAM-ICU], Nursing-Delirium Screening Scale [Nu-DESC]) but often at the expense of sensitivity.<sup>86</sup> Most of the screening tools are more specific than sensitive for delirium.<sup>87,88</sup> As a result, some cases of delirium may be missed, but a positive assessment on routine screening has a very high likelihood for delirium.

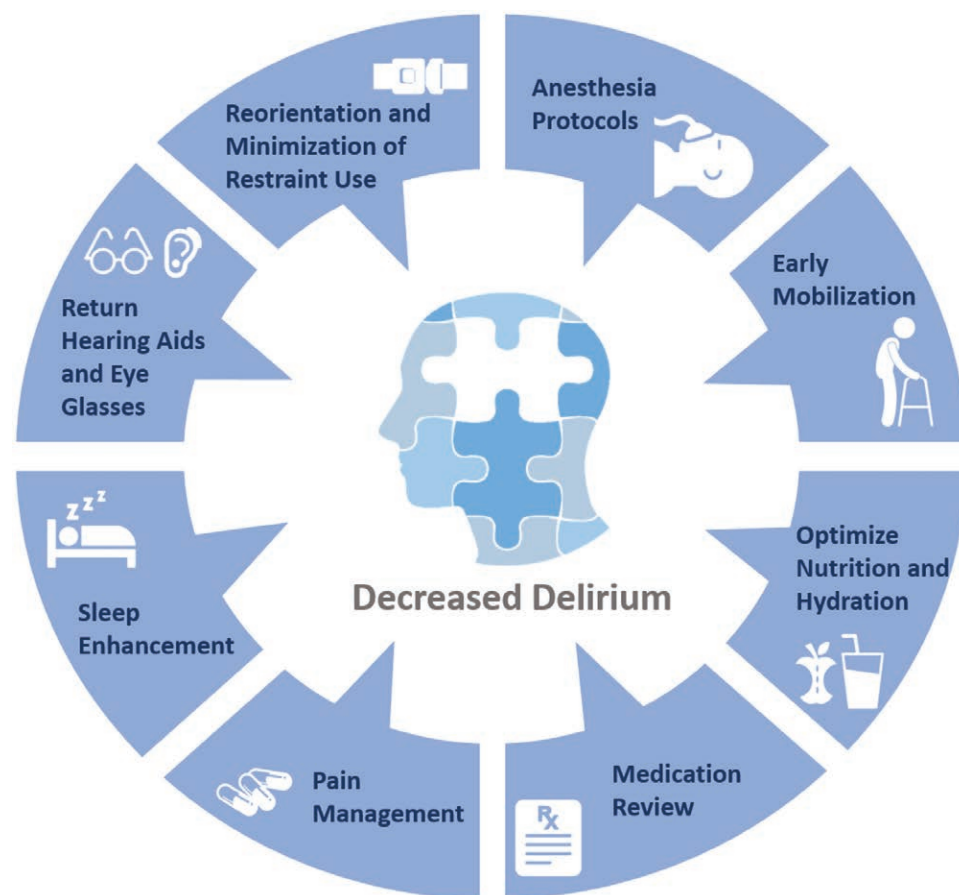
The optimal timing and implementation of delirium screening in the postoperative period needs to be defined by future research, particularly within the postanesthesia care unit (PACU) setting. This also includes within ambulatory surgery centers where incidence of delirium remains largely unknown. Further research should focus on specific assessment tools in the PACU and postoperative ward, including which individual tools are easiest to implement and have the best predictive power for outcomes in the postoperative population.

### Strategies to Reduce Delirium Risk

**We recommend the use of multicomponent non-pharmacologic interventions for the prevention of postoperative delirium in older high-risk patients (Strong recommendation, grade B).**

Delirium prevention programs frequently consist of multicomponent interventions that combine

evidence-based prevention techniques. Overall, these bundled nonpharmacologic interventions have been shown to reduce postoperative delirium with no evidence of associated harm.<sup>89–91</sup> The components of these multifactorial bundles, however, are often varied and institution-specific. As such, current published data do not support a specific intervention bundle. Successful delirium reduction programs, however, often contain items summarized in Figure 2.<sup>92</sup> Early mobilization, pain management, orienting communication, medication review, sleep enhancement, nutritional assistance, and restoration of hearing and vision aids can all be modified and implemented to fit the type of patient, surgery, and hospital setting. The Hospital Elder Life Program intervention was one of the first successful multidisciplinary programs to reduce delirium.<sup>93</sup> This type of protocol is associated with a lower rate of incident delirium, shortened length of stay, greater patient satisfaction, and lower overall hospital cost.<sup>94</sup> Subsequent modified and shortened (ie, reorienting, nutritional assistance, early mobilization only) versions have been shown to reduce delirium incidence, severity, and duration in abdominal surgery or orthopedic fracture patients.<sup>46,95–98</sup> Geriatrics consultation is often a component of bundled interventions. Tested individually, perioperative geriatric consultation has



**Figure 2.** Multicomponent interventions to decrease postoperative delirium. Figure reused with the permission of the Perioperative Quality Initiative (POQI). For permission requests, contact [info@poqi.org](mailto:info@poqi.org).

been shown to reduce delirium in older hip fracture patients<sup>99,100</sup> but not in other populations.<sup>101</sup> Finally, there is insufficient evidence to recommend for or against specialized hospital units to reduce postoperative delirium, as most of the data are focused on medical patients.<sup>5,102</sup> Future research priorities include the assessment of vital components for bundle effectiveness and cost versus benefit of bundled interventions.

**We recommend minimization of medications known to be associated with an increased risk of postoperative delirium in older high-risk surgical patients (strong recommendation, grade C).**

In the hospitalized older high-risk patient, both the number of medications<sup>103</sup> and their psychoactive effects<sup>104</sup> are associated with the development of delirium. For this reason, we strongly recommend minimization of both number and dosage of high-risk medications. Specific medications that have been identified are listed in Table 3. Generally, polypharmacy is to be avoided in older adults given multiple drug interactions that can have deleterious central nervous system effects. The Beers criteria list drugs that are potentially inappropriate for older adults for a variety of reasons (eg, drug–drug interactions, risk–benefit profile).<sup>105</sup> The most pertinent drugs to avoid are those with anticholinergic effects (including diphenhydramine) and benzodiazepines.<sup>104,106–110</sup> Among opioids, meperidine has been associated with the development of postoperative delirium and should be avoided,<sup>104</sup> while differences in other opioids appear small.<sup>111,112</sup> Subanesthetic doses of ketamine can cause psychosis and increased risk of postoperative delirium.<sup>113–115</sup> In the perioperative period, however, exposure to many of these medications is often unavoidable, and, thus, we recommend limiting exposure as much as possible. Despite limited prospective data regarding whether avoidance of these medications in the perioperative period reduces delirium<sup>116</sup> (except for benzodiazepines in the ICU), there is little risk in the conscientious effort to minimize exposure.

Medication reconciliation should be performed before patients transfer between locations or phases of care. This is especially important in patients transferring out of the ICU, as the majority of inappropriate medications in elderly patients are initiated in the ICU and inappropriately continued on the ward or after discharge.<sup>117,118</sup> Future research is required to show whether avoidance of potentially inappropriate medications that increase risk of delirium can decrease incidence of postoperative delirium. There is some suggestion that fast-track or enhanced recovery protocols that incorporate multimodal analgesia and limit opioid administration may be effective,<sup>119</sup> but further studies are warranted, particularly those that include appropriate control groups.

**There is insufficient evidence to recommend using processed EEG monitoring in older high-risk surgical patients undergoing general anesthesia to reduce the risk of postoperative delirium (additional evidence published after conference which changed recommendation statement).**

At the time of the POQI-6 conference, several large studies, systematic reviews, and meta-analyses had been performed evaluating the use of processed EEG to reduce the incidence of postoperative delirium in patients undergoing general anesthesia for major elective or cardiothoracic surgery.<sup>120–123</sup> These studies suggested that the use of processed EEG in older patients undergoing general anesthesia likely reduces the risk of postoperative delirium. The mechanism for this finding was unclear given the differences in study designs and questionable impact of the depth of anesthesia on postoperative delirium (see following section). Subsequent to the POQI-6 conference, however, a large robustly designed study with low risk of bias found that the use of processed EEG to guide anesthetic management did not decrease the incidence or duration of postoperative delirium in older patients ( $\geq 60$  years of age) undergoing cardiac and major noncardiac surgery with general anesthesia.<sup>44,124</sup> Thus, a meta-analysis was performed utilizing data from the 4 trials<sup>44,120–122</sup> that examined the effects of processed EEG on postoperative delirium in patients undergoing general anesthesia. There was no significant difference in postoperative delirium incidence between processed EEG guidance and controls (relative risk [95% confidence interval] of 0.80 [0.60–1.07]). Whether the use of processed EEG is useful to prevent delirium in more vulnerable older patients or other patient populations, therefore, still needs to be determined by further studies, and the recommendation was updated to its current form.

Current findings generally show a benefit in the use of EEG for avoidance of deep anesthesia, specifically burst suppression.<sup>44,120,121</sup> Periods of intraoperative burst suppression have been associated with increased incidence of postoperative delirium,<sup>125,126</sup> but education and instructions to primarily avoid burst suppression (and secondarily avoid oversedation) did not lead to a reduction in delirium in the ENGAGES trial.<sup>44</sup> It is also unclear whether EEG suppression is a modifiable factor or simply a marker of the patient's preexistent vulnerability (ie, sensitive brain hypothesis).<sup>127</sup> Future research should focus on how processed EEG monitoring benefits delirium outcomes and the best methods to reduce delirium risk, such as targeting a specific depth of anesthesia or avoiding burst suppression. In addition, the potential benefits of intraoperative raw EEG and spectrogram analysis in preventing postoperative delirium require investigation.<sup>10</sup> This topic will be discussed in further detail in the American Society

for Enhanced Recovery (ASER) and POQI Joint Consensus Statement on Processed EEG.

It should be noted that 5 POQI participants (P.L.P., P.S.G., M.D.M., M.H., S.K.) voted against this statement and desired to express the dissenting view that there is sufficient evidence to support a weak recommendation to use processed EEG monitoring in older high-risk surgical patients undergoing general anesthesia to reduce the risk of postoperative delirium. The dissenting view contains the following key points. First, 3 large randomized controlled trials (RCTs)<sup>120–122</sup> have demonstrated a decrease in postoperative delirium if intraoperative EEG-guided depth of anesthesia was used, leading to the avoidance of Bispectral Index (BIS) level below 20, 40, and 45, respectively. Second, a key source of dissent stems from the fact that in the recent ENGAGES trial,<sup>44</sup> use of processed EEG did not meaningfully modify anesthetic exposure (as opposed to the prior Cognitive Dysfunction after Anesthesia [CODA] trial).<sup>121</sup> Third, it should be noted that in comparing patients with and without delirium (in both EEG-guided and usual care groups), EEG suppression and periods with BIS indices <40 were prolonged in delirious patients, something not discussed in the ENGAGES manuscript (see Figure 2 in ENGAGES publication).<sup>44</sup> The complete statement of dissent can be found in Supplemental Digital Content, Material, Section F, <http://links.lww.com/AA/D5>.

**There is insufficient evidence to recommend specific anesthetic agents or doses to reduce the risk of postoperative delirium.**

Studies do not support the use of specific anesthetic agents to reduce the development of postoperative delirium. Rates of postoperative delirium are similar between patients receiving total intravenous propofol versus inhalational anesthetics<sup>128–132</sup> and between sevoflurane versus desflurane.<sup>132,133</sup> In addition, xenon or the use of N<sub>2</sub>O with inhalational anesthetics has no effect on the incidence of postoperative delirium in older surgical patients.<sup>134–137</sup>

Depth of anesthesia may provide a modifiable target to reduce postoperative delirium but separating the effects of anesthetic depth versus simply using processed EEG is difficult given current evidence. Studies have shown EEG guidance leads to lighter average depth of anesthesia and less delirium,<sup>121</sup> no change in average depth of anesthesia and less delirium,<sup>120</sup> and less volatile anesthetic administration with no difference in delirium.<sup>44</sup> Further, low volatile anesthetic concentration has been associated with increased delirium.<sup>122</sup> This inconsistency applies to neuraxial anesthesia as well where targeted lighter sedation depth (with or without processed EEG guidance) has shown conflicting results in influencing the incidence of postoperative delirium when compared to deeper sedation targets.<sup>138,139</sup>

Future research is needed to further evaluate the role of individual anesthetic agents and different balanced anesthetic techniques on postoperative delirium. In addition, studies attempting to distinguish the differential effects of anesthetic depth, burst suppression, anesthetic sensitivity, and processed EEG guidance on postoperative delirium are needed to determine if doses of anesthesia can be optimized to reduce the risk of delirium.

**There is insufficient evidence to recommend regional/neuraxial blockade as the primary anesthetic technique to reduce the risk of postoperative delirium.**

Several large studies and systematic reviews have investigated the role of general anesthesia in postoperative delirium by comparing general anesthesia to regional/neuraxial blockade as the primary anesthetic technique, typically in patients with lower extremity fractures. There does not appear to be an increased risk associated with general anesthesia,<sup>140</sup> even among patients with baseline cognitive impairment.<sup>141,142</sup> The 1 retrospective study that did show a significant reduction in delirium associated with neuraxial anesthesia had an overall low postoperative delirium rate of 2.2%,<sup>115</sup> making generalizability and potentially quality of delirium detection in the sample difficult to interpret. Importantly, the majority of these results are in patients with lower extremity orthopedic procedures, and results may not be applicable to other surgical procedures. In addition, sedative medication exposure in addition to the regional/neuraxial blockade is generally not well accounted for and may affect delirium incidence. Thus, further studies controlling for this are warranted along with studies exploring the potentially separate effects of regional/neuraxial blockade for primarily intraoperative anesthetic management versus blockade for postoperative pain management.

**We recommend optimization of postoperative pain control to reduce the risk of postoperative delirium (weak recommendation, grade C).**

Adequate pain control is an important patient-centered objective in perioperative care. An association between poor postoperative pain control and the development of delirium has been demonstrated,<sup>143–145</sup> with adequate pain control considered an important part of delirium prevention.<sup>5</sup> Opioids have been the mainstay in postoperative pain management. The association between opioid use and development of delirium has been inconsistent,<sup>4,108,146–150</sup> but their potential deliriogenic properties and other side effects may limit utility in high-risk patients. Clinical guidelines<sup>5</sup> for postoperative delirium prevention in the elderly, thus advocate for multimodal medication and regional nerve block techniques to improve pain control, reduce opioid exposure, and help prevent delirium.

Effective pain control with regional techniques in orthopedic<sup>151–153</sup> and colonic<sup>154,155</sup> surgery patients have demonstrated decreased incidences of delirium along with reduced opioid administration, usually as part of an enhanced recovery after surgery (ERAS) protocol. Perioperative parecoxib and acetaminophen use in joint replacement and cardiac surgery, respectively, has been shown to reduce opioid consumption and decrease delirium.<sup>156,157</sup> Translation of these concepts across other surgical specialties, however, has not been as effective in decreasing delirium despite decreased postoperative opioid use with perioperative regional analgesia,<sup>158,159</sup> gabapentin,<sup>160</sup> or ketamine.<sup>161,162</sup> In addition, bolus ketamine may actually increase risk for psychosis and postoperative delirium.<sup>113–115</sup>

Thus, there is currently insufficient evidence to recommend for or against specific pain management adjuncts, including intravenous lidocaine infusions, intravenous ketamine infusions, or scheduled gabapentin for the intention of decreasing postoperative delirium. Further investigation into ERAS or fast-track recovery protocols and their impact on delirium remains an important area of research, including the interplay between pain control, opioid exposure, and delirium.

**There is insufficient evidence to recommend the administration of prophylactic medications to reduce the risk of postoperative delirium.**

The medications reviewed included antipsychotics, sedatives and analgesics, steroids, and other miscellaneous agents. Table 4 displays RCTs examining prophylactic medications to prevent postoperative delirium.

Small studies investigating the prophylactic use of antipsychotic medications to prevent postoperative delirium have produced inconclusive results,<sup>163–170</sup> limited by both study size and quality. A meta-analysis, however, compiling 7 studies comparing antipsychotics with placebo or no treatment for postoperative delirium prevention found no significant effect on delirium incidence.<sup>171</sup> Further, a large multicenter study of prophylactic haloperidol performed in ICU patients found no difference in delirium outcomes, including in surgical and trauma subgroups.<sup>172</sup> Importantly, there are potential harms associated with prophylactic administration of antipsychotics for prevention of postoperative delirium, including sedation, extrapyramidal symptoms, postural hypotension, and arrhythmia.<sup>173</sup>

With regard to sedatives or analgesics, the agents reviewed included dexmedetomidine, ketamine, and gabapentin. Results on prophylactic dexmedetomidine infusion (as opposed to dexmedetomidine for sedation) to prevent delirium are mixed with benefit

shown in some subgroups and administration patterns<sup>174–176</sup> but not in others.<sup>51,177,178</sup> Intraoperative ketamine bolus following induction has not been shown to reduce delirium after surgery<sup>179</sup> despite initial promising results.<sup>180</sup> In addition, the potential harms associated with 1 single dose of ketamine included postoperative hallucinations and nightmares.<sup>179</sup> Data are currently insufficient regarding the effects of intraoperative or postoperative ketamine infusion on postoperative delirium; however, there is a suggestion of potential role for decreasing incidence.<sup>181</sup> Perioperative gabapentin administration did not affect delirium occurrence in 2 orthopedic and spine trials.<sup>160,182</sup> Finally, parecoxib<sup>156</sup> and acetaminophen<sup>157</sup> have been shown to reduce delirium in single trials.

The use of steroids to prevent postoperative delirium is not recommended.<sup>183–186</sup> Likewise, data do not support prophylactic statin administration to prevent delirium.<sup>187–189</sup> There is insufficient evidence to recommend the use of other miscellaneous agents to prevent delirium, including melatonin<sup>190,191</sup> and rivastigmine.<sup>192,193</sup>

The resource-intensiveness of nonpharmacologic interventions, and the ease of administration of pharmacologic options, mandate research into identifying prophylactic medications to prevent delirium in older surgical patients. Which patient subgroups may benefit from prophylaxis with atypical antipsychotics, dexmedetomidine, other  $\alpha$ -2 agonists, and sleep aids remains unclear. Trials involving new agents and pathway modifications will need to coincide with advancing research in the mechanisms of postoperative delirium to formulate more accurate and targeted patient-care plans.

**We recommend using ICU protocols that include sedation with dexmedetomidine to reduce the risk of postoperative delirium in patients requiring postoperative mechanical ventilation (strong recommendation, grade B).**

One hospital setting with established successful delirium prevention techniques is the ICU. Deeper levels of sedation have been associated with increased risk of delirium,<sup>194,195</sup> and sedative regimens that focus on targeted arousal levels and light sedation have improved the rates of delirium.<sup>196–200</sup> The use of dexmedetomidine for sedation has improved delirium outcomes in RCTs of medical, surgical, and cardiothoracic ICU patients when compared to lorazepam, midazolam, propofol, or morphine.<sup>201–207</sup> Two trials showing no difference between dexmedetomidine and propofol sedation with regard to delirium<sup>208,209</sup> both had methodologic limitations regarding targeted sedation goals and delirium outcome measurements.

Early mobilization with either nursing protocol and/or physical and occupational therapy has been



**Table 4. Continued**

Drug	Setting Studied	Studies Supporting Use	Studies Reporting Use	Quality of Evidence
NAC	Academic hospital; >65 y, scheduled hip arthroplasty under SA (N = 203, 4 groups) Liver resection (N = 206)	Sultan (2010) <sup>191</sup> ...	... Grendar et al (2016) <sup>218</sup>	Low Low
Nimodipine	Scheduled spine surgery under GA (N = 60)	Li et al (2017) <sup>219</sup>	...	Low
Ondansetron	>40 y, scheduled for femoral or hip fracture rehabilitation surgery with GA (N = 106)	Papadopoulos et al (2014) <sup>220</sup>	...	Low
Rivastigmine	Femoral neck or intertrochanter fracture, cognitive impairment (MMSE 10–26) (N = 62)	Youn et al (2017) <sup>192</sup>	...	Low
TJ-54 (Yokukansan)	≥65 y, elective cardiac surgery with cardiopulmonary bypass (N = 120)	...	Gamberini et al (2009) <sup>193</sup>	Low
Tryptophan	≥70 y, surgery for gastrointestinal or lung malignancy (N = 186) ≥60 y, elective surgery with a planned ICU admission (N = 301)	... ...	Sugano et al (2017) <sup>221</sup> Robinson et al (2014) <sup>222</sup>	Low Low

Abbreviations: ARDS, acute respiratory distress syndrome; CABG, coronary artery bypass grafting; CPB, cardiopulmonary bypass; ICU, intensive care unit; GA, general anesthesia; MMSE, Mini-Mental State Examination; NAC, N-acetylcysteine; POD, postoperative delirium; RCT, randomized controlled trial; SA, spinal anesthesia.

demonstrated to reduce both ICU and in-hospital delirium.<sup>210,211</sup> In the ICU, care bundles involving key components of pain control, awakening and breathing trial coordination, light sedation, minimizing benzodiazepine use, delirium monitoring and management, early mobility, and family engagement (ie, the ABCDEF bundle) have shown less delirium with a significant independent effect of the bundle on decreasing delirium and improving survival.<sup>47,212,213</sup>

For patients requiring postoperative mechanical ventilation, future research needs to identify the best methods for transitioning operative care to ICU care, including initiation of appropriate medications and avoidance of prolonged periods of deep sedation on arrival to the ICU from the operating room.

### Additional Areas of Future Research

In addition to the research items identified for each recommendation statement, several other research initiatives are now required to advance our understanding of postoperative delirium:

1. Mechanistic work into neuroinflammation and other potential pathophysiological causes of postoperative delirium.
2. Causal relationship and mechanistic link between postoperative delirium and worse long-term outcomes.
3. Outcomes associated with delirium in the PACU and with delirium after ambulatory procedures.
4. Delirium duration, severity, and subtype (eg, motoric or clinical phenotypes) after surgery in addition to delirium prevalence.
5. Therapeutic options to treat delirium once it has developed.

### CONCLUSIONS

This POQI group offers current expert consensus recommendations on the prevention of postoperative delirium developed through a robust Delphi process and literature review. Institutional processes to identify high-risk patients, inform them of their risk, and initiate routine delirium assessments are required. Techniques to reduce the risk of delirium include multicomponent nonpharmacologic interventions, minimization of precipitating events and medications, optimization of postoperative pain control, and use of ICU sedation protocols with dexmedetomidine. The state of current evidence precludes recommendations on specific anesthetic agents or doses, regional/neuraxial blockade as the primary anesthetic, or the administration of prophylactic medications to reduce the risk of postoperative delirium. Numerous gaps in high-quality evidence exist with regard to reducing postoperative delirium and its associated untoward

outcomes. In summary, postoperative delirium occurs commonly and is independently associated with worse patient outcomes and increased health care resource utilization. Preventing postoperative delirium should be of paramount importance to perioperative providers and to hospitals and health systems and is critical to improving perioperative patient care.



#### CONTRIBUTORS

Perioperative Quality Initiative (POQI) 6 workgroup participants: POQI chairs: Matthew D. McEvoy, MD, Department of Anesthesiology, Vanderbilt University Medical Center, Nashville, TN; Timothy E. Miller, MD, Department of Anesthesiology, Duke University Medical Center, Durham, NC; Tong J. Gan, MD, MHS, FRCA, MBA, Department of Anesthesiology, Stony Brook University Renaissance School of Medicine, Stony Brook, NY. Postoperative Delirium Workgroup: Christopher G. Hughes, MD, MS, Department of Anesthesiology, Critical Illness, Brain Dysfunction, and Survivorship (CIBS) Center and the Center for Health Services Research, Vanderbilt University Medical Center, Nashville, TN; Christina S. Boncyk, MD, Department of Anesthesiology, Critical Illness, Brain Dysfunction, and Survivorship (CIBS) Center, Vanderbilt University Medical Center, Nashville, TN; Deborah J. Culley, MD, Department of Anesthesiology, Perioperative and Pain Medicine, Harvard Medical School, Boston, MA; Lee A. Fleisher, MD, Department of Anesthesiology & Critical Care, Penn Center for Perioperative Outcomes Research and Transformation, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; Jacqueline M. Leung, MD, MPH, Department of Anesthesia and Perioperative Care, University of California San Francisco, San Francisco, CA; David L. McDonagh, MD, Departments of Anesthesiology and Pain Management, Neurological Surgery, and Neurology and Neurotherapeutics, University of Texas Southwestern Medical Center, Dallas, TX. Electroencephalogram Workgroup: Matthew T. V. Chan, MB, BS, PhD, FHKCA, FANZCA, FHKAM, Department of Anaesthesia and Intensive Care, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China; Traci L. Hedrick, MD, MS, Department of Surgery, University of Virginia Health System, Charlottesville, VA; Talmage D. Egan, MD, Department of Anesthesiology, University of Utah School of Medicine, Salt Lake City, UT; Paul Garcia, MD, PhD, Department of Anesthesiology, Columbia University, New York, NY; Susanne Koch, MD, Department of Anaesthesiology and Intensive Care Medicine, Campus Virchow-Klinikum and Campus Charité Mitte, Charité-Universitätsmedizin, Berlin, Germany; Patrick L. Purdon, PhD, Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, and Department of Anesthesia, Harvard Medical School, Boston, MA; Michael A. Ramsay, MD, FRCA, Department of Anesthesiology and Pain Management, Baylor University Medical Center, Dallas, TX. Spectroscopy Workgroup: Robert H. Thiele,

MD, Departments of Anesthesiology and Biomedical Engineering, Divisions of Cardiac, Thoracic, and Critical Care Anesthesiology, University of Virginia School of Medicine, Charlottesville, VA; Andrew Shaw, MB, FRCA, FFICM, FCCM, MMHC, Department of Anesthesiology and Pain Medicine, University of Alberta, Edmonton, Alberta, Canada; Karsten Bartels, MD, PhD, Department of Anesthesiology, University of Colorado, Aurora, CO; Charles Brown, MD, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University, Baltimore, MD; Hilary Grocott, MD, FRCPC, FASE, Department of Anesthesiology, Perioperative and Pain Medicine, University of Manitoba, Winnipeg, Manitoba, Canada; Matthias Heringlake, Department of Anesthesiology and Intensive Care Medicine, University of Lübeck, Germany, Lübeck, Germany.

#### ACKNOWLEDGMENTS

We acknowledge Matthew Chan for his performance of the meta-analysis of studies examining the effects of processed EEG on postoperative delirium. We acknowledge Man-Ling Wang, MD, from the Department of Anesthesiology, National Taiwan University Hospital and National Taiwan University College of Medicine for her assistance in systematic literature search and review.

#### DISCLOSURES

**Name:** Christopher G. Hughes, MD, MS.

**Contribution:** This author helped with primary drafting and writing of the manuscript and creation of figures, manuscript editing at all stages of preparation and submission, and was chair of the postoperative delirium workgroup.

**Conflicts of Interest:** C. G. Hughes received research grants from Dr Franz Kohler Chemie GMBH and National Institutes of Health (NIH) R01HL111111, R01GM120484.

**Name:** Christina S. Boncyk, MD.

**Contribution:** This author helped write, review, and edit the manuscript, and was a member of the postoperative delirium workgroup.

**Conflicts of Interest:** C. S. Boncyk received research grants from NIH 5T32GM108554.

**Name:** Deborah J. Culley, MD.

**Contribution:** This author helped write, review, and edit the manuscript, and was a member of the postoperative delirium workgroup.

**Conflicts of Interest:** D. J. Culley received research grants from NIH/NIA: R21 AG061696, R56 AG055833, R01 AG05181.

**Name:** Lee A. Fleisher, MD.

**Contribution:** This author helped write, review, and edit the manuscript, and was a member of the postoperative delirium workgroup.

**Conflicts of Interest:** None.

**Name:** Jacqueline M. Leung, MD, MPH.

**Contribution:** This author helped write, review, and edit the manuscript, and was a member of the postoperative delirium workgroup.

**Conflicts of Interest:** J. M. Leung received research grants from NIH R21AG053715.

**Name:** David L. McDonagh, MD.

**Contribution:** This author helped write, review, and edit the manuscript, and was a member of the postoperative delirium workgroup.

**Conflicts of Interest:** D. L. McDonagh received research grant from Lungpacer, Inc.

**Name:** Tong J. Gan, MD, MHS, FRCA.

**Contribution:** This author helped write, review, and edit the manuscript, and served as POQI Conference Organizer.

**Conflicts of Interest:** T. J. Gan is a consultant for Acacia, Edwards Lifesciences, Mallinckrodt, Medtronic and Merck.

**Name:** Matthew D. McEvoy, MD.

**Contribution:** This author helped write, review, and edit the manuscript, and served as POQI Conference Organizer.

**Conflicts of Interest:** M. D. McEvoy received research grants from Edwards Lifescience, Cheetah Medical, Tennessee Department of Health, and GE Foundation.

**Name:** Timothy E. Miller, MB, ChB, FRCA.

**Contribution:** This author helped write, review, and edit the manuscript, and served as POQI Conference Organizer.

**Conflicts of Interest:** T. E. Miller received research grant and is a consultant for Edwards Life sciences.

**This manuscript was handled by:** Jean-Francois Pittet, MD.

## REFERENCES

1. Evered L, Silbert B, Knopman DS, et al; Nomenclature Consensus Working Group. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Anesth Analg*. 2018;127:1189–1195.
2. Association AP. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Washington, DC: American Psychiatric Association; 2013.
3. Inouye SK, Foreman MD, Mion LC, Katz KH, Cooney LM Jr. Nurses' recognition of delirium and its symptoms: comparison of nurse and researcher ratings. *Arch Intern Med*. 2001;161:2467–2473.
4. Card E, Pandharipande P, Tomes C, et al. Emergence from general anaesthesia and evolution of delirium signs in the post-anaesthesia care unit. *Br J Anaesth*. 2015;115:411–417.
5. American Geriatrics Society Expert Panel on Postoperative Delirium in Older A. American Geriatrics Society abstracted clinical practice guideline for postoperative delirium in older adults. *J Am Geriatr Soc*. 2015;63:142–150.
6. Vasilevskis EE, Han JH, Hughes CG, Ely EW. Epidemiology and risk factors for delirium across hospital settings. *Best Pract Res Clin Anaesthesiol*. 2012;26:277–287.
7. Neufeld KJ, Leoutsakos JM, Sieber FE, et al. Outcomes of early delirium diagnosis after general anesthesia in the elderly. *Anesth Analg*. 2013;117:471–478.
8. Sharma PT, Sieber FE, Zakriya KJ, et al. Recovery room delirium predicts postoperative delirium after hip-fracture repair. *Anesth Analg*. 2005;101:1215–1220.
9. Hernandez BA, Lindroth H, Rowley P, et al. Post-anaesthesia care unit delirium: incidence, risk factors and associated adverse outcomes. *Br J Anaesth*. 2017;119:288–290.
10. Hesse S, Kreuzer M, Hight D, et al. Association of electroencephalogram trajectories during emergence from anaesthesia with delirium in the postanaesthesia care unit: an early sign of postoperative complications. *Br J Anaesth*. 2019;122:622–634.
11. Franco K, Litaker D, Locala J, Bronson D. The cost of delirium in the surgical patient. *Psychosomatics*. 2001;42:68–73.
12. Gleason LJ, Schmitt EM, Kosar CM, et al. Effect of delirium and other major complications on outcomes after elective surgery in older adults. *JAMA Surg*. 2015;1–7.
13. Brown CHt, LaFlam A, Max L, et al. Delirium after spine surgery in older adults: incidence, risk factors, and outcomes. *J Am Geriatr Soc*. 2016;64:2101–2108.
14. Bickel H, Gradinger R, Kochs E, Förstl H. High risk of cognitive and functional decline after postoperative delirium. A three-year prospective study. *Dement Geriatr Cogn Disord*. 2008;26:26–31.
15. Rudolph JL, Inouye SK, Jones RN, et al. Delirium: an independent predictor of functional decline after cardiac surgery. *J Am Geriatr Soc*. 2010;58:643–649.
16. Abelha FJ, Luís C, Veiga D, et al. Outcome and quality of life in patients with postoperative delirium during an ICU stay following major surgery. *Crit Care*. 2013;17:R257.
17. Hughes CG, Patel MB, Jackson JC, et al; MIND-ICU, BRAIN-ICU investigators. Surgery and anesthesia exposure is not a risk factor for cognitive impairment after major noncardiac surgery and critical illness. *Ann Surg*. 2017;265:1126–1133.
18. Saczynski JS, Marcantonio ER, Quach L, et al. Cognitive trajectories after postoperative delirium. *N Engl J Med*. 2012;367:30–39.
19. Inouye SK, Marcantonio ER, Kosar CM, et al. The short-term and long-term relationship between delirium and cognitive trajectory in older surgical patients. *Alzheimers Dement*. 2016;12:766–775.
20. Lingehall HC, Smulter NS, Lindahl E, et al. Preoperative cognitive performance and postoperative delirium are independently associated with future dementia in older people who have undergone cardiac surgery: a longitudinal cohort study. *Crit Care Med*. 2017;45:1295–1303.
21. Brown CHt, Probert J, Healy R, et al. Cognitive decline after delirium in patients undergoing cardiac surgery. *Anesthesiology*. 2018;129:406–416.
22. Sprung J, Roberts RO, Weingarten TN, et al. Postoperative delirium in elderly patients is associated with subsequent cognitive impairment. *Br J Anaesth*. 2017;119:316–323.
23. Neerland BE, Krogseth M, Juliebø V, et al. Perioperative hemodynamics and risk for delirium and new onset dementia in hip fracture patients; a prospective follow-up study. *PLoS One*. 2017;12:e0180641.
24. Oresanya LB, Lyons WL, Finlayson E. Preoperative assessment of the older patient: a narrative review. *JAMA*. 2014;311:2110–2120.
25. Berian JR, Zhou L, Russell MM, et al. Postoperative delirium as a target for surgical quality improvement. *Ann Surg*. 2018;268:93–99.
26. Aldecoa C, Bettelli G, Bilotta F, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. *Eur J Anaesthesiol*. 2017;34:192–214.
27. Berger M, Schenning KJ, Brown CH 4th, et al; Perioperative Neurotoxicity Working Group. Best practices for postoperative brain health: recommendations from the Fifth International Perioperative Neurotoxicity Working Group. *Anesth Analg*. 2018;127:1406–1413.
28. Miller TE, Shaw AD, Mythen MG, Gan TJ; Perioperative Quality Initiative (POQI) I Workgroup. Evidence-based perioperative medicine comes of age: the Perioperative Quality Initiative (POQI): the 1st consensus conference of the Perioperative Quality Initiative (POQI). *Perioper Med (Lond)*. 2016;5:26.
29. Gan TJ, Scott M, Thacker J, Hedrick T, Thiele RH, Miller TE. American Society for enhanced recovery: advancing enhanced recovery and perioperative medicine. *Anesth Analg*. 2018;126:1870–1873.
30. Kellum JA, Bellomo R, Ronco C. Acute Dialysis Quality Initiative (ADQI): methodology. *Int J Artif Organs*. 2008;31:90–93.
31. Kellum JA, Mythen MG, Shaw AD. The 12<sup>th</sup> consensus conference of the Acute Dialysis Quality Initiative (ADQI XII). *Br J Anaesth*. 2014;113:729–731.
32. Chawla LS, Ince C, Chappell D, et al; ADQI XII Fluids Workgroup. Vascular content, tone, integrity, and haemodynamics for guiding fluid therapy: a conceptual approach. *Br J Anaesth*. 2014;113:748–755.

33. Brunetti M, Shemilt I, Pregno S, et al. GRADE guidelines: 10. Considering resource use and rating the quality of economic evidence. *J Clin Epidemiol*. 2013;66:140–150.
34. Guyatt GH, Oxman AD, Santesso N, et al. GRADE guidelines: 12. Preparing summary of findings tables-binary outcomes. *J Clin Epidemiol*. 2013;66:158–172.
35. Guyatt G, Oxman AD, Sultan S, et al. GRADE guidelines: 11. Making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. *J Clin Epidemiol*. 2013;66:151–157.
36. Guyatt GH, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence–imprecision. *J Clin Epidemiol*. 2011;64:1283–1293.
37. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence–inconsistency. *J Clin Epidemiol*. 2011;64:1294–1302.
38. Guyatt GH, Oxman AD, Montori V, et al. GRADE guidelines: 5. Rating the quality of evidence–publication bias. *J Clin Epidemiol*. 2011;64:1277–1282.
39. Guyatt GH, Oxman AD, Kunz R, et al; GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence–indirectness. *J Clin Epidemiol*. 2011;64:1303–1310.
40. Guyatt GH, Oxman AD, Sultan S, et al; GRADE Working Group. GRADE guidelines: 9. Rating up the quality of evidence. *J Clin Epidemiol*. 2011;64:1311–1316.
41. Guyatt GH, Oxman AD, Vist G, et al. GRADE guidelines: 4. Rating the quality of evidence–study limitations (risk of bias). *J Clin Epidemiol*. 2011;64:407–415.
42. Balshem H, Helfand M, Schünemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64:401–406.
43. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction–GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64:383–394.
44. Wildes TS, Mickle AM, Ben Abdallah A, et al; ENGAGES Research Group. Effect of electroencephalography-guided anesthetic administration on postoperative delirium among older adults undergoing major surgery: the ENGAGES randomized clinical trial. *JAMA*. 2019;321:473–483.
45. Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. *Nat Rev Neurol*. 2009;5:210–220.
46. Chen CC, Li HC, Liang JT, et al. Effect of a modified hospital elder life program on delirium and length of hospital stay in patients undergoing abdominal surgery: a cluster randomized clinical trial. *JAMA Surg*. 2017;152:827–834.
47. Pun BT, Balas MC, Barnes-Daly MA, et al. Caring for critically ill patients with the ABCDEF bundle: results of the ICU liberation collaborative in over 15,000 adults. *Crit Care Med*. 2019;47:3–14.
48. Scholz AF, Oldroyd C, McCarthy K, Quinn TJ, Hewitt J. Systematic review and meta-analysis of risk factors for postoperative delirium among older patients undergoing gastrointestinal surgery. *Br J Surg*. 2016;103:e21–e28.
49. Zhu Y, Wang G, Liu S, et al. Risk factors for postoperative delirium in patients undergoing major head and neck cancer surgery: a meta-analysis. *Jpn J Clin Oncol*. 2017;47:505–511.
50. Shi C, Yang C, Gao R, Yuan W. Risk factors for delirium after spinal surgery: a meta-analysis. *World Neurosurg*. 2015;84:1466–1472.
51. Yang Y, Zhao X, Dong T, Yang Z, Zhang Q, Zhang Y. Risk factors for postoperative delirium following hip fracture repair in elderly patients: a systematic review and meta-analysis. *Aging Clin Exp Res*. 2017;29:115–126.
52. Gosselt AN, Slooter AJ, Boere PR, Zaal IJ. Risk factors for delirium after on-pump cardiac surgery: a systematic review. *Crit Care*. 2015;19:346.
53. Zaal IJ, Devlin JW, Peelen LM, Slooter AJ. A systematic review of risk factors for delirium in the ICU. *Crit Care Med*. 2015;43:40–47.
54. Watt J, Tricco AC, Talbot-Hamon C, et al. Identifying older adults at risk of delirium following elective surgery: a systematic review and meta-analysis. *J Gen Intern Med*. 2018;33:500–509.
55. Galyfos GC, Geropoulos GE, Sianou A, Sigala F, Filis K. Risk factors for postoperative delirium in patients undergoing vascular surgery. *J Vasc Surg*. 2017;66:937–946.
56. Berger M, Terrando N, Smith SK, Browndyke JN, Newman MF, Mathew JP. Neurocognitive function after cardiac surgery: from phenotypes to mechanisms. *Anesthesiology*. 2018;129:829–851.
57. Culley DJ, Flaherty D, Fahey MC, et al. Poor performance on a preoperative cognitive screening test predicts postoperative complications in older orthopedic surgical patients. *Anesthesiology*. 2017;127:765–774.
58. Ali R, Schwab JM, Nerenz DR, Antoine HJ, Rubinfeld I. Use of the modified frailty index to predict 30-day morbidity and mortality from spine surgery. *J Neurosurg Spine*. 2016;25:537–541.
59. Jung P, Pereira MA, Hiebert B, et al. The impact of frailty on postoperative delirium in cardiac surgery patients. *J Thorac Cardiovasc Surg*. 2015;149:869–75.e1.
60. Leung JM, Tsai TL, Sands LP. Brief report: preoperative frailty in older surgical patients is associated with early postoperative delirium. *Anesth Analg*. 2011;112:1199–1201.
61. Persico I, Cesari M, Morandi A, et al. Frailty and delirium in older adults: a systematic review and meta-analysis of the literature. *J Am Geriatr Soc*. 2018;66:2022–2030.
62. Brown CH, Max L, LaFlam A, et al. The association between preoperative frailty and postoperative delirium after cardiac surgery. *Anesth Analg*. 2016;123:430–435.
63. Rudolph JL, Jones RN, Levkoff SE, et al. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. *Circulation*. 2009;119:229–236.
64. Gillis C, Li C, Lee L, et al. Prehabilitation versus rehabilitation: a randomized control trial in patients undergoing colorectal resection for cancer. *Anesthesiology*. 2014;121:937–947.
65. Topp R, Swank AM, Quesada PM, Nyland J, Malkani A. The effect of prehabilitation exercise on strength and functioning after total knee arthroplasty. *PM R*. 2009;1:729–735.
66. Nielsen PR, Jørgensen LD, Dahl B, Pedersen T, Tønnesen H. Prehabilitation and early rehabilitation after spinal surgery: randomized clinical trial. *Clin Rehabil*. 2010;24:137–148.
67. Bruns ER, van den Heuvel B, Buskens CJ, et al. The effects of physical prehabilitation in elderly patients undergoing colorectal surgery: a systematic review. *Colorectal Dis*. 2016;18:O267–O277.
68. Moran J, Guinan E, McCormick P, et al. The ability of prehabilitation to influence postoperative outcome after intra-abdominal operation: a systematic review and meta-analysis. *Surgery*. 2016;160:1189–1201.
69. Barberan-García A, Ubré M, Roca J, et al. Personalised prehabilitation in high-risk patients undergoing elective major abdominal surgery: a Randomized Blinded Controlled Trial. *Ann Surg*. 2018;267:50–56.
70. Shaughnessy G, Howard R, Englesbe M. Patient-centered surgical prehabilitation. *Am J Surg*. 2018;216:636–638.
71. Furze G, Dumville JC, Miles JN, Irvine K, Thompson DR, Lewin RJ. “Prehabilitation” prior to CABG surgery improves physical functioning and depression. *Int J Cardiol*. 2009;132:51–58.
72. Radtke FM, Franck M, MacGuill M, et al. Duration of fluid fasting and choice of analgesic are modifiable factors for early postoperative delirium. *Eur J Anaesthesiol*. 2010;27:411–416.

73. Williams-Russo P, Sharrock NE, Mattis S, et al. Randomized trial of hypotensive epidural anesthesia in older adults. *Anesthesiology*. 1999;91:926–935.
74. Wang NY, Hirao A, Sieber F. Association between intraoperative blood pressure and postoperative delirium in elderly hip fracture patients. *PLoS One*. 2015;10:e0123892.
75. Hori D, Brown C, Ono M, et al. Arterial pressure above the upper cerebral autoregulation limit during cardiopulmonary bypass is associated with postoperative delirium. *Br J Anaesth*. 2014;113:1009–1017.
76. Saager L, Duncan AE, Yared JP, et al. Intraoperative tight glucose control using hyperinsulinemic normoglycemia increases delirium after cardiac surgery. *Anesthesiology*. 2015;122:1214–1223.
77. Lopez MG, Pandharipande P, Morse J, et al. Intraoperative cerebral oxygenation, oxidative injury, and delirium following cardiac surgery. *Free Radic Biol Med*. 2017;103:192–198.
78. Aya AGM, Pouchain PH, Thomas H, Ripart J, Cuvillon P. Incidence of postoperative delirium in elderly ambulatory patients: a prospective evaluation using the FAM-CAM instrument. *J Clin Anesth*. 2019;53:35–38.
79. Tomlinson JH, Partridge JS. Preoperative discussion with patients about delirium risk: are we doing enough? *Perioper Med (Lond)*. 2016;5:22.
80. Giampieri M. Communication and informed consent in elderly people. *Minerva Anesthesiol*. 2012;78:236–242.
81. Hogan KJ, Bratzke LC, Hogan KL. Informed consent and cognitive dysfunction after noncardiac surgery in the elderly. *Anesth Analg*. 2018;126:629–631.
82. Partridge JS, Martin FC, Harari D, Dhesei JK. The delirium experience: what is the effect on patients, relatives and staff and what can be done to modify this? *Int J Geriatr Psychiatry*. 2013;28:804–812.
83. Auerswald KB, Charpentier PA, Inouye SK. The informed consent process in older patients who developed delirium: a clinical epidemiologic study. *Am J Med*. 1997;103:410–418.
84. Spronk PE, Riekerk B, Hofhuis J, Rommes JH. Occurrence of delirium is severely underestimated in the ICU during daily care. *Intensive Care Med*. 2009;35:1276–1280.
85. Peterson JF, Pun BT, Dittus RS, et al. Delirium and its motoric subtypes: a study of 614 critically ill patients. *J Am Geriatr Soc*. 2006;54:479–484.
86. Hargrave A, Bastiaens J, Bourgeois JA, et al. Validation of a nurse-based delirium-screening tool for hospitalized patients. *Psychosomatics*. 2017;58:594–603.
87. Gusmao-Flores D, Salluh JI, Chalhuh RÁ, Quarantini LC. The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and meta-analysis of clinical studies. *Crit Care*. 2012;16:R115.
88. Neufeld KJ, Leoutsakos JS, Sieber FE, et al. Evaluation of two delirium screening tools for detecting post-operative delirium in the elderly. *Br J Anaesth*. 2013;111:612–618.
89. Siddiqi N, Harrison JK, Clegg A, et al. Interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database Syst Rev*. 2016;3:CD005563.
90. Abraha I, Trotta F, Rimland JM, et al. Efficacy of non-pharmacological interventions to prevent and treat delirium in older patients: a systematic overview. The SENATOR project ONTOP series. *PLoS One*. 2015;10:e0123090.
91. Zhang H, Lu Y, Liu M, et al. Strategies for prevention of postoperative delirium: a systematic review and meta-analysis of randomized trials. *Crit Care*. 2013;17:R47.
92. Reston JT, Schoelles KM. In-facility delirium prevention programs as a patient safety strategy: a systematic review. *Ann Intern Med*. 2013;158:375–380.
93. Inouye SK, Bogardus ST Jr, Charpentier PA, et al. A multi-component intervention to prevent delirium in hospitalized older patients. *N Engl J Med*. 1999;340:669–676.
94. Rubin FH, Neal K, Fenlon K, Hassan S, Inouye SK. Sustainability and scalability of the hospital elder life program at a community hospital. *J Am Geriatr Soc*. 2011;59:359–365.
95. Björkelund 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 Anaesthesiol Scand*. 2010;54:678–688.
96. Lundström M, Edlund A, Lundström G, Gustafson Y. Reorganization of nursing and medical care to reduce the incidence of postoperative delirium and improve rehabilitation outcome in elderly patients treated for femoral neck fractures. *Scand J Caring Sci*. 1999;13:193–200.
97. Milisen K, Foreman MD, Abraham IL, et al. A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients. *J Am Geriatr Soc*. 2001;49:523–532.
98. Chen CC, Lin MT, Tien YW, Yen CJ, Huang GH, Inouye SK. Modified hospital elder life program: effects on abdominal surgery patients. *J Am Coll Surg*. 2011;213:245–252.
99. Deschodt M, Braes T, Flamaing J, et al. Preventing delirium in older adults with recent hip fracture through multidisciplinary geriatric consultation. *J Am Geriatr Soc*. 2012;60:733–739.
100. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *J Am Geriatr Soc*. 2001;49:516–522.
101. 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:e64834.
102. Lundström M, Olofsson B, Stenvall M, et al. Postoperative delirium in old patients with femoral neck fracture: a randomized intervention study. *Aging Clin Exp Res*. 2007;19:178–186.
103. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA*. 1996;275:852–857.
104. Marcantonio ER, Juarez G, Goldman L, et al. The relationship of postoperative delirium with psychoactive medications. *JAMA*. 1994;272:1518–1522.
105. By the American Geriatrics Society Beers Criteria Update Expert P. American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2015;63:2227–2246.
106. McPherson JA, Wagner CE, Boehm LM, et al. Delirium in the cardiovascular ICU: exploring modifiable risk factors. *Crit Care Med*. 2013;41:405–413.
107. Lepoué C, Lautner CA, Liu L, Gomis P, Leon A. Emergence delirium in adults in the post-anaesthesia care unit. *Br J Anaesth*. 2006;96:747–753.
108. Pandharipande P, Cotton BA, Shintani A, et al. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *J Trauma*. 2008;65:34–41.
109. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology*. 2006;104:21–26.
110. Dyer CB, Ashton CM, Teasdale TA. Postoperative delirium. A review of 80 primary data-collection studies. *Arch Intern Med*. 1995;155:461–465.

111. Fong HK, Sands LP, Leung JM. The role of postoperative analgesia in delirium and cognitive decline in elderly patients: a systematic review. *Anesth Analg*. 2006;102:1255–1266.
112. Swart LM, van der Zanden V, Spies PE, de Rooij SE, van Munster BC. The comparative risk of delirium with different opioids: a systematic review. *Drugs Aging*. 2017;34:437–443.
113. Krystal JH, Karper LP, Seibyl JP, et al. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry*. 1994;51:199–214.
114. Bornemann-Cimenti H, Wejborra M, Michaeli K, Edler A, Sandner-Kiesling A. The effects of minimal-dose versus low-dose S-ketamine on opioid consumption, hyperalgesia, and postoperative delirium: a triple-blinded, randomized, active- and placebo-controlled clinical trial. *Minerva Anesthesiol*. 2016;82:1069–1076.
115. Weinstein SM, Poultsides L, Baaklini LR, et al. Postoperative delirium in total knee and hip arthroplasty patients: a study of perioperative modifiable risk factors. *Br J Anaesth*. 2018;120:999–1008.
116. Oh CS, Rhee KY, Yoon TG, Woo NS, Hong SW, Kim SH. Postoperative delirium in elderly patients undergoing hip fracture surgery in the sugammadex era: a Retrospective Study. *Biomed Res Int*. 2016;2016:1054597.
117. Morandi A, Vasilevskis E, Pandharipande PP, et al. Inappropriate medication prescriptions in elderly adults surviving an intensive care unit hospitalization. *J Am Geriatr Soc*. 2013;61:1128–1134.
118. Morandi A, Vasilevskis EE, Pandharipande PP, et al. Inappropriate medications in elderly ICU survivors: where to intervene? *Arch Intern Med*. 2011;171:1032–1034.
119. Petersen PB, Jørgensen CC, Kehlet H; Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group. Delirium after fast-track hip and knee arthroplasty - a cohort study of 6331 elderly patients. *Acta Anaesthesiol Scand*. 2017;61:767–772.
120. Radtke FM, Franck M, Lendner J, Krüger S, Wernecke KD, Spies CD. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. *Br J Anaesth*. 2013;110 Suppl 1:i98–105.
121. Chan MT, Cheng BC, Lee TM, Gin T; CODA Trial Group. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol*. 2013;25:33–42.
122. Whitlock EL, Torres BA, Lin N, et al. Postoperative delirium in a substudy of cardiothoracic surgical patients in the BAG-RECALL clinical trial. *Anesth Analg*. 2014;118:809–817.
123. MacKenzie KK, Britt-Spells AM, Sands LP, Leung JM. Processed electroencephalogram monitoring and postoperative delirium: a systematic review and meta-analysis. *Anesthesiology*. 2018;129:417–427.
124. Abbott TEF, Pearce RM. Depth of anesthesia and postoperative delirium. *JAMA*. 2019;321:459–460.
125. Soehle M, Dittmann A, Ellerkmann RK, Baumgarten G, Putensen C, Guenther U. Intraoperative burst suppression is associated with postoperative delirium following cardiac surgery: a prospective, observational study. *BMC Anesthesiol*. 2015;15:61.
126. Fritz BA, Kalarickal PL, Maybrier HR, et al. Intraoperative electroencephalogram suppression predicts postoperative delirium. *Anesth Analg*. 2016;122:234–242.
127. Fritz BA, Maybrier HR, Avidan MS. Intraoperative electroencephalogram suppression at lower volatile anaesthetic concentrations predicts postoperative delirium occurring in the intensive care unit. *Br J Anaesth*. 2018;121:241–248.
128. Royse CF, Andrews DT, Newman SN, et al. The influence of propofol or desflurane on postoperative cognitive dysfunction in patients undergoing coronary artery bypass surgery. *Anaesthesia*. 2011;66:455–464.
129. Tanaka P, Goodman S, Sommer BR, Maloney W, Huddleston J, Lemmens HJ. The effect of desflurane versus propofol anesthesia on postoperative delirium in elderly obese patients undergoing total knee replacement: A randomized, controlled, double-blinded clinical trial. *J Clin Anesth*. 2017;39:17–22.
130. Nishikawa K, Nakayama M, Omote K, Namiki A. Recovery characteristics and post-operative delirium after long-duration laparoscope-assisted surgery in elderly patients: propofol-based vs. sevoflurane-based anesthesia. *Acta Anaesthesiol Scand*. 2004;48:162–168.
131. Miller D, Lewis SR, Pritchard MW, et al. Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery. *Cochrane Database Syst Rev*. 2018;8:CD012317.
132. Meineke M, Applegate RL 2<sup>nd</sup>, Rasmussen T, et al. Cognitive dysfunction following desflurane versus sevoflurane general anesthesia in elderly patients: a randomized controlled trial. *Med Gas Res*. 2014;4:6.
133. Magni G, Rosa IL, Melillo G, Savio A, Rosa G. A comparison between sevoflurane and desflurane anesthesia in patients undergoing craniotomy for supratentorial intracranial surgery. *Anesth Analg*. 2009;109:567–571.
134. Leung JM, Sands LP, Vaurio LE, Wang Y. Nitrous oxide does not change the incidence of postoperative delirium or cognitive decline in elderly surgical patients. *Br J Anaesth*. 2006;96:754–760.
135. Stoppe C, Fahlenkamp AV, Rex S, et al. Feasibility and safety of xenon compared with sevoflurane anaesthesia in coronary surgical patients: a randomized controlled pilot study. *Br J Anaesth*. 2013;111:406–416.
136. Al Tmimi L, Van Hemelrijck J, Van de Velde M, et al. Xenon anaesthesia for patients undergoing off-pump coronary artery bypass graft surgery: a prospective randomized controlled pilot trial. *Br J Anaesth*. 2015;115:550–559.
137. Coburn M, Sanders RD, Maze M et al; HIPELD Study Investigators. The hip fracture surgery in elderly patients (HIPELD) study to evaluate xenon anaesthesia for the prevention of postoperative delirium: a multicentre, randomized clinical trial. *Br J Anaesth*. 2018;120:127–137.
138. Sieber FE, Zakriya KJ, Gottschalk A, et al. Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. *Mayo Clin Proc*. 2010;85:18–26.
139. Sieber FE, Neufeld KJ, Gottschalk A, et al. Effect of depth of sedation in older patients undergoing hip fracture repair on postoperative delirium: the STRIDE Randomized Clinical Trial. *JAMA Surg*. 2018;153:987–995.
140. Guay J, Parker MJ, Gajendragadkar PR, Kopp S. Anaesthesia for hip fracture surgery in adults. *Cochrane Database Syst Rev*. 2016;2:CD000521.
141. Slor CJ, de Jonghe JF, Vreeswijk R, et al. Anesthesia and postoperative delirium in older adults undergoing hip surgery. *J Am Geriatr Soc*. 2011;59:1313–1319.
142. Mason SE, Noel-Storr A, Ritchie CW. The impact of general and regional anesthesia on the incidence of post-operative cognitive dysfunction and post-operative delirium:

- a systematic review with meta-analysis. *J Alzheimers Dis.* 2010;22 Suppl 3:67–79.
143. Lynch EP, Lazor MA, Gellis JE, Orav J, Goldman L, Marcantonio ER. The impact of postoperative pain on the development of postoperative delirium. *Anesth Analg.* 1998;86:781–785.
  144. Vaurio LE, Sands LP, Wang Y, Mullen EA, Leung JM. Postoperative delirium: the importance of pain and pain management. *Anesth Analg.* 2006;102:1267–1273.
  145. Robinson S, Vollmer C. Undermedication for pain and precipitation of delirium. *Medsurg Nurs.* 2010;19:79–83; .
  146. Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. *JAMA.* 1990;263:1097–1101.
  147. 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;27:1297–1304.
  148. Agarwal V, O'Neill PJ, Cotton BA, et al. Prevalence and risk factors for development of delirium in burn intensive care unit patients. *J Burn Care Res.* 2010;31:706–715.
  149. Morrison RS, Magaziner J, Gilbert M, et al. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. *J Gerontol A Biol Sci Med Sci.* 2003;58:76–81.
  150. Sieber FE, Mears S, Lee H, Gottschalk A. Postoperative opioid consumption and its relationship to cognitive function in older adults with hip fracture. *J Am Geriatr Soc.* 2011;59:2256–2262.
  151. Mouzopoulos G, Vasiliadis G, Lasanianos N, Nikolaras G, Morakis E, Kaminaris M. Fascia iliaca block prophylaxis for hip fracture patients at risk for delirium: a randomized placebo-controlled study. *J Orthop Traumatol.* 2009;10:127–133.
  152. Kinjo S, Lim E, Sands LP, Bozic KJ, Leung JM. Does using a femoral nerve block for total knee replacement decrease postoperative delirium? *BMC Anesthesiol.* 2012;12:4.
  153. Krenk L, Rasmussen LS, Hansen TB, Bogø S, Søballe K, Kehlet H. Delirium after fast-track hip and knee arthroplasty. *Br J Anaesth.* 2012;108:607–611.
  154. Kurbegovic S, Andersen J, Krenk L, Kehlet H. Delirium in fast-track colonic surgery. *Langenbecks Arch Surg.* 2015;400:513–516.
  155. Jia Y, Jin G, Guo S, et al. Fast-track surgery decreases the incidence of postoperative delirium and other complications in elderly patients with colorectal carcinoma. *Langenbecks Arch Surg.* 2014;399:77–84.
  156. Mu DL, Zhang DZ, Wang DX, et al. Parecoxib supplementation to morphine analgesia decreases incidence of delirium in elderly patients after hip or knee replacement surgery: a Randomized Controlled Trial. *Anesth Analg.* 2017;124:1992–2000.
  157. Subramaniam B, Shankar P, Shaefi S, et al. Effect of intravenous acetaminophen vs placebo combined with propofol or dexmedetomidine on postoperative delirium among older patients following cardiac surgery: the DEXACET Randomized Clinical Trial. *JAMA.* 2019;321:686–696.
  158. Mann C, Pouzeratte Y, Boccara G, et al. Comparison of intravenous or epidural patient-controlled analgesia in the elderly after major abdominal surgery. *Anesthesiology.* 2000;92:433–441.
  159. Strike E, Arklina B, Stradins P, et al. Postoperative pain management strategies and delirium after transapical aortic valve replacement: a Randomized Controlled Trial. *J Cardiothorac Vasc Anesth.* 2019;33:1668–1672.
  160. Leung JM, Sands LP, Chen N, et al; Perioperative Medicine Research Group. Perioperative gabapentin does not reduce postoperative delirium in older surgical patients: a Randomized Clinical Trial. *Anesthesiology.* 2017;127:633–644.
  161. Nielsen RV, Fomsgaard JS, Siegel H, et al. Intraoperative ketamine reduces immediate postoperative opioid consumption after spinal fusion surgery in chronic pain patients with opioid dependency: a randomized, blinded trial. *Pain.* 2017;158:463–470.
  162. Jouguelet-Lacoste J, La Colla L, Schilling D, Chelly JE. The use of intravenous infusion or single dose of low-dose ketamine for postoperative analgesia: a review of the current literature. *Pain Med.* 2015;16:383–403.
  163. Fukata S, Kawabata Y, Fujishiro K, et al. Haloperidol prophylaxis for preventing aggravation of postoperative delirium in elderly patients: a randomized, open-label prospective trial. *Surg Today.* 2017;47:815–826.
  164. Wang W, Li HL, Wang DX, et al. Haloperidol prophylaxis decreases delirium incidence in elderly patients after non-cardiac surgery: a randomized controlled trial\*. *Crit Care Med.* 2012;40:731–739.
  165. Larsen KA, Kelly SE, Stern TA, et al. Administration of olanzapine to prevent postoperative delirium in elderly joint-replacement patients: a randomized, controlled trial. *Psychosomatics.* 2010;51:409–418.
  166. Hakim SM, Othman AI, Naoum DO. Early treatment with risperidone for subsyndromal delirium after on-pump cardiac surgery in the elderly: a randomized trial. *Anesthesiology.* 2012;116:987–997.
  167. Prakanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. *Anaesth Intensive Care.* 2007;35:714–719.
  168. Fukata S, Kawabata Y, Fujisiro K, et al. Haloperidol prophylaxis does not prevent postoperative delirium in elderly patients: a randomized, open-label prospective trial. *Surg Today.* 2014;44:2305–2313.
  169. Page VJ, Ely EW, Gates S, 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. *Lancet Respir Med.* 2013;1:515–523.
  170. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. *J Am Geriatr Soc.* 2005;53:1658–1666.
  171. Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM. Antipsychotic medication for prevention and treatment of delirium in hospitalized adults: a systematic review and meta-analysis. *J Am Geriatr Soc.* 2016;64:705–714.
  172. van den Boogaard M, Slooter AJC, Brüggemann RJM, et al; REDUCE Study Investigators. Effect of haloperidol on survival among critically ill adults with a high risk of delirium: the REDUCE Randomized Clinical Trial. *JAMA.* 2018;319:680–690.
  173. Muench J, Hamer AM. Adverse effects of antipsychotic medications. *Am Fam Physician.* 2010;81:617–622.
  174. Liu Y, Ma L, Gao M, Guo W, Ma Y. Dexmedetomidine reduces postoperative delirium after joint replacement in elderly patients with mild cognitive impairment. *Aging Clin Exp Res.* 2016;28:729–736.
  175. Su X, Meng ZT, Wu XH, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet.* 2016;388:1893–1902.
  176. Skrobik Y, Duprey MS, Hill NS, Devlin JW. Low-dose nocturnal dexmedetomidine prevents ICU delirium. A Randomized, Placebo-controlled Trial. *Am J Respir Crit Care Med.* 2018;197:1147–1156.
  177. Deiner S, Luo X, Lin HM, et al; and the Dexlirium Writing Group. Intraoperative infusion of dexmedetomidine for

- prevention of postoperative delirium and cognitive dysfunction in elderly patients undergoing major elective noncardiac surgery: a Randomized Clinical Trial. *JAMA Surg.* 2017;152:e171505.
178. Li X, Yang J, Nie XL, et al. Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: a randomized controlled trial. *PLoS One.* 2017;12:e0170757.
  179. Avidan MS, Maybrier HR, Abdallah AB, et al; PODCAST Research Group. Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. *Lancet.* 2017;390:267–275.
  180. Hudetz JA, Patterson KM, Iqbal Z, et al. Ketamine attenuates delirium after cardiac surgery with cardiopulmonary bypass. *J Cardiothorac Vasc Anesth.* 2009;23:651–657.
  181. Perbet S, Verdonk F, Godet T, et al. Low doses of ketamine reduce delirium but not opiate consumption in mechanically ventilated and sedated ICU patients: a randomised double-blind control trial. *Anaesth Crit Care Pain Med.* 2018;37:589–595.
  182. Dighe K, Clarke H, McCartney CJ, Wong CL. Perioperative gabapentin and delirium following total knee arthroplasty: a post-hoc analysis of a double-blind randomized placebo-controlled trial. *Can J Anaesth.* 2014;61:1136–1137.
  183. Sauër AM, Slooter AJ, Veldhuijzen DS, van Eijk MM, Devlin JW, van Dijk D. Intraoperative dexamethasone and delirium after cardiac surgery: a randomized clinical trial. *Anesth Analg.* 2014;119:1046–1052.
  184. Mardani D, Bigdelian H. Prophylaxis of dexamethasone protects patients from further post-operative delirium after cardiac surgery: a randomized trial. *J Res Med Sci.* 2013;18:137–143.
  185. Roysse CF, Saager L, Whitlock R, et al. Impact of methylprednisolone on postoperative quality of recovery and delirium in the steroids in Cardiac Surgery Trial: a Randomized, Double-blind, Placebo-controlled Substudy. *Anesthesiology.* 2017;126:223–233.
  186. Whitlock RP, Devereaux PJ, Teoh KH, et al; SIRS Investigators. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): a randomised, double-blind, placebo-controlled trial. *Lancet.* 2015;386:1243–1253.
  187. Billings FT, Hendricks PA, Schildcrout JS, et al. High-dose perioperative atorvastatin and acute kidney injury following cardiac surgery: a Randomized Clinical Trial. *JAMA.* 2016;315(9):877–888.
  188. Needham DM, Colantuoni E, Dinglas VD, et al. Rosuvastatin versus placebo for delirium in intensive care and subsequent cognitive impairment in patients with sepsis-associated acute respiratory distress syndrome: an ancillary study to a randomised controlled trial. *Lancet Respir Med.* 2016;4:203–212.
  189. Page VJ, Casarin A, Ely EW, et al. Evaluation of early administration of simvastatin in the prevention and treatment of delirium in critically ill patients undergoing mechanical ventilation (MoDUS): a randomised, double-blind, placebo-controlled trial. *Lancet Respir Med.* 2017;5:727–737.
  190. de Jonghe A, van Munster BC, Goslings JC, et al; 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;186:E547–E556.
  191. Sultan SS. Assessment of role of perioperative melatonin in prevention and treatment of postoperative delirium after hip arthroplasty under spinal anesthesia in the elderly. *Saudi J Anaesth.* 2010;4:169–173.
  192. Youn YC, Shin HW, Choi BS, Kim S, Lee JY, Ha YC. Rivastigmine patch reduces the incidence of postoperative delirium in older patients with cognitive impairment. *Int J Geriatr Psychiatry.* 2017;32:1079–1084.
  193. Gamberini M, Bolliger D, Lurati Buse GA, et al. Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery—a randomized controlled trial. *Crit Care Med.* 2009;37:1762–1768.
  194. Shehabi Y, Bellomo R, Kadiman S, et al; Sedation Practice in Intensive Care Evaluation (SPICE) Study Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Sedation intensity in the first 48 hours of mechanical ventilation and 180-day mortality: a Multinational Prospective Longitudinal Cohort Study. *Crit Care Med.* 2018;46:850–859.
  195. Stephens RJ, Dettmer MR, Roberts BW, et al. Practice patterns and outcomes associated with early sedation depth in mechanically ventilated patients: a systematic review and meta-analysis. *Crit Care Med.* 2018;46:471–479.
  196. Shehabi Y, Bellomo R, Reade MC, et al; Sedation Practice in Intensive Care Evaluation Study Investigators; Australian and New Zealand Intensive Care Society Clinical Trials Group. Early goal-directed sedation versus standard sedation in mechanically ventilated critically ill patients: a pilot study\*. *Crit Care Med.* 2013;41:1983–1991.
  197. Dale CR, Kannas DA, Fan VS, et al. Improved analgesia, sedation, and delirium protocol associated with decreased duration of delirium and mechanical ventilation. *Ann Am Thorac Soc.* 2014;11:367–374.
  198. Hager DN, Dinglas VD, Subhas S, et al. Reducing deep sedation and delirium in acute lung injury patients: a quality improvement project. *Crit Care Med.* 2013;41:1435–42.
  199. Needham DM, Korupolu R, Zanni JM, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. *Arch Phys Med Rehabil.* 2010;91:536–542.
  200. Hayhurst CJ, Pandharipande PP, Hughes CG. Intensive care unit delirium: a review of diagnosis, prevention, and treatment. *Anesthesiology.* 2016;125:1229–1241.
  201. Djaiani G, Silvertown N, Fedorko L, et al. Dexmedetomidine versus propofol sedation reduces delirium after cardiac surgery: a Randomized Controlled Trial. *Anesthesiology.* 2016;124:362–368.
  202. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA.* 2007;298:2644–2653.
  203. Riker RR, Shehabi Y, Bokesch PM, et al; SEDCOM (Safety and Efficacy of Dexmedetomidine Compared With Midazolam) Study Group. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA.* 2009;301:489–499.
  204. Shehabi Y, Grant P, Wolfenden H, et al. 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;111:1075–1084.
  205. Maldonado JR, Wysong A, van der Starre PJ, Block T, Miller C, Reitz BA. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. *Psychosomatics.* 2009;50:206–217.
  206. Ji F, Li Z, Nguyen H, et al. Perioperative dexmedetomidine improves outcomes of cardiac surgery. *Circulation.* 2013;127:1576–1584.
  207. Ji F, Li Z, Young N, Moore P, Liu H. Perioperative dexmedetomidine improves mortality in patients undergoing

- coronary artery bypass surgery. *J Cardiothorac Vasc Anesth.* 2014;28:267–273.
208. Jakob SM, Ruokonen E, Grounds RM, et al; Dexmedetomidine for Long-Term Sedation Investigators. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. *JAMA.* 2012;307:1151–1160.
  209. Kawazoe Y, Miyamoto K, Morimoto T, et al; Dexmedetomidine for Sepsis in Intensive Care Unit Randomized Evaluation (DESIRE) Trial Investigators. Effect of dexmedetomidine on mortality and ventilator-free days in patients requiring mechanical ventilation with sepsis: a Randomized Clinical Trial. *JAMA.* 2017;317:1321–1328.
  210. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet.* 2009;373:1874–1882.
  211. Schaller SJ, Anstey M, Blobner M, et al; International Early SOMS-guided Mobilization Research Initiative. Early, goal-directed mobilisation in the surgical intensive care unit: a randomised controlled trial. *Lancet.* 2016;388:1377–1388.
  212. Balas MC, Vasilevskis EE, Olsen KM, et al. Effectiveness and safety of the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle. *Crit Care Med.* 2014;42:1024–1036.
  213. Barnes-Daly MA, Phillips G, Ely EW. Improving hospital survival and reducing brain dysfunction at seven California community hospitals: implementing PAD guidelines via the ABCDEF bundle in 6,064 patients. *Crit Care Med.* 2017;45:171–178.
  214. Yang X, Li Z, Gao C, Liu R. Effect of dexmedetomidine on preventing agitation and delirium after microvascular free flap surgery: a randomized, double-blind, control study. *J Oral Maxillofac Surg.* 2015;73:1065–1072.
  215. Mohammadi M, Ahmadi M, Khalili H, Cheraghchi H, Arbabi M. Cyproheptadine for the prevention of postoperative delirium: a pilot study. *Ann Pharmacother.* 2016;50:180–187.
  216. Liptzin B, Laki A, Garb JL, Fingerroth R, Krushell R. Donepezil in the prevention and treatment of post-surgical delirium. *Am J Geriatr Psychiatry.* 2005;13:1100–1106.
  217. Xin X, Xin F, Chen X, et al. Hypertonic saline for prevention of delirium in geriatric patients who underwent hip surgery. *J Neuroinflammation.* 2017;14:221.
  218. Grendar J, Ouellet JF, McKay A, et al. Effect of N-acetylcysteine on liver recovery after resection: a randomized clinical trial. *J Surg Oncol.* 2016;114:446–450.
  219. Li YN, Zhang Q, Yin CP, et al. Effects of nimodipine on postoperative delirium in elderly under general anesthesia: a prospective, randomized, controlled clinical trial. *Medicine (Baltimore).* 2017;96:e6849.
  220. Papadopoulos G, Pouangare M, Papathanakos G, Arnaoutoglou E, Petrou A, Tzimas P. The effect of ondansetron on postoperative delirium and cognitive function in aged orthopedic patients. *Minerva Anesthesiol.* 2014;80:444–451.
  221. Sugano N, Aoyama T, Sato T, et al. Randomized phase II study of TJ-54 (Yokukansan) for postoperative delirium in gastrointestinal and lung malignancy patients. *Mol Clin Oncol.* 2017;7:569–573.
  222. Robinson TN, Dunn CL, Adams JC, et al. Tryptophan supplementation and postoperative delirium—a randomized controlled trial. *J Am Geriatr Soc.* 2014;62:1764–1771.