Title

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Journal

Anesthesia & Analgesia, 130(6)

ISSN

0003-2999

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Publication Date

2020-06-01

DOI

10.1213/ane.0000000000004641

Peer reviewed

HHS Public Access

Author manuscript

Anesth Analg. Author manuscript; available in PMC 2020 July 24.

Published in final edited form as:

Anesth Analg. 2020 June ; 130(6): 1572–1590. doi:10.1213/ANE.0000000000004641.

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

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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).

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Abstract

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 identity 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.

Postoperative delirium is a geriatric syndrome occurring after anesthesia and surgery[1] which manifests as acute alterations in mental status, involving changes in cognition, attention, and levels of consciousness that tend to fluctuate.[2] 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 routinely.[3,4] The incidence of postoperative delirium varies widely depending on the patient population, surgical procedure, and frequency of assessment[5] but is reported to be 10%–50% with the highest rates occurring in older patients undergoing cardiac and major noncardiac surgery.[6] In patients admitted postoperatively to an intensive care unit (ICU), incidence can be as high as 80%.[6]

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.[7–13] Patients with postoperative delirium are more likely to have functional decline and dependency in activities of daily living after discharge.[14–16] Furthermore, the development of postoperative delirium is one of the strongest predictors of cognitive impairment after surgery,[14,17–23] 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.[24,25] 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.[5,26] In addition, several reviews and recommendation statements[27] 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.[28,29] 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[30–32] 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).[33–43] 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[44] 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.[12] The importance of delirium to patients, health care systems, and payors mandates this strong 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,[25,45] and delirium reduction protocols across some high risk surgical and ICU patient populations have shown success in reducing incidence and/or duration.[46,47] 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.[48–56] 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.[57–62] 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[63] for patient or surgery 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.[64–71] 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,[72] intraoperative hypotension or hypertension,[73,74] cerebral autoregulation limits,[75] blood glucose control,[76] and intraoperative hyperoxia.[77] 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.[78]

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[79] 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.[80] 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.[81] 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.[82] 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.[80] 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.[83] 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.[3,84,85]

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.[2] 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.[86] Most of the screening tools are more specific than sensitive for delirium.[87,88] 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 nonpharmacologic 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.[89–91] 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.[92] 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.[93] 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.[94] 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.[46,95–98] Geriatrics consultation is often a component of bundled interventions. Tested individually, perioperative geriatric consultation has been shown to reduce delirium in older hip fracture patients[99,100] but not in other populations.[101] 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.[5,102] 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[103] and their psychoactive effects[104] 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).[105] The most pertinent drugs to avoid are those with anticholinergic effects (including diphenhydramine) and benzodiazepines.[104,106–110] Among opioids, meperidine has been associated with the development of postoperative delirium and should be avoided,[104] while differences in other opioids appear small.[111,112] Subanesthetic doses of ketamine can cause psychosis and increased risk of postoperative delirium.[113–115] 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[116] (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.[117,118] 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,[119] 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.[120–123] 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 (≥60 years of age) undergoing cardiac and major noncardiac surgery with general anesthesia.[44,124] Thus, a meta-analysis was performed utilizing data from the 4 trials[44,120–122] 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.[44,120,121] Periods of intraoperative burst suppression have been associated with increased incidence of postoperative delirium,[125,126] 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.[44] It is also unclear whether EEG suppression is a modifiable factor or simply a marker of the patien's preexistent vulnerability (ie, sensitive brain hypothesis).[127] 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.[10] 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)[120–122] 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,[44] use of processed EEG did not meaningfully modify anesthetic exposure (as opposed to the prior Cognitive Dysfunction after Anesthesia [CODA] trial).[121] 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).[44] 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[128–132] and between sevoflurane versus desflurane.[132,133] In addition, xenon or the use of N_2O with inhalational anesthetics has no effect on the incidence of postoperative delirium in older surgical patients.[134–137]

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,[121] no change in average depth of anesthesia and less delirium,[120] and less volatile anesthetic administration with no difference in delirium.[44] Further, low volatile anesthetic concentration has been associated with increased delirium.[122] 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.[138,139]

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,[140] even among patients with baseline cognitive impairment.[141,142] 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%,[115] 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,[143–145] with adequate pain control considered an important part of delirium prevention.[5] Opioids have been the mainstay in postoperative pain management. The association between opioid use and development of delirium has been inconsistent, [4,108,146–150] but their potential deliriogenic properties and other side effects may limit utility in high-risk patients. Clinical guidelines[5] 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[151–153] and colonic[154,155] 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. [156,157] 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,[158,159] gabapentin,[160] or ketamine.[161,162] In addition, bolus ketamine may actually increase risk for psychosis and postoperative delirium.[113–115]

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,[163–170] 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.[171] Further, a large multicenter study of prophylactic haloperidol performed in ICU patients found no difference in delirium outcomes, including in surgical and trauma subgroups.[172] Importantly, there are potential harms associated with prophylactic administration of antipsychotics for prevention of postoperative delirium, including sedation, extrapyramidal symptoms, postural hypotension, and arrhythmia.[173]

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[174–176] but not in others.[51,177,178] Intraoperative ketamine bolus following induction has not been shown to reduce delirium after surgery[179] despite initial promising results.[180] In addition, the potential harms associated with 1 single dose of ketamine included postoperative hallucinations and nightmares.[179] 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.[181] Perioperative gabapentin administration did not affect delirium occurrence in 2 orthopedic and spine trials.[160,182] Finally, parecoxib[156] and acetaminophen[157] have been shown to reduce delirium in single trials.

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

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 α-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,[194,195] and sedative regimens that focus on targeted arousal levels and light sedation have improved the rates of delirium.[196–200] 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.[201–207] Two trials showing no difference between dexmedetomidine and propofol sedation with regard to delirium[208,209] 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 demonstrated to reduce both ICU and in-hospital delirium.[210,211] 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.[47,212,213]

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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.

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.

DISCLOSURES

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

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

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

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

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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

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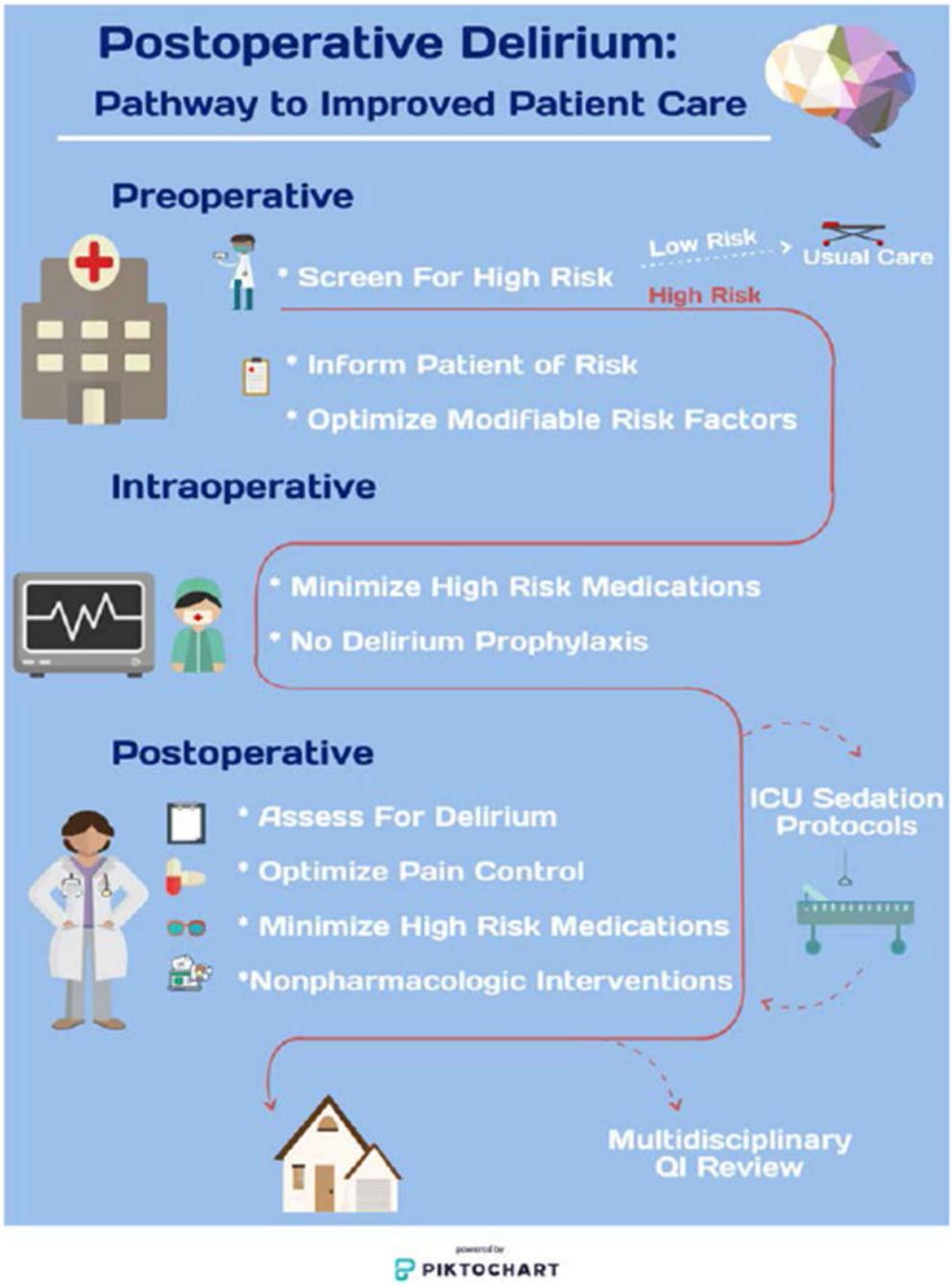

Figure 1.

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.

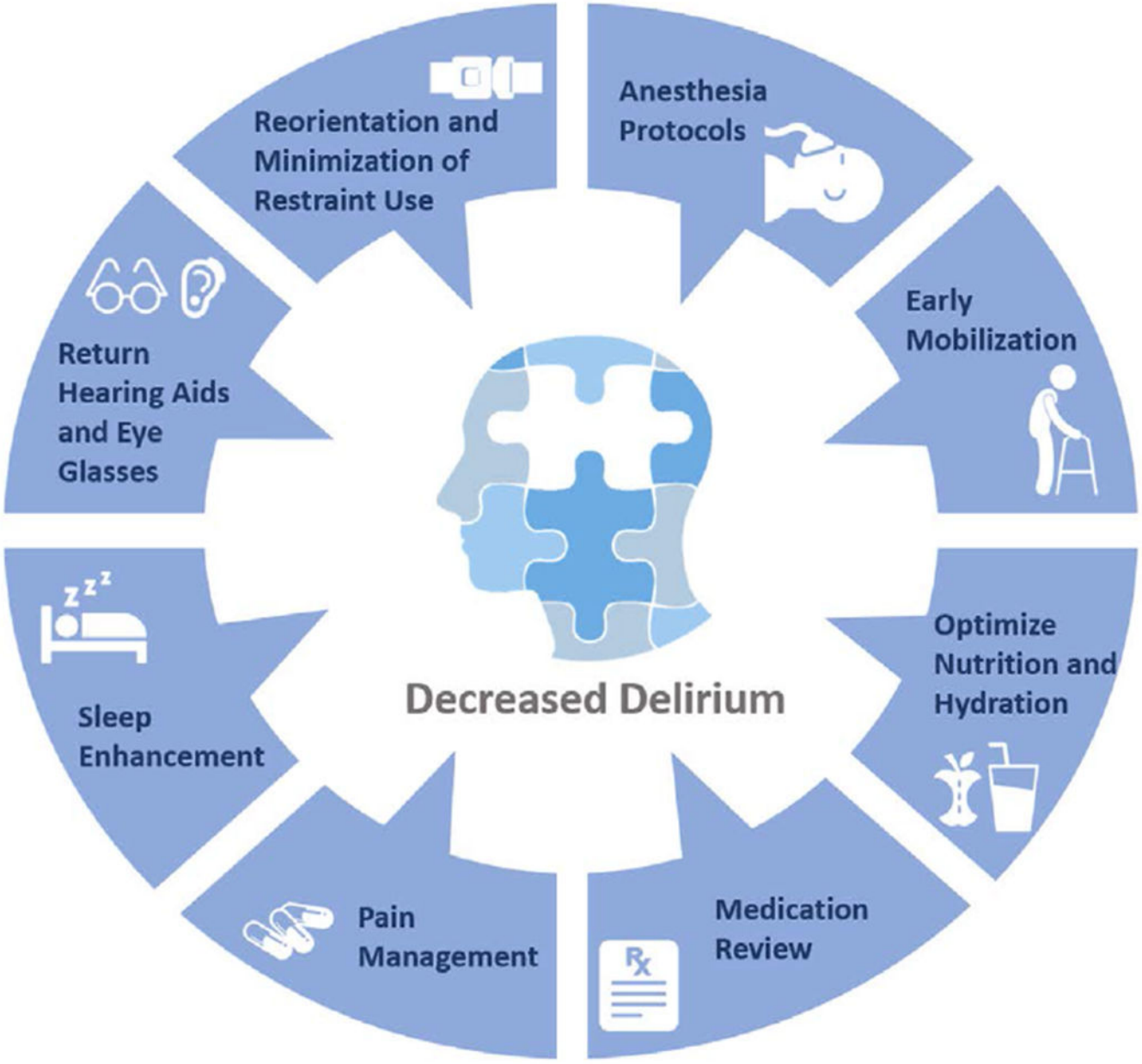

Figure 2.

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

Table 1.

Consensus Statements and Recommendations

Statement	Strength[a]	LOE[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.[c]	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.

[a] Strength of recommendation per GRADE process.

[b] Level of evidence per GRADE process.

[c] Additional evidence published after consensus conference which led to a change in recommendation statement.

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

Table 4.

RCTs of Prophylactic Pharmacologic Treatment to Prevent Postoperative Delirium

Drug	Setting Studied	Studies Supporting Use	Studies Reputing Use	Quality of Evidence
Antipsychotics				
Haloperidol	≥18 y, critically ill (N = 1789, including 828 surgical and 68 trauma)	…	van den Boogaard 2018[172]	Strong
	≥75 y, abdominal or orthopedic surgery (N = 201)	Fukata et al (2017)[163]	…	Low
	≥75 y, elective abdominal surgery under GA or elective orthopedic surgery under GA/SA (N = 121)	…	Fukata et al (2014)[168]	Low
	≥18 y, requiring mechanical ventilation (N = 141, including 50 surgical)	…	Page et al (2013)[169]	Moderate
	≥65 y, admitted to the intensive care unit after noncardiac surgery (N = 457)	Wang et al (2012)[164]	…	Moderate
	≥70 y, acute or elective hip surgery (N = 430)	…	Kalisvaart et al (2005)[170]	Moderate
Olanzapine	≥65 y and those <65 y with a history of POD, scheduled for elective total knee- or total hip-replacement surgery (N = 495)	Larsen et al (2010)[165]	…	Moderate
Risperidone	≥68 y, cardiac surgery with cardiopulmonary bypass, postoperative subsyndromal delirium (N = 100)	Hakim et al (2012)[166]	…	Low
	>40 y, elective cardiac surgery with cardiopulmonary bypass (N = 126)	Prakanrattana et al (2007)[167]	…	Low
Sedative and analgesic agents				
Dexmedetomidine	Nondelirious ICU adults requiring sedation (N = 100, including 27 surgical)	Skrobik et al (2018)[176]	…	Moderate
	≥68 y, major elective noncardiac surgery (N = 404)	…	Deiner et al (2017)[177]	Moderate
	≥60 y, elective CABG and/or valve replacement surgery (N = 285)	…	Li et al (2017)[178]	Moderate
	65–80 y, total hip joint or knee joint or shoulder joint surgery with GA (N = 200)	Liu et al (2016)[174]	…	Low
	≥65 y, elective noncardiac surgery under GA, admitted to the ICU after surgery before 2000 h (N = 700)	Su et al (2016)[175]	…	Moderate
	18–80 y, selected maxillofacial surgery with microvascular free flap reconstruction (N = 80)	…	Yang et al (2015)[214]	Low
Ketamine bolus	Major cardiac and noncardiac surgery under GA (N = 672)	…	Avidan et al (2017)[179]	High
	≥55 y, elective CABG surgery or valve replacement/repair with CPB (N = 58)	Hudetz et al (2009)[180]	…	Low
Ketamine infusion	≥18 y, critical illness with mechanical ventilation (N = 162, including 52 surgical)	Perbet et al (2018)[181]	…	Low
Gabapentin	Medical center; ≥65 y, spine or joint replacement surgery (N = 697)	…	Leung et al (2017)[160]	High
	18–75 y, total knee arthroplasty (N = 179)	…	Dighe et al (2014)[182]	Low
Parecoxib	≥60 y, elective total hip or knee replacement surgery (N = 620)	Mu et al (2017)[156]	…	High
Acetaminophen, intravenous	≥60 y, on-pump CABG and valve surgery (N = 120)	Subramaniam et al (2019)[157]	…	Moderate

Drug	Setting Studied	Studies Supporting Use	Studies Reputing Use	Quality of Evidence
Steroids				
Dexamethasone	≥18 y, cardiac surgery with CPB (substudy within a large RCT, N = 737)	…	Sauer et al (2014)[183]	Low
	CABG surgery (N = 93)	…	Mardani et al (2013)[184]	Low
Methylprednisolone	Cardiac surgery with cardiopulmonary bypass (N = 555)	…	Royse et al (2017)[185]	Low
	Cardiac surgery with cardiopulmonary bypass (N = 7507)	…	Whitlock et al (2015)[186]	Moderate
Statins				
Atorvastatin	≥18 y, elective cardiac surgery (N = 615)	…	Billings et al (2016)[187]	Moderate
Rosuvastatin	Sepsis associated ARDS (N = 329, including 111 surgical)	…	Needham et al (2016)[188]	Moderate
Simvastatin	≥18 y, requiring mechanical ventilation (N = 142, including 36 surgical)	…	Page et al (2017)[189]	Moderate
Miscellaneous agents				
Cyproheptadine	16–65 y, noncardiac surgery, admitted to ICU (N = 45)	Mohammadi et al (2016)[215]	…	Low
Donepezil	>50 y, elective joint replacement (N = 80)	…	Liptzin et al (2005)[216]	Low
Hypertonic saline	>65 y, hip arthroplasty for femoral neck fracture surgery (N = 120)	Xin et al (2017)[217]	…	Low
Melatonin	≥65 y, hip fracture surgery (N = 378)	…	De Jonghe et al (2014)[190]	Moderate
	Academic hospital; >65 y, scheduled hip arthroplasty under SA (N = 203, 4 groups)	Sultan (2010)[191]	…	Low
NAC	Liver resection (N = 206)	…	Grendar et al (2016)[218]	Low
Nimodipine	Scheduled spine surgery under GA (N = 60)	Li et al (2017)[219]	…	Low
Ondansetron	>40 y, scheduled for femoral or hip fracture rehabilitation surgery with GA (N = 106)	Papadopoulos et al (2014)[220]	…	Low
Rivastigmine	Femoral neck or intertrochanter fracture, cognitive impairment (MMSE 10–26) (N = 62)	Youn et al (2017)[192]	…	Low
	>65 y, elective cardiac surgery with cardiopulmonary bypass (N = 120)	…	Gamberini et al (2009)[193]	Low
TJ-54 (Yokukansan)	≥70 y, surgery for gastrointestinal or lung malignancy (N = 186)	…	Sugano et al (2017)[221]	Low
Tryptophan	≥60 y, elective surgery with a planned ICU admission (N = 301)	…	Robinson et al (2014)[222]	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-acetylcystine; POD, postoperative delirium; RCT, randomized controlled trial; SA, spinal anesthesia.