

2025 American Society of Anesthesiologists Practice Advisory for Perioperative Care of Older Adults Scheduled for Inpatient Surgery

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Purpose

This advisory provides evidence-based recommendations regarding the management of older adults undergoing inpatient surgery. Recommendations concerning care of ambulatory surgical patients were not made as the scientific evidence only focused on inpatient surgery.

The focus of this advisory includes aspects of preoperative, intraoperative, and postoperative care of specific relevance to older adults, *i.e.*, 65 yr or older. The advisory

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addresses approaches to minimizing complications of anesthesia common among older patients.

Background

Improving the quality of perioperative care for older adults is a major priority for healthcare providers, policy makers, and the public. In the next 30 years, the population of U.S. adults aged 65 yr and older will double (from 46 to 98 million).¹ The U.S. population 85 yr and older will triple (from 6 to 20 million).¹ Even though adults older than 65 yr comprise only 15% of the U.S. population, they undergo more than 30% of all inpatient² and outpatient surgeries.³ This demographic shift means that anesthesiologists will increasingly be asked to care for older surgical patients, who are at much greater risk of adverse postoperative outcomes than younger patients.

Preserving independence is a vital goal for older adults undergoing surgery. However, age-related physiologic changes, comorbidities, cognitive decline, frailty, and the surgical stress response all contribute to postoperative complications, prolonged hospital stays, and resulting decline in functional abilities and cognitive recovery.⁴ Unfortunately, loss of independence is common in older adults after surgery, with the incidence increasing with age. Nineteen percent of patients aged 80 to 89 yr and 26% of patients 90 yr or older exhibited functional decline that persisted for 30 days after a surgical procedure.⁵ While the postsurgical decline may be temporary, many older adults do not recover from this loss in function. Thirty-five percent of older adults with a new disability after surgery have no recovery 6 months later.⁶ These findings highlight the vulnerability of older patients who are undergoing surgery. The results also pinpoint the need for targeted perioperative interventions to preserve the independence of older adults.

Neurocognitive Disorders

With more older patients presenting for surgery, anesthesiologists will routinely be required to care for patients with preoperative neurocognitive disorders. A preoperative neurocognitive disorder increases the risk of delayed neurocognitive recovery after surgery. Previously diagnosed neurocognitive disorders were present in 18% of older patients scheduled for elective noncardiac surgery.⁷ Additionally, 37% of patients without known neurocognitive deficits were found to have significant cognitive impairment on preoperative testing.⁷

Preoperative neurocognitive disorders are associated with a greater likelihood of developing postoperative delirium.^{8,9} Postoperative delirium is associated with adverse in-hospital and patient-reported outcomes.^{8,9} Patients who experience postoperative delirium have more impaired functional recovery in the month after surgery than their counterparts without delirium.¹⁰ Delirium is associated with long-term cognitive decline.¹¹ Cognitive decline after surgery is also associated with loss of ability to perform independent

activities of daily living.¹⁰ These findings highlight the importance of recognizing and addressing preoperative neurocognitive disorders in older patients, as emphasized by the ASA Perioperative Brain Health Initiative.¹²

Frailty

Frailty is a multidimensional loss of reserve due to accumulation of age- and disease-related deficits.¹³ Because older adults with frailty live with multidimensional deficits, they are vulnerable to even minor stressors. Faced with the major physical, physiologic, and psychosocial stressors of invasive procedures and surgery, people with frailty represent one of the highest risk strata of the perioperative population in terms of their risks of major morbidity, delirium, cognitive decline, impaired functional recovery, and mortality. Specifically, frailty is associated with a two- to fivefold greater risk of complications, mortality, nonhome discharge, and development of a new disability.¹⁴ Preoperative frailty is also one of the strongest predictors of postoperative delirium, increasing risk more than fourfold.^{15,16}

The overall prevalence of frailty in older patients living in the community averages 10.7%, but varies considerably depending on the operationalization of frailty status.¹⁷ The prevalence of frailty increases with age.^{17,18} Frailty rates are higher in African American¹⁸ and female patients.^{17,18} Patients with less education, lower income, and poorer health also have a higher prevalence of frailty.¹⁸ Twenty-five percent to 40% of older surgical patients live with a meaningful degree of frailty before surgery,¹⁴ a higher prevalence than among older patients living in the community.¹⁸ Thus, anesthesiologists will encounter frailty among surgical patients at a much greater rate than in age-matched older adults not having surgery.

Frailty can be identified using one of several instruments, including the Risk Analysis Index, Clinical Frailty Scale, Fried Phenotype, Frailty Index, or Edmonton Frail Scale. Preoperative identification of frailty status may allow optimization of one or more of the deficits present in physical, cognitive, nutritional, and/or mental health domains before surgery.^{14,19}

Possible Methods to Improve Postoperative Outcomes

A variety of approaches might improve surgical outcomes in older adults. These approaches include enhanced preoperative assessment, optimal choice of primary anesthetic technique, and pharmacologic regimens specifically tailored to the needs of older patients. Enhanced preoperative assessment of older adults may include a focus on frailty, mood and anxiety issues, malnutrition risk, baseline function, polypharmacy, and preoperative cognition status.²⁰ Intraoperatively, management of the older patient entails its own set of considerations. The role of anesthetic technique in determining postoperative outcomes remains debated. Recent multicenter trials have failed to prove superiority of either neuraxial or general anesthesia, at least in patients with hip fractures.²¹ Similarly, whether maintenance of

general anesthesia with inhaled anesthesia or total intravenous anesthesia enhances recovery is not known.²²

Other key questions in perioperative pharmacology for the older patient include considerations of medications with potential delirium prophylaxis and medications with central nervous system effects.²³ While a trend toward elimination of perioperative administration of these drugs is emerging, questions remain as to the management of patients with chronic use, and the safety of drug discontinuation immediately before surgery. Questions remain as to whether use of certain drugs, such as α_2 agonists, may reduce the incidence and/or severity of delirium in older patients having anesthesia and surgery.

While acknowledging the potential importance of anesthesia depth monitoring and postoperative pain management

in preventing complications like delirium in older adults, these topics were not addressed in this advisory due to the limited and conflicting nature of the available evidence. Evidence from both meta-analyses^{24,25} and recent randomized clinical trials conducted in East Asia²⁶ and Spain²⁷ suggested that processed electroencephalogram (EEG) monitoring may reduce the incidence of postoperative delirium and hospital stay. On the other hand, large randomized clinical trials conducted in North America (Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes [ENGAGES]^{28,29} and SHaping Anesthesia techniques to Reduce Post-operative delirium [SHARP]³⁰) failed to demonstrate a clear benefit of EEG-guided anesthetic depth reduction on postoperative delirium in older adults undergoing major surgery. Additionally, no reduction in 1-yr mortality was observed.³¹ There is an ongoing debate regarding the specific link between deep anesthesia and delirium, suggesting that baseline patient vulnerabilities might be more influential.^{32–35} While adequate postoperative pain control is widely recognized as crucial,³⁶ there is a scarcity of high-quality research (randomized clinical trials) to definitively determine its impact on delirium in older adults.

Both the ASA Brain Health Initiative¹² and a recent brain health statement³⁷ offer recommendations based on expert and practitioner experience for putting a brain health program into action, specifically focusing on perioperative care for older adults. However, unlike these initiatives, this practice advisory seeks to address specific clinical management questions about anesthesia for older adults and develop recommendations for practice that are based on a systematic review and meta-analysis of relevant literature that includes using a known approach to grading the quality of evidence and strength of recommendations.

Materials and Methods

The advisory task force included physicians (anesthesiologists with expertise in caring for older adults, a geriatrician, and a geriatric surgeon), a patient representative, and epidemiology-trained methodologists. ASA requires all task force members to disclose all relationships that might pose a conflict of interest. None of the disclosed relationships posed a conflict. The task force was responsible for developing key questions; defining the patient populations, interventions, comparators, and outcomes for each key question; and determining the importance of each outcome in relation to the decision-making process (Supplemental Digital Content 1, Protocol, <https://links.lww.com/ALN/D638>). A scale of 1 to 9 (1 to 3, limited importance; 4 to 6, important; and 7 to 9, critical)³⁸ was used to survey the task force. The evidence synthesis focused on outcomes rated as critical and important.

The systematic review supporting the development of the recommendations in this advisory was guided by the following key questions:

- Key Question 1: Among older patients undergoing inpatient surgery and anesthesia, does expanded preoperative

Recommendations

Recommendation	Strength of Recommendation	Strength of Evidence
1. Consider expanded preoperative evaluation in older adults scheduled for inpatient procedures to reduce the risk of postoperative delirium. If patients are identified with cognitive impairment and/or frailty, changes in patient care can be initiated. These changes include, but are not limited to, involvement of a multidisciplinary care team and geriatrician or geriatric nurse visits, and patient and family education on postoperative delirium risk.	Conditional	Low
2. We recommend choosing either neuraxial or general anesthesia for older adults when either is clinically appropriate, based on shared decision-making. The evidence suggests no superiority with either technique in reducing postoperative delirium.	Strong	Moderate
3. Either total intravenous or inhaled anesthesia is acceptable for general anesthesia in the older population. The evidence is inconclusive with respect to the comparative risk of postoperative delirium.	Conditional	Low
4. Among older patients scheduled for inpatient procedures, it is reasonable to consider dexmedetomidine to lower risk of postoperative delirium while also considering its effects on bradycardia and/or hypotension.	Conditional	Moderate

Best Practice Statement

Consider the risks and benefits of medications with potential central nervous system effects in older adults, as these drugs may increase the risk of postoperative delirium.

evaluation that includes frailty, cognitive impairment, physical function, or psychosocial screening lead to improved postoperative outcomes?

- Key Question 2: Among older patients undergoing surgery, does neuraxial anesthesia as the primary anesthetic technique improve postoperative outcomes compared with general anesthesia?
- Key Question 3: Among older patients undergoing surgery with general anesthesia, does intravenous anesthesia for maintenance improve postoperative outcomes compared with inhaled volatile anesthesia?
- Key Question 4: Among older patients undergoing surgery and anesthesia, does dexmedetomidine administered during the perioperative period decrease the risk of postoperative delirium or other adverse cognitive outcomes?
- Key Question 5: Among older patients undergoing surgery and anesthesia, do medications with potential central nervous system effects (*i.e.*, benzodiazepines, antipsychotics, anticholinergics, ketamine, corticosteroids, gabapentin, or nonsteroidal anti-inflammatory drugs [NSAIDs]) administered during the perioperative period increase the risk of postoperative delirium or other adverse outcomes?

In the next section, we define the populations, interventions, comparators, and outcomes for each key question.

Populations, Interventions, Comparators, and Outcomes

- Population: The target population included older adults scheduled for or undergoing surgery with general or neuraxial anesthesia. This population can be defined by age (65 yr or older), as the review concerns clinically important age-dependent loss of physiologic or cognitive reserves. However, limiting study inclusion to only those enrolling participants 65 yr or older would have significantly narrowed the evidence base. Accordingly, we defined age-based inclusion criteria as (1) enrolled only patients 65 yr or older, (2) enrolled patients with a mean age 65 yr or older, (3) reported subgroup analysis for patients 65 yr or older, or (4) enrolled patients with a mean age 60 to 65 yr with either the upper bound of range 80 yr or older or twice the standard deviation greater than or equal to 80 yr.
- Interventions and comparators
 - Key Question 1: Preoperative evaluations including frailty, cognitive, functional, psychosocial, nutritional assessments, involvement of a multidisciplinary hospital team, and review of current medications and comorbidities *versus* standard preoperative evaluation
 - Key Question 2: Neuraxial *versus* general anesthesia
 - Key Question 3: Total intravenous *versus* inhaled anesthesia
 - Key Question 4: Dexmedetomidine, melatonin, or melatonin receptor agonists (*e.g.*, ramelteon) for delirium prophylaxis *versus* none

- Key Question 5: Medications with potential central nervous system effects (*i.e.*, benzodiazepines, antipsychotics, anticholinergics, corticosteroids, H₂-receptor agonists, NSAIDs, ketamine, and gabapentin) *versus* none
- Outcomes: Critical outcomes included postoperative delirium, neurocognitive disorder less than 30 days, and neurocognitive disorder 30 days or more to 1 yr. Assessment tools for postoperative delirium included but were not limited to the Confusion Assessment Method, Confusion Assessment Method–Intensive Care Unit, Delirium Rating Scale, Diagnostic and Statistical Manual of Mental Disorders, and Intensive Care Delirium Screening Checklist. Assessment tools for neurocognitive disorder included but were not limited to the Mini-Mental State Examination, Montreal Cognitive Assessment, and Digit Span Test. Other outcomes rated as important included discharge location (institution *vs.* independent living), complications, physical function, patient and/or caregiver satisfaction, length of stay, and mortality.

Literature Search

Comprehensive searches were conducted per key question by a medical librarian for literature published from January 2000 through June 2023 and updated in October 2023 using the following databases: PubMed, Embase, Scopus, and Cochrane. The search start date was chosen to preserve applicability of results (the restriction is unlikely to meaningfully reduce search sensitivity).³⁹ In addition, task force members provided relevant references; citations in systematic reviews and meta-analyses were hand-searched; and trial registries were queried. The literature search strategy and Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) are available in the Supplemental Digital Content (Supplemental Digital Content 2, Search Strategy, <https://links.lww.com/ALN/D639>; and Supplemental Digital Content 3, PRISMA Flow Chart, <https://links.lww.com/ALN/D640>). The methodologies used for this advisory for study screening, data extraction, and data management are

Table 1. GRADE Strength of Evidence Definitions

GRADE	Interpretation
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.

similar to the methodology implemented in previous ASA guidelines^{40,41} and are described in the systematic review protocol (Supplemental Digital Content 1, Protocol, <https://links.lww.com/ALN/D638>; and Supplemental Digital Content 4, Methodology, <https://links.lww.com/ALN/D641>). Methodology specific to this advisory or requiring additional emphasis is presented below.

Risk of Bias Assessment

Risk of bias for individual studies was evaluated using tools relevant for the study design: for randomized clinical trials, the Cochrane risk of bias tool, version 2, and for nonrandomized studies, ROBINS-I (Risk of Bias in Non-randomised Studies-or Interventions)^{42,43} (Supplemental Digital Content 5, Risk of Bias, <https://links.lww.com/ALN/D642>).

Evidence Synthesis

The body of evidence was first described according to overall study characteristics and treatment arms. Results were then summarized in tabular form by outcome. When relevant, decision-informative, and practicable, pairwise, and network meta-analyses were performed. Analyses were conducted in R.⁴⁴ Details concerning the meta-analyses can be found in Supplemental Digital Content 4, Methodology (<https://links.lww.com/ALN/D641>; e.g., choice of effect measure, pooling method, between-study variance estimators, examination of small study effects, prediction intervals, and other considerations).

Strength of Evidence

Methodologists rated the overall strength of evidence by comparators and outcome using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system of rating evidence from high to very low (table 1). Evidence from randomized clinical trials starts at high strength of evidence, and evidence from nonrandomized studies starts at low. The strength was downgraded based on summary study-level risk of bias, inconsistency, indirectness, imprecision, and other considerations including small study effect due to suspected publication bias (Supplemental Digital Content 4, Methodology, <https://links.lww.com/ALN/D641>).⁴⁵

Strength of Recommendations

For each key question, results of the evidence synthesis for important benefits and harms were summarized. Randomized clinical trials were prioritized for analysis when assessing outcomes and developing the recommendations. Nonrandomized studies, including before-after/time series, cohort, and case-control designs,⁴⁶ were only analyzed when insufficient numbers of randomized clinical trials were available to evaluate harms and for supportive

confirmatory evidence. After reviewing the evidence summary and relevant details, the task force developed recommendations and rated the corresponding strength of the recommendations consistent with the body of evidence (table 2).

Expanded Preoperative Evaluation *versus* Standard Evaluation

Key Question

Among older patients undergoing inpatient surgery and anesthesia, does expanded preoperative evaluation that includes frailty, cognitive impairment, physical function, or psychosocial screening lead to improved postoperative outcomes?

Recommendation

Consider expanded preoperative evaluation in older adults scheduled for inpatient procedures to reduce the risk of postoperative delirium. If patients are identified with cognitive impairment and/or frailty, changes in patient care can be initiated. These changes include, but are not limited to, involvement of a multidisciplinary care team and geriatrician or geriatric nurse visits, and patient and family education on postoperative delirium risk.

- Strength of evidence: Low
- Strength of recommendation: Conditional

Summary of Evidence for Critical and Important Outcomes

Pooled results from six randomized trials suggest lower risk of postoperative delirium for patients receiving expanded preoperative evaluation (risk ratio, 0.77; 95% CI, 0.60 to 0.99; table 3).^{47–52} Evidence from nonrandomized studies supports this effect (Supplemental Digital Content 6, Supporting Evidence, <https://links.lww.com/ALN/D643>).^{53–60} The strength of the evidence for delirium was rated low due to limitations in study level risk of bias and potential publication bias due to small study effects (Supplemental Digital Content 6, Supporting Evidence, <https://links.lww.com/ALN/D643>). Evidence for other critical outcomes was limited. The findings of one nonrandomized study suggest no difference in neurocognitive disorders less than 30 days between patients receiving expanded *versus* standard preoperative evaluation (table 3).⁵⁴ No studies were identified for neurocognitive disorders from 30 days or more to 1 yr. Evidence for other outcomes is presented in table 3 and discussed in the appendix and Supplemental Digital Content 6, Supporting Evidence (<https://links.lww.com/ALN/D643>).

Comment

A review of the evidence suggests that older patients undergoing inpatient surgeries who received one or more preoperative

Table 2. Strength of Recommendations Definitions

Strength of Recommendation	Level of Evidence	Interpretation
Strong	High to moderate	Task force believes that all or almost all clinicians would choose (or not) the specific action or approach.
Conditional	Low to very low	Task force believes that most, but not all, would choose (or not choose) the action or approach.
Best practice statements	Ungraded	Best practice statements are statements for which there is sparse direct evidence or limitations in the available evidence that does not make them amenable to the GRADE process. However, they may be valuable for anesthesiologists to consider in the management of patient care.

GRADE, Grading of Recommendations, Assessment, Development, and Evaluation.

Table 3. Summary and Strength of Evidence for Critical and Important Outcomes in Studies Evaluating Expanded Preoperative Evaluation Compared to Standard Care

Outcome	Randomized Clinical Trials	Nonrandomized Studies	Expanded	Standard	Strength of Evidence	Effect		
			n (Total)	n (Total)		Measure	Estimate (95% CI)	P
Delirium	6		189 (662)	253 (703)	Low	Risk ratio	0.77 (0.60 to 0.99)	26%
Neurocognitive disorder < 30 days		1	13 (96)	16 (84)	Very low	Risk ratio	0.71 (0.36 to 1.39)	
Neurocognitive disorder ≥ 30 days to 1 yr	0	0						
Physical function	5		(563)	(576)	Very low	Standardized mean difference	0.09 (−0.16 to 0.31)	71%
Complications*	4	9			Very low		See Supplement 6†	
Patient satisfaction		1	32 (32)	29 (30)	Very low	Risk difference‡	3.3 (−5.3 to 12.0)§	
Length of stay (days)	8		(968)	(1001)	Very low	Mean difference	0.0 (−1.7 to 1.7)	94%
Discharged to institution	4		252 (419)	271 (424)	Low	Risk ratio	0.98 (0.76 to 1.27)	80%
Mortality (in-hospital and 30-day)	4		19 (498)	19 (526)	Very low	Risk ratio	1.02 (0.30 to 3.53)	60%

*Cardiovascular, pulmonary, and acute kidney injury. †<https://links.lww.com/ALN/D643>. ‡Per 100. §High vs. lower satisfaction.

evaluations for frailty, cognitive impairment, physical function, nutrition, and psychosocial issues may experience lower rates of delirium. Although the studies are heterogeneous in the combinations of components used in the preoperative evaluations for older patients, what was consistent among the studies was the gathering of information in a systematic manner. This approach provided the care team with knowledge about the patients' comorbidities and health vulnerabilities before surgery. Comprehensive geriatric assessment^{48–52} evaluated comorbidities, nutritional status, physical activity, and cognitive function, and uncovered improvement opportunities such as comanagement, fall prevention, and medication management. The ASA task force's recommendations are consistent with recommendations from a systematic review of 13 other clinical practice guidelines for care of older adults living with frailty.⁶¹

Changes in Patient Care Resulting from Expanded Preoperative Assessment

Interventions for patients identified as cognitively impaired, psychologically vulnerable, nutritionally compromised, and/

or frail differed among the studies. Interventions described in the randomized and nonrandomized studies included but were not limited to multidisciplinary team involvement in 26 of 31 (84%) of the studies, de-prescribing in 13 of 31 (42%) studies, nutritional supplementation in 9 of 31 (29%) studies, and geriatric visits in 11 of 31 studies (35%). Four of 31 (13%) studies reported an active delirium screen. Multidisciplinary care may include but is not limited to hospitalists, geriatric nurse champions, psychiatry, pharmacy, physical/occupational therapy, nutritionists, chaplaincy, and volunteer services. Optimized care of chronic medical conditions occurred in the inpatient^{50,52} and outpatient settings, as well as during the prehospital phase.⁵⁵ Treatment plans for at-risk patients involved geriatric care throughout hospitalization, with some implementing daily visits,^{48,50} and others occurring at prescribed stages of the study.

Research Gaps

There is a need for well-designed randomized clinical trials assessing the effects of preoperative frailty screening,

cognitive evaluation, and nutritional assessments on postoperative outcomes in older patients. There is also a need for studies evaluating the interventions implemented after identification of an at-risk patient.

Neuraxial *versus* General Anesthesia

Key Question

Among older patients undergoing surgery, does neuraxial anesthesia as the primary anesthetic technique improve postoperative outcomes compared with general anesthesia?

Recommendation

We recommend choosing either neuraxial or general anesthesia for older adults when either is clinically appropriate, based on shared decision-making. The evidence suggests no superiority with either technique in reducing postoperative delirium.

- Strength of recommendation: Strong
- Strength of evidence: Moderate

Summary of Evidence for Critical and Important Outcomes

The evidence synthesis found neither neuraxial nor general anesthesia accompanied by a lower risk for delirium (table 4). This finding was similar in the subgroup of patients undergoing hip fracture repair (risk ratio, 1.05; 95% CI, 0.76 to 1.43),^{21,62–66} and non-hip fracture procedures (risk ratio, 0.74; 95% CI, 0.35 to 1.60).^{67–70} The strength of evidence for delirium was rated moderate due to concerns related to imprecision of the effect estimate (*i.e.*, CI compatible with either neuraxial or general anesthesia being favored). Evidence concerning neurocognitive disorders less than 30 days and 30 days or greater to 1 yr was limited but also did not favor either primary anesthetic approach.^{70–73} Evidence for important and limited outcomes is presented in table 4 and further discussed in the appendix and Supplemental Digital Content 6, Supporting Evidence (<https://links.lww.com/ALN/D643>).

Comment

These results, obtained from randomized clinical trials of mostly patients with hip fractures, support the conclusion that the choice of neuraxial or general anesthesia is unlikely to affect the risk of delirium. Accordingly, anesthesiologists should consider individual patient preferences and characteristics when choosing an optimal primary anesthetic technique. Regarding complications on other organ systems, neuraxial anesthesia may reduce risk of acute kidney injury/failure^{21,64,67,74} and pneumonia.^{21,62–64,67,74,75} However, the strength of the evidence was low to very low in these studies, and confirmatory

trials are necessary. In contrast to settings in which a single choice has overriding benefits *versus* others, the choice between neuraxial and general anesthesia for hip fracture is likely to involve tradeoffs for most patients. As a result, this is likely to be a “preference-sensitive” decision in many cases and a suitable target for shared decision-making.⁷⁶

Research Gaps

When comparing neuraxial *versus* general anesthesia, there was a lack of randomized clinical trials that included patient-centered outcomes such as physical function and patient satisfaction. As these outcomes are important for decision-making, future studies should consider assessing these measures.

Total Intravenous Anesthesia *versus* Inhaled Volatile Anesthesia

Key Question

Among older patients undergoing surgery with general anesthesia, does intravenous anesthesia for maintenance improve postoperative outcomes compared with inhaled volatile anesthesia?

Recommendations

Either total intravenous or inhaled anesthesia is acceptable for general anesthesia in the older population. The evidence is inconclusive with respect to the comparative risk of postoperative delirium.

- Strength of recommendation: Conditional
- Strength of evidence: Low

Summary of Evidence for Critical and Important Outcomes

The pooled estimate from eight randomized clinical trials did not favor total intravenous or inhaled anesthesia with respect to risk of postoperative delirium.^{77–84} The overall strength of evidence rating for delirium was rated low due to limitations in study level risk of bias and imprecision of the effect estimate (*i.e.*, wide CI). And while the pooled estimate from five randomized clinical trials suggests lower risk of neurocognitive disorder up to 30 days postprocedure for patients receiving total intravenous anesthesia, the evidence was limited by variability in how (*e.g.*, differences in scales and thresholds) and when (*e.g.*, day of ascertainment) this outcome was measured.^{85–89} A single randomized clinical trial⁹⁰ and three nonrandomized studies^{91–93} assessed the effects of total intravenous *versus* inhaled agents on neurocognitive disorder at 30 days or more to 1 yr and did not detect a difference (table 5). Evidence for important and limited outcomes is discussed in the appendix and

Table 4. Summary and Strength of Evidence for Critical and Important Outcomes in Studies Evaluating Neuraxial Compared to General Anesthesia

Outcome	Randomized Clinical Trials	Neuraxial	General	Strength of Evidence	Effect		
		n (Total)	n (Total)		Measure	Estimate (95% CI)	P
Delirium	10	215 (1,840)	213 (1,908)	Moderate	Risk ratio	1.06 (0.84 to 1.33)	21%
Neurocognitive disorder < 30 days	4	78 (336)	88 (355)	Low	Risk ratio	0.91 (0.56 to 1.48)	52%
Neurocognitive disorder ≥ 30 days to 1 yr	1	23 (176)	25 (188)	Very low	Risk ratio	0.98 (0.58 to 1.67)	
Physical function	3	(355)	(371)	Very low	Standardized mean difference	0.01 (−0.39 to 0.42)*	85%
Complications†	13			Low/very low		See Supplement 6‡	
Patient satisfaction	10	913 (1,055)	839 (991)	Low	Risk ratio	1.02 (0.98 to 1.05)§	46%
Length of stay (days)	13	(2,355)	(2,373)	Low	Mean difference	−0.4 (−1.1 to 0.3)	97%
Discharged to institution	1	576 (777)	586 (777)	Very low	Risk ratio	0.98 (0.93 to 1.04)	
Mortality (in-hospital and 30-day)	6	19 (1,789)	31 (1,859)	Low	Risk ratio	0.66 (0.28 to 1.50)	9%

*Using Neuman 2021 primary result of inability to walk 60 feet without human assistance in a sensitivity analysis including 1,644 patients yielded a pooled standardized mean difference of −0.07 (95% CI, −0.25 to 0.12).²¹ †Cardiovascular, pulmonary, and acute kidney injury. ‡<https://links.lww.com/ALN/D643>. §Comparing higher/highest category or categories compared to lower ones.

Supplemental Digital Content 6, Supporting Evidence (<https://links.lww.com/ALN/D643>).

Comment

The complexity of surgical procedures across diverse studies complicates direct outcome comparisons between total intravenous and inhaled anesthesia for both delirium and delayed neurocognitive recovery. Consequently, drawing definitive conclusions about the specific impact of surgery type on these outcomes proves challenging. Pooled estimates of randomized clinical trials did not demonstrate differences in delirium rates between total intravenous and inhaled anesthesia. And while low strength of evidence suggests that total intravenous anesthesia is associated with a decrease in neurocognitive disorder up to 30 days postprocedure, the findings are not consistent at later time points. There were limited randomized clinical trials comparing complications between total intravenous anesthesia and inhalational anesthesia. Most evidence suggests no difference in complications studied except for low-grade evidence favoring decreased pulmonary embolism^{77,94–97} and respiratory failure^{77,90,96,97} associated with total intravenous anesthesia. Further, data suggest that patients undergoing ophthalmologic or gastrointestinal/abdominal surgery and receiving total intravenous anesthesia tend to report higher satisfaction levels compared to those receiving inhaled anesthesia (appendix). Notably, these findings are specific to certain surgical procedures and patient populations.

Research Gaps

Additional well-designed randomized clinical trials in older adults comparing total intravenous anesthesia to

inhaled agents across various procedures are needed, as inconsistencies are present in the current evidence base. Trials building on the recently published feasibility pilot trial Trajectories of Recovery after Intravenous Propofol *versus* Inhaled Volatile anesthesia,⁹⁸ funded by the Patient-Centered Outcomes Research Institute (Washington, D.C.), are needed.

Pharmacologic Delirium Prevention

Key Question

Among older patients undergoing surgery and anesthesia, does dexmedetomidine administered during the perioperative period decrease the risk of postoperative delirium or other adverse cognitive outcomes?

Recommendation

Among older patients scheduled for inpatient procedures, it is reasonable to consider dexmedetomidine to lower risk of postoperative delirium while also considering its effects on bradycardia and/or hypotension.

- Strength of recommendation: Conditional
- Strength of evidence: Moderate

Summary of Evidence for Critical and Important Outcomes

Pooled results of 31 randomized clinical trials suggested that patients receiving dexmedetomidine may experience lower postoperative delirium compared with patients receiving placebo or no intervention (risk ratio, 0.58; 95% CI, 0.49 to 0.67). The overall strength of the evidence was rated

Table 5. Summary and Strength of Evidence for Critical and Important Outcomes in Studies Evaluating Total Intravenous Anesthesia Compared to General Anesthesia with Inhaled Anesthesia Volatiles

Outcome	Randomized Clinical Trials	Nonrandomized Studies	Total Intravenous Anesthesia	Inhalation	Strength of Evidence	Effect		
			n (Total)	n (Total)		Measure	Estimate (95% CI)	I ²
Delirium	8		143 (1,001)	158 (995)	Low	Risk ratio	0.94 (0.62 to 1.43)	46%
Neurocognitive disorder < 30 days	5		125 (704)	175 (703)	Moderate	Risk ratio	0.72 (0.54 to 0.96)	22%
Neurocognitive disorder ≥ 30 days to 1 yr	1		4 (96)	6 (97)	Very low	Risk ratio	0.67 (0.20 to 2.31)	
Physical function	0	0						
Complications*	10	9			Very low		See Supplement 6†	
Patient satisfaction	3		90 (109)	82 (141)	Low	Risk ratio	1.39 (1.19 to 1.63)‡	0%
Length of stay (days)	6		(1,343)	(1,341)	Very low	Mean difference	0.0 (−1.5 to 1.4)	75%
Discharged to institution		1	8 (9)	26 (20)	Very low	Risk ratio	1.46 (0.69 to 3.41)	
Mortality (in-hospital and 30-day)	4		11 (377)	8 (375)	Very low	Risk ratio	1.17 (0.47 to 2.89)	0%

*Cardiovascular, pulmonary, and acute kidney injury. †<https://links.lww.com/ALN/D643>. ‡Comparing higher/highest category or categories with lower ones.

moderate due primarily to limitations in study level risk of bias (table 6).^{99–129} Similarly, pooled results of nine randomized clinical trials suggested lower incidence of neurocognitive disorder less than 30 days postprocedure among patients receiving dexmedetomidine,^{119,129–136} and results of two small randomized clinical trials showed a reduction in neurocognitive disorder at 30 days or more to 1 yr (table 6).^{100,137}

These findings, however, should be interpreted with consideration of an increased risk of bradycardia and hypotension associated with dexmedetomidine. A pooled analysis of 17 randomized clinical trials showed an increased risk of bradycardia in patients receiving dexmedetomidine,^{102,107,109,114,115,119,122,123,128,129,133,138–143} and a pooled analysis of 20 randomized trials showed an increased risk of hypotension.^{99,102,103,107,109,111,114,115,118,119,121,124,125,128,129,133,139–141,143,144} Evidence for other outcomes is presented in table 6 and further discussed in the appendix and Supplemental Digital Content 6, Supporting Evidence (<https://links.lww.com/ALN/D643>).

Comment

The body of evidence supports the role of dexmedetomidine in delirium prophylaxis—weighing the increased risks of hypotension and bradycardia. However, additional aspects of the evidence require consideration: varying effects by country, baseline risk, optimal dose and timing, potential publication bias, variation according to surgery, and optimal nonpharmacologic care to prevent delirium. First, stronger and more homogeneous effects were reported from trials conducted in China (figure 1). How completely those trial results generalize

to all target populations is unclear. Next, the relative effect appeared to diminish with decreasing baseline risk; when the risk of delirium is low, the tradeoff between avoiding delirium *versus* hypotension and bradycardia will accordingly be less favorable. The timing of administration (*i.e.*, preoperatively, intraoperatively, or postoperatively) did not clearly modify results. We did not examine dose, but wide variations across trials were not apparent (Supplemental Digital Content 6, Supporting Evidence, <https://links.lww.com/ALN/D643>). Small-study effects were apparent with potential publication bias—the pooled result may overstate the true effect. However, we judged the severity of publication bias required to negate the results unlikely. Although the effect magnitudes were generally consistent across types of surgeries, the degree of heterogeneity varied considerably. For example, there was little variability in orthopedic and thoracic surgery trials but wide variation across cardiac trials and those including multiple procedures (Supplemental Digital Content 6, Supporting Evidence, <https://links.lww.com/ALN/D643>). Finally, the extent to which similar effects would have been observed in settings of optimal nonpharmacologic care diminishing baseline risk should be considered. In summary, although there is substantial evidence concerning dexmedetomidine for reducing the risk of delirium, the decision calculus is not entirely straightforward.

Research Gaps

Further randomized clinical trials need to be performed to determine what patient risk characteristics, type of surgery, doses/timing of administration, level of anesthesia, and use

Table 6. Summary and Strength of Evidence for Critical and Important Outcomes in Studies Evaluating Dexmedetomidine Compared to Placebo

Outcome	Randomized Clinical Trials	Dexmedetomidine	Placebo	Strength of Evidence	Effect		
		n (Total)	n (Total)		Measure	Estimate (95% CI)	P
Delirium—overall	31	457 (4,035)	666 (3,739)	Moderate	Risk ratio	0.58 (0.49 to 0.67)	46%
Neurocognitive disorder < 30 days	9	68 (666)	83 (392)	Moderate	Risk ratio	0.54 (0.39 to 0.73)	0%
Neurocognitive disorder ≥ 30 days to 1 yr	2	5 (50)	22 (50)	Very low	Risk ratio	0.24 (0.11 to 0.55)	0%
Physical function	1	(30)	(31)	Very low	Standardized mean difference	0.39 (−1.57 to 2.34)	
Bradycardia	17	236 (2,031)	129 (1,755)	High	Risk ratio	1.52 (1.22 to 1.88)	0%
Hypotension	20	611 (2,797)	409 (2,539)	High	Risk ratio	1.37 (1.11 to 1.69)	49%
Complications*	27					See Supplement 6†	
Length of stay (days)	20	(3,051)	(3,075)	Low	Mean difference	−0.8 (−1.3 to −0.2)	95%
Mortality (in-hospital and 30-day)	12	19 (2,345)	39 (2,424)	Low	Risk ratio	0.58 (0.32 to 1.04)	0%

*Cardiovascular, pulmonary, and acute kidney injury. †<https://links.lww.com/ALN/D643>.

of other medications are optimal to further our understanding of the use dexmedetomidine for reducing postoperative delirium.

Perioperative Use of Medications with Potential Central Nervous System Effects

Key Question

Among older patients undergoing surgery and anesthesia, do medications with potential central nervous system effects (*i.e.*, benzodiazepines, antipsychotics, anticholinergics, ketamine, corticosteroids, gabapentin, or NSAIDs) administered during the perioperative period increase the risk of postoperative delirium or other adverse outcomes?

Best Practice Statement

Consider the risks and benefits of medications with potential central nervous system effects in older adults, as these drugs may increase the risk of postoperative delirium.

- Strength of evidence: Not applicable

Summary of Evidence

Studies evaluating postoperative delirium when benzodiazepines, antipsychotics, anticholinergics, ketamine, corticosteroids, gabapentin, or NSAIDs are administered differed in drug administration timing and dosage. Postoperative delirium was measured using different scales and at different times during the postoperative period. Due to the heterogeneity of the studies, pooled analyses of postoperative delirium incidence could only be conducted for studies assessing ketamine. Below, we provide a brief narrative synthesis of select evidence for each drug. Evidence

for important and limited outcomes is discussed in the appendix and Supplemental Digital Content 6, Supporting Evidence (<https://links.lww.com/ALN/D643>).

Benzodiazepines. Four randomized clinical trials^{101,145–147} and four nonrandomized studies^{148–151} did not detect a difference in delirium incidence comparing short-acting benzodiazepines with placebo or no drug. However, two large retrospective database studies reported lower incidence of delirium with short-acting benzodiazepines but a higher incidence with long-acting benzodiazepines.^{152,153}

Antipsychotics. Five randomized clinical trials reported lower delirium incidence with antipsychotics *versus* placebo or no drug.^{154–158} However, three randomized trials were inconclusive concerning delirium incidence.^{159–161}

Ketamine. Pooled analysis of four randomized clinical trials comparing ketamine with placebo did not detect a difference in delirium.^{160,162–164} Details on the full body of evidence are reported in the appendix.

Other Drugs.

- Two studies examined the use of anticholinergics. One small randomized clinical trial evaluated an anticholinergic not available in the United States,¹⁶⁵ and one retrospective study did not detect a difference in delirium incidence comparing any anticholinergic with placebo.¹⁶⁶
- Four randomized clinical trials^{167–170} were inconclusive concerning delirium incidence with corticosteroids *versus* placebo or no drug, while two randomized clinical trials^{171,172} reported lower delirium incidence with corticosteroids *versus* no drug.

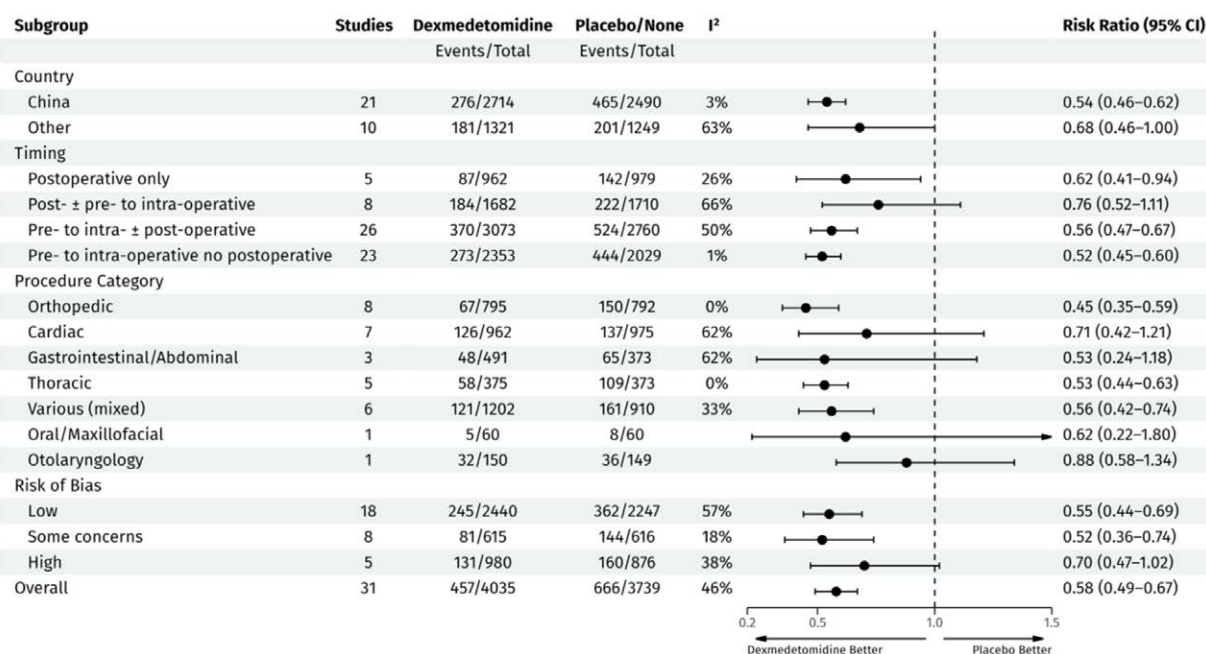


Fig. 1. Subgroup analysis of delirium risk in studies evaluating dexmedetomidine compared with placebo.

- Two large retrospective database studies reported lower incidence of delirium with NSAIDs compared to no drug.^{152,153}
- One randomized clinical trial did not detect a difference in incidence of delirium between gabapentin and placebo¹⁷³; however, one large retrospective study found an increase in delirium incidence.¹⁷⁴

Comment

Studies assessing the effect of these drugs on incidence of delirium demonstrated heterogeneity in both dosing and timing of medication administration, and the evidence was inconclusive for postoperative delirium.

Based on current evidence, we cannot recommend or advise against administering these medications. We do recommend weighing the risks and benefits of giving these medications based on the patient's condition and chronic medications, comorbidities such as pre-existing neurocognitive disorders, and the planned procedure. Currently published randomized clinical trials are heterogenous, involving different medications and comparators given in different doses and at different times in the perioperative period. Thus, opportunities exist for more well-designed randomized clinical trials to strengthen the evidence for either administering or withholding common medications used in daily practice of anesthesia. When weighing the risk–benefit profile, one should also consider the issue of polypharmacy, a known risk factor for delirium, as well as any potential drug–drug interactions with medications that

the patient may be taking chronically beyond the perioperative period. This best practice statement aligns with the American Geriatrics Society (New York, New York) 2023 Beer's Criteria of Potentially Inappropriate Medications.¹⁷⁵

Research Gaps

There is opportunity for more well-designed randomized clinical trials to strengthen evidence for either including or withholding drugs with potential central nervous system effects to older adults in the perioperative period. For instance, the soon to be published B-FREE trial (Benzodiazepine-Free for Cardiac Anesthesia for Reduction of Postoperative Delirium in ICU), a multicenter, randomized cluster cross-over trial evaluating restrictive *versus* liberal use of benzodiazepines among patients undergoing cardiovascular surgery (mean age, 65 yr), found no difference between restrictive *versus* liberal use on the incidence of delirium within 72 h of surgery (14.0% *vs.* 14.9%, respectively).¹⁷⁶

Prehabilitation

Prehabilitation is an important issue for older adults; however, this topic was not included as a key question in the systematic review for this advisory due to the lack of studies focusing on older adults.

Comment

Prehabilitation is the process of enhancing capacity and reserve before an acute stressor (*e.g.*, surgery) to improve tolerance of the upcoming injury.^{177,178} To date, prehabilitation

before surgery has included physical exercise, nutritional supplementation, and/or cognitive training interventions. In adult patients undergoing specific major surgical procedures, there is moderate-certainty evidence that prehabilitation improves functional recovery and low-certainty evidence that prehabilitation improves other outcomes such as complications and length of stay.^{177,179} However, minimal data are currently available specific to older adults undergoing surgery, especially vulnerable populations living with frailty or sarcopenia.^{180,181} This lack of data specific to older people, combined with low certainty evidence for most well-studied outcomes, limits our ability to make specific recommendations about prehabilitation for older adults requiring anesthesia and surgery.^{178,180} Additionally, major limitations in the evidence base across all adult patients include lack of an adequate understanding of what prehabilitation components (e.g., physical exercise *vs.* nutrition *vs.* cognitive training¹⁸²) are most effective for improving outcomes for older patients. In addition, little is known about what intervention intensity and duration are required to enhance preoperative reserve in a manner that translates into improved postoperative outcomes. Thus, whether and how prehabilitation programs should be optimally designed and delivered to meet the needs of vulnerable older patients must be addressed, including what structure and support programs are required to achieve safety, adequate adherence, and efficacy.

Research Gaps

- The efficacy of physical exercise and/or nutritional supplementation prehabilitation in improving outcomes specifically for older adults requiring anesthesia and surgery remains to be determined. Randomized clinical trials that target older patients, and in particular vulnerable populations living with frailty or sarcopenia, are required and should address outcomes that are prioritized by older patients, such as maintenance of independence (including returning to preoperative living situation), and physical and cognitive recovery.^{177,181} The PREPARE trial, a multicenter trial powered to detect meaningful differences in patient-reported disability and complication rates specifically in older surgical patients with frailty, should provide important insights in the near future.
- Key questions related to optimal intervention design for older patients must be addressed. Further research is required to identify optimal components of an effective prehabilitation program, the minimal required duration of participation, appropriate intervention intensity, ideal program location (e.g., home *vs.* facility-based, use of technology), and the best supervisory approaches (e.g., concurrent *vs.* nonconcurrent coaching).¹⁸⁰
- For older patients, and especially those with frailty and sarcopenia, baseline medical complexity and disease-related

symptom burden are recognized barriers to participation in prehabilitation.¹⁸³ Strategies to enhance adherence to support prehabilitation efficacy for this vulnerable population are needed before recommending routine use of prehabilitation.

- There is a need for additional studies designed to evaluate the efficacy of different cognitive prehabilitation interventions (e.g., product interface, target pathways, timing, intensity). While early evidence is promising for reduction of delirium, primary results remain inconclusive. Future research powered for more realistic effect sizes is required to determine if cognitive prehabilitation is an efficacious intervention for older adults preparing for anesthesia and surgery.¹⁸²

Conclusions

This practice advisory makes clinical recommendations on perioperative anesthesia care in older adults to minimize adverse cognitive outcomes. For older adults scheduled for inpatient procedures, expanded preoperative evaluation that includes cognitive and frailty screening should be considered to reduce the risk of postoperative delirium. Care for patients found with cognitive or frailty impairments should include multidisciplinary teams and geriatric specialists when possible. However, this recommendation is conditional because the strength of the evidence for delirium prevention was rated low. Either neuraxial or general anesthesia, and total intravenous or inhalation agents, are acceptable for older patients. Consideration of the risks and benefits of drugs with potential central nervous system effects in older adults is suggested. Dexmedetomidine may be helpful to reduce the risk of delirium in older surgical patients, but it can be associated with bradycardia and hypotension, and there is uncertainty around the effects of dexmedetomidine for patients at different levels of baseline risk for delirium, different surgeries, timing of administration and dosage, and use with other medications.

Appendix

Expanded Preoperative Evaluation

Study and Patient Characteristics

The body of evidence included 31 studies (33 publications) of patients scheduled for inpatient surgeries (9 randomized clinical trials^{47–52,184–188} and 22 nonrandomized studies^{53–60,189–202}). Supplemental Digital Content 6, Supporting Evidence (<https://links.lww.com/ALN/D643>), provides additional study and patient characteristic details.

Six of the nine randomized clinical trials (67%) involved orthopedic surgery, including hip fracture repair or total hip arthroplasty, and the remaining were cardiac, gastrointestinal, and multiple surgeries. Nonrandomized studies included 27% orthopedic and 23% abdominal or gastrointestinal, and the remaining included various surgeries.

The most common vulnerability measured preoperatively was impaired cognition. Studies providing evidence for this recommendation used the following validated cognitive tools: Mini-Mental State Examination, Montreal Cognitive Assessment, Trail Making Test, and Digit Symbol Test. Validated frailty screening tools used in the studies include Clinical Frailty Scale, Edmonton Frail Scale, and the Fatigue, Resistance, Ambulation, Illnesses, and Loss of weight questionnaire (FRAIL). Tools to measure psychosocial status included the Geriatric Depression Scale, Short Form (SF)-36 Mental Health, and State-Trait Operation Anxiety Inventory. Studies that measured physical function used various tools, including the Groningen Activity Restriction Scale, Short Physical Performance Battery, and SF-36 Physical Functioning.

Findings for Other Outcomes

The task force identified the following as important or limited outcomes: physical function, complications, patient satisfaction, length of stay, discharge to institution, and mortality (in-hospital and 30-day). Pooled analyses of randomized clinical trials did not detect a difference between extended *versus* standard preoperative evaluation in physical function,^{51,52,184,186,188} length of stay,^{47–52,186,188} discharge to institution,^{47,48,185,186} or in-hospital or 30-day mortality.^{47,50,51,185,188} However, evidence from nonrandomized studies suggested a decrease in length of in-hospital stay,^{53,54,56–60,189,190,192,194–196,198,201} 30-day mortality,^{55–60,189–195,200,201} and institutional discharge.^{53,58,59,190,195,198} Evidence from one nonrandomized study suggested no difference in patient satisfaction among patients receiving expanded *versus* standard preoperative evaluation.¹⁹⁷

Complications

Evidence was inconclusive concerning any differences in complications—cardiac arrest,^{49,195} myocardial infarction,^{50,53,55,58,195} pneumonia,^{49,50,53,55–58,192,195} respiratory failure,¹⁹⁵ pulmonary embolism,^{53,55,56,195} and acute kidney injury^{47,51,55,59,192,195}—between patients receiving expanded preoperative evaluation and standard care.

Neuraxial *versus* General Anesthesia

Study and Patient Characteristics

The body of evidence included 37 randomized clinical trials (39 publications) comparing neuraxial to general anesthesia.^{21,62–75,203–226} General anesthesia maintenance included either total intravenous or inhaled agents. Neuraxial anesthesia included spinal, epidural, and combined spinal epidural anesthesia. Demographic race data was reported in only two (5%) randomized clinical trials. Baseline cognitive assessment data for Mini-Mental State Examination was reported in 10 (27%) randomized clinical trials. Most of the randomized clinical trials (54%) involved orthopedic surgery, including hip fracture repair, total hip arthroplasty, and total knee arthroplasty. Supplemental Digital Content 6,

Supporting Evidence (<https://links.lww.com/ALN/D643>), provides additional study and patient characteristic details.

Findings for Other Outcomes

The evidence concerning other important outcomes was limited due to a lack of reporting across randomized clinical trials. Randomized clinical trials assessed the following important/limited outcomes: physical function, patient satisfaction, length of stay, institutional discharge, 30-day mortality, and complications. Physical function was measured using various scales across three randomized clinical trials, and a difference was not detected between neuraxial and general anesthesia in a pooled analysis.^{21,218,222} Although conclusions regarding patient satisfaction,^{204,205,208,212–215,217,220,225} length of hospital stay,^{21,63–68,70,75,205,209,219,225} and institutional discharge²¹ were limited by the very low strength of evidence, pooled results did not suggest an effect of the choice of primary anesthetic technique. Mortality rates, reported as a secondary outcome in most studies, were low among the trials, and the pooled estimate was inconclusive with wide CI.^{21,63–65,67,70} Finally, the results suggested that pneumonia and renal complications might be less frequent after neuraxial anesthesia, but events were uncommon, and the strength of evidence was low. Definitions of renal complications varied, and the inconsistent outcome definitions more broadly across complications generally hinder conclusions.²²⁷

Complications

There was a lack of convincing evidence supporting regional anesthesia to general anesthesia across complications (no strength of evidence greater than low). Pooled results from randomized clinical trials were inconclusive for lower risk of myocardial infarction^{21,63,64,67,74} and cardiac arrest²¹ due to limitations in study-level risk of bias, inconsistency of effects, and imprecision. Stroke was reported in three randomized clinical trials, and no difference was found between the two types of anesthetic techniques.^{21,63,67} Pooled analysis concerning renal complications seems to favor neuraxial anesthesia but was influenced by data from one large randomized clinical trial.^{21,64,67,74} Evidence shows lower relative but not absolute risk for pneumonia with neuraxial anesthesia, but few events were observed.^{21,62–64,67,74,75} Inconclusive evidence was found for pulmonary embolism and limited by study risk of bias and imprecision for low event rates.^{21,64,67,70,74,209}

Total Intravenous Anesthesia *versus* Inhalation Anesthesia

Study and Patient Characteristics

The body of evidence included 51 studies (34 randomized clinical trials,^{77–90,94,228–246} 1 nonrandomized study,²⁴⁷ 13 retrospective cohort studies,^{92,95–97,248–256} and 3 prospective cohort studies^{91,93,257}) evaluating two methods of

maintenance anesthesia: total intravenous and inhaled volatile anesthesia.

Inhaled volatile agents used for maintenance reported among the randomized clinical trials and the nonrandomized studies included sevoflurane, isoflurane, and desflurane. Intravenous agents included propofol, fentanyl, remifentanyl, and sufentanil. Procedures included were gastrointestinal or abdominal (23.5%), mixed (23.5%), cardiac (11.8%), orthopedic (9.8%), thoracic (9.8%), ophthalmologic (3.9%), otolaryngological (3.9%), spine (3.9%), urologic (2.0%), head and neck (2.0%), and vascular (2.0%). Demographic race data were reported in only two (6%) randomized clinical trials and in none of the nonrandomized studies. Baseline cognitive assessment data for Mini-Mental State Examination were reported in 19 (56%) randomized clinical trials and in 3 (17.6%) nonrandomized studies. Supplemental Digital Content 6, Supporting Evidence (<https://links.lww.com/ALN/D643>), provides additional study and patient characteristic details.

Findings for Other Outcomes

Evidence for important and limited outcomes was generally limited. The pooled analyses from randomized clinical trials reporting on length of stay^{77,78,86,89,94,236} and mortality^{78,90,94,246} indicated no difference between total intravenous and inhaled anesthesia agents. However, the pooled results from three randomized clinical trials suggested higher patient satisfaction with total intravenous anesthesia.^{82,231,237} These findings were, however, limited by trial risk of bias and small sample size. The evidence for cardiac, pulmonary, and renal complications was inconclusive. No randomized clinical trials were identified that reported on physical function, and only one nonrandomized study reported on discharge to institution, in which the findings suggested no difference between total intravenous and inhaled agents.

Complications

There was a lack of convincing evidence supporting total intravenous across important complication outcomes. Although a pooled analysis combining randomized clinical trials and nonrandomized studies suggested lower incidence of myocardial infarction in patients administered total intravenous anesthesia, confounding bias was present in all nonrandomized studies.^{90,95–97,250,251} Pooled analysis combining randomized clinical trials and nonrandomized studies also suggests lower respiratory failure with total intravenous compared to inhaled anesthesia.^{77,90,96,97} However, the finding is limited by trial risk of bias. No difference was detected in cardiac arrest,^{77,95} bradycardia,^{82,89,237,243,247} hypotension,^{77,243,247,248} stroke,^{77,96} acute kidney injury,^{77,97,248,250,254,255} pneumonia,^{86,90,94,96,250} or pulmonary edema/congestion.^{95,97} Pooled analysis suggests increased risk of pulmonary embolism with total intravenous anesthesia; however, results were influenced by one large nonrandomized study.^{77,94–97}

Pharmacologic Delirium Prevention

Dexmedetomidine

Study and Patient Characteristics. The body of evidence included 57 randomized clinical trials^{99–143,258–268} and 6 nonrandomized studies^{113,149,269–272} comparing the effects of dexmedetomidine with placebo or no intervention on patient outcomes. An additional eight studies were not included in the analyses because they compared dexmedetomidine to other drugs.

Demographic race data was reported in 56 (79%) randomized clinical trials and in 14 (93%) nonrandomized studies. There was heterogeneity in the dosing and timing of dexmedetomidine administration. Trials administered dexmedetomidine preoperatively, at induction, intraoperatively, postoperatively, or in combinations of times (for example, induction and intraoperatively, or intraoperatively and postoperatively). Loading doses ranged from 0.2 to 4.0 mcg/kg, and maintenance doses ranged from 0.1 to 1.5 mcg · kg⁻¹ · h⁻¹. Supplemental Digital Content 6, Supporting Evidence (<https://links.lww.com/ALN/D643>), provides additional study and patient characteristic details.

Findings for Other Outcomes. Evidence was lacking supporting shorter length of stay^{99,100,102,105,109–111,113–115,117,118,120–123,126,139,261} or mortality^{99,109,110,114,115,117,118,120,121,123,136,269} for dexmedetomidine compared to placebo.

Complications. There was a lack of convincing evidence supporting dexmedetomidine compared with placebo or no intervention across complications. Pooled results from randomized clinical trials were inconclusive for risk of myocardial infarction,^{99,114,121} cardiac arrest,²⁶⁹ stroke,^{99,109,114,118,120,121} and renal complications.^{100,109,117,120,121} Evidence for pneumonia,^{99,120,123} pulmonary congestion,⁹⁹ pulmonary embolism,⁹⁹ and respiratory failure⁹⁹ was inconclusive.

Melatonin or Ramelteon

Studies were included in the systematic review, and analyses were conducted looking at the effects of melatonin or ramelteon compared with placebo or no intervention on patient outcomes; however, no recommendations were made.

Study and Patient Characteristics. The analyses included 20 studies (15 randomized clinical trials,^{145,273–286} 2 nonrandomized studies,^{287,288} 2 before–after design,^{289,290} and 1 retrospective²⁹¹) comparing melatonin/ramelteon to placebo.

Types of surgery included were 30% orthopedic (6 of 20), 30% cardiac (6 of 20), 10% gastrointestinal/abdominal (2 of 20), 10% thoracic (2 of 20), and 20% other (4 of 20). Three studies administered melatonin/ramelteon only preoperatively, 10 studies administered the drug both preoperatively

and postoperatively, and 2 studies administered the drug only postoperatively. Supplemental Digital Content 6, Supporting Evidence (<https://links.lww.com/ALN/D643>), provides additional study and patient characteristic details.

Summary of Evidence. Although a pooled analysis of 13 randomized clinical trials suggests there may be a lower risk of delirium in patients receiving melatonin/ramelteon,^{145,273–275,277–281,283–286} it was limited by potential bias in 2 of the ramelteon studies and high variance across studies.^{284,286}

There was a lack of evidence supporting melatonin/ramelteon across most important outcomes. A single randomized clinical trial evaluated neurocognitive disorder at 30 days or more to 1 yr and suggests there may be a lower risk in patients receiving melatonin/ramelteon compared with patients receiving placebo or no intervention²⁷³; no evidence concerning neurocognitive disorder of less than 30 days was identified. Evidence was inconclusive for complications,^{289,290} length of stay,^{273,276,278,280,285} and mortality.^{273,280,285}

There was a lack of convincing evidence supporting melatonin or ramelteon compared with placebo or no intervention in pneumonia (risk ratio, 0.82; 95% CI, 0.21 to 3.18; very low strength of evidence).^{289,290}

Comment. Interpretation of the evidence for use of melatonin/ramelteon was limited due to different dosages and duration of intervention across randomized clinical trials. In addition, formulations of melatonin were inconsistent. As a result, optimal dosage, formulation, and duration of treatment remain unanswered. A further limitation to making firm recommendations concerning use of melatonin/ramelteon concerns the heterogeneity of patient populations and clinical settings studied.

Perioperative Use of Medications with Potential Central Nervous System Effects. The taskforce considered the impact of medications with potential central nervous system effects (*i.e.*, benzodiazepines, antipsychotics, anticholinergics, ketamine, corticosteroids, gabapentin, or NSAIDs) on risk of delirium. Below, we summarize key characteristics of the studies included as evidence for these medications and present additional information about the findings from studies that are not presented in the main body of guideline document.

Benzodiazepines

Studies evaluating short-acting benzodiazepines included 27 studies (15 randomized clinical trials^{101,134,141,145–147,292–300} and 12 nonrandomized studies^{148–153,301–306}). There was heterogeneity in the dosing and timing of administration.

Ketamine

Studies evaluating ketamine included 20 studies (13 randomized clinical trials,^{137,160,162–164,307–314} 3 prospective

cohorts,^{149,315,316} and 4 retrospective studies^{152,153,317,318}). Types of surgical procedures included 40% orthopedic (8 of 20), 15% cardiac (3 of 20), 15% gastrointestinal/abdominal (3 of 20), 10% various (2 of 20), 10% ophthalmologic (2 of 20), and 1 each of thoracic and spinal.

There was heterogeneity in the dosing and timing of ketamine administration. Trials administered ketamine preoperatively, at induction, intraoperatively, postoperatively, or in combinations of times (for example, induction and intraoperatively, or intraoperatively and postoperatively). Doses ranged from 0.25 mg/kg to 1.0 mg/kg (Supplemental Digital Content 6, Supporting Evidence (<https://links.lww.com/ALN/D643>)).

Antipsychotics

The body of evidence included eight randomized clinical trials^{154–161} and two nonrandomized studies.^{304,319} Medications included haloperidol, risperidone, and olanzapine, or any antipsychotic. There was heterogeneity in the dosing and timing of administration.

Anticholinergics

The body of evidence included one randomized clinical trial comparing the effects of preoperative administration of penhexylidene with placebo.¹⁶⁵ One retrospective study evaluated any anticholinergics *versus* none.¹⁶⁶

Corticosteroids

The body of evidence included 12 randomized clinical trials^{167–172,320–325} and 6 nonrandomized studies.^{152,153,317,326–328} Medications included dexamethasone, methylprednisolone, or any corticosteroid.

Nonsteroidal Anti-inflammatory Drugs

The body of evidence included three randomized clinical trials^{329–331} and three nonrandomized studies^{152,153,332} comparing the effects of NSAIDs with placebo or none. Medications used included celecoxib preoperatively, ketoprofen, and flurbiprofen both pre- and intraoperatively.

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Supplemental Digital Content

Supplemental Digital Content 1, Protocol, <https://links.lww.com/ALN/D638>

Supplemental Digital Content 2, Search Strategy, <https://links.lww.com/ALN/D639>

Supplemental Digital Content 3, PRISMA Flow Chart, <https://links.lww.com/ALN/D640>

Supplemental Digital Content 4, Methodology, <https://links.lww.com/ALN/D641>

Supplemental Digital Content 5, Risk of Bias, <https://links.lww.com/ALN/D642>

Supplemental Digital Content 6, Supporting Evidence, <https://links.lww.com/ALN/D643>

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