

PERIOPERATIVE BRAIN PROTECTION IN MODERN ANESTHESIA: NEUROINFLAMMATION, CEREBRAL AUTOREGULATION, AND STRATEGIES TO PREVENT POSTOPERATIVE NEUROCOGNITIVE DISORDERS

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ABSTRACT

Perioperative neurocognitive disorders threaten functional recovery after surgery, particularly in older adults with cognitive impairment, frailty, or cerebrovascular disease. Their prevention requires a framework that connects surgical inflammation with cerebral perfusion, anesthetic exposure, and the conditions of postoperative recovery. This narrative review examines the biological basis and clinical evidence for perioperative brain protection, with particular attention to neuroinflammation, cerebral autoregulation, and interventions intended to prevent postoperative delirium and subsequent cognitive decline. Experimental studies implicate damage-associated molecular signals, cytokine-mediated blood-brain barrier dysfunction, recruitment of peripheral immune cells, and altered microglial activity in postoperative memory impairment. Human biomarker studies support inflammatory and neuronal-injury associations but have not established a clinically actionable molecular phenotype. Cerebral autoregulation offers a rationale for individualized perfusion management; however, promising cardiac surgical studies have not established a universal blood pressure target or a consistent reduction in longer-term neurocognitive disorders. Trials of electroencephalography-guided anesthesia have produced conflicting results, and major hip-fracture trials have not demonstrated that regional anesthesia alone prevents delirium. Dexmedetomidine has the strongest current pharmacological evidence for reducing postoperative delirium in selected settings, although heterogeneous regimens and cardiovascular adverse effects require careful interpretation. Evidence for preventing persistent postoperative neurocognitive disorder remains substantially less secure. Multicomponent care that identifies baseline vulnerability, supports physiological stability, provides effective analgesia, preserves sleep and mobility, and detects delirium systematically remains central to practice. Future studies should combine mechanistic phenotyping with standardized cognitive outcomes, rigorous follow-up, and implementation assessment. Contemporary perioperative brain protection is best understood as individualized, coordinated care across the surgical pathway, with interventions judged by patient-centered recovery rather than physiological or biomarker changes alone.

KEYWORDS: perioperative neurocognitive disorders; postoperative delirium; neuroinflammation; cerebral autoregulation; brain protection; anesthesia; dexmedetomidine; cognitive recovery.

1 INTRODUCTION

The success of anesthesia can no longer be assessed solely by survival, cardiovascular stability, or uncomplicated emergence. For many older adults, the outcome that matters most is returning to independent living with preserved memory, attention, and the ability to manage everyday activities. Cognitive deterioration after surgery can undermine these goals even when the procedure achieves its technical objective. The contemporary term perioperative neurocognitive disorders encompasses several conditions that differ in presentation, timing, and diagnostic requirements [1]. Recognizing those differences is essential because an

intervention that reduces acute delirium cannot automatically be assumed to prevent cognitive impairment months later.

Perioperative brain health has therefore become a substantive responsibility of anesthesiology and perioperative medicine. Expert recommendations emphasize preoperative cognitive assessment, communication about neurocognitive risk, appropriate intraoperative management, and follow-up when recovery is incomplete. These responsibilities extend beyond choosing an anesthetic agent. They require collaboration with surgeons, nurses, geriatricians, rehabilitation professionals, patients, and families, because relevant exposures accumulate before surgery and continue after discharge. The 2024 European guideline similarly places delirium prevention within a comprehensive perioperative pathway, while acknowledging that the evidence supporting particular interventions varies considerably [2, 3].

The problem is clinically established, although estimates of its frequency depend heavily on what is measured. In the landmark ISPOCD1 study, postoperative cognitive dysfunction was identified in 25.8% of older patients one week after major noncardiac surgery and in 9.9% at three months. These findings arose from a research definition based on neuropsychological testing and should not be treated as current diagnostic rates for every surgical population. Nevertheless, they demonstrated that postoperative cognitive change could persist beyond the period ordinarily attributed to residual anesthetic effects. Subsequent terminology has improved conceptual clarity, but variation in cognitive instruments, thresholds, assessment intervals, and patient selection continues to complicate comparisons [1, 4].

Delirium is especially consequential because it identifies patients whose recovery may remain impaired after the acute episode resolves. In a prospective cardiac surgical cohort, patients who developed delirium experienced a more pronounced early cognitive decline and a slower recovery trajectory. In the Successful Aging after Elective Surgery cohort, postoperative delirium was associated with greater long-term cognitive decline over three years. Neither observation proves that delirium independently causes neurodegeneration: baseline disease, vascular injury, and shared susceptibility may contribute to both outcomes. The findings do, however, challenge the assumption that postoperative confusion is a transient inconvenience without lasting implications [5, 6].

Two interacting biological domains provide a useful foundation for prevention. The first is neuroinflammation: peripheral surgical injury can activate immune pathways that influence the blood–brain barrier, glial function, and neuronal communication. The second is cerebrovascular regulation: adequate arterial pressure does not necessarily ensure appropriate cerebral blood flow, particularly when vascular reserve, carbon dioxide responsiveness, or autoregulatory function is abnormal. These domains intersect at the neurovascular unit, where endothelial cells, pericytes, astrocytes, microglia, and neurons participate in maintaining the cerebral environment. Their interaction explains why a single intervention may improve one measurable exposure without altering the overall clinical outcome.

This review critically examines perioperative brain protection through those complementary perspectives. It evaluates the distinction between mechanistic plausibility and clinical effectiveness, interprets major randomized trials in their procedural context, and develops a practical approach to prevention across the surgical pathway. The principal focus is adult perioperative care, particularly older adults undergoing major noncardiac and cardiac surgery. Pediatric anesthetic neurodevelopment, neurosurgical disease-specific neuroprotection, and acute management of established stroke are outside the review's primary scope.

2 Review Approach and Clinical Framework

2.1 Narrative approach and interpretation of evidence

This article is an evidence-informed narrative review. Targeted searches for PubMed-indexed articles and primary journal publications were completed on 17 October 2026 using combinations of perioperative neurocognitive disorders, postoperative delirium, postoperative cognitive dysfunction, neuroinflammation, blood–brain barrier, cerebral autoregulation, blood pressure, electroencephalography, cerebral oximetry, anesthetic technique, dexmedetomidine, and multicomponent prevention. Landmark studies were considered alongside contemporary trials, systematic reviews, and peer-reviewed consensus documents. Reference lists and related publications were used to identify influential mechanistic and clinical studies. Bibliographic details were checked against PubMed records or journal publications; full texts were consulted where accessible.

Selection prioritized studies that clarified terminology, established plausible biological pathways, tested a clinical intervention, or materially changed interpretation of an established practice. Animal experiments were used to discuss biological mechanisms and were distinguished from human observational research and randomized trials. Clinical conclusions were interpreted according to study design, population, treatment contrast, outcome ascertainment, follow-up, and adverse effects. No pooled analysis, formal risk-of-bias scoring, or comprehensive systematic search was undertaken. Consequently, the review provides a critical synthesis rather than an exhaustive inventory, a registered systematic review, or a formal evidence-grading exercise.

2.2 Definitions and the importance of outcome selection

The 2018 consensus nomenclature aligns perioperative cognitive diagnoses with established neurocognitive terminology. Delayed neurocognitive recovery describes decline within 30 days, while postoperative mild or major neurocognitive disorder applies from 30 days to 12 months. The major category involves interference with independence. The postoperative descriptor indicates timing rather than proven anesthetic causation, and is

not retained beyond 12 months [1]. Postoperative delirium is distinguished by acute, fluctuating disturbances of attention and awareness, accompanied by additional cognitive change. These categories require different assessments and should not be combined into an undifferentiated postoperative cognitive endpoint [7].

The clinical distinctions and their implications for research are summarized in Table 1. A low screening score alone does not establish postoperative neurocognitive disorder. Interpretation requires an appropriate baseline, evidence of change, consideration of patient or informant concern, functional assessment, and exclusion of alternative explanations. Likewise, delirium cannot be inferred from a decline in a global cognitive score. Its fluctuating attentional features require specific assessment, and residual sedation, pain, sleep deprivation, language barriers, and sensory impairment can complicate examination. Consistent definitions are particularly important when comparing older studies labeled postoperative cognitive dysfunction with contemporary diagnostic frameworks.

Table 1. Clinical categories within the perioperative neurocognitive framework

Category	Timing and defining feature	Assessment implication
Preexisting neurocognitive disorder	Cognitive impairment established before surgery	Document cognition and everyday function before interpreting postoperative change.
Postoperative delirium	Acute, fluctuating inattention and altered awareness; usually early after surgery	Use a validated delirium assessment repeatedly and investigate precipitants.
Delayed neurocognitive recovery	Cognitive decline identified within 30 days	Compare with baseline; account for ongoing illness, medication effects, and recovery.
Postoperative mild neurocognitive disorder	Decline from 30 days to 12 months with independence substantially preserved	Combine objective testing with reported concern and functional assessment.
Postoperative major neurocognitive disorder	Decline from 30 days to 12 months that interferes with independence	Establish functional consequences and investigate competing neurological causes.

Clinical framework informed by the nomenclature recommendations and diagnostic review [1, 7]. Timing alone is insufficient for diagnosis; residual drug effects require separate consideration.

An additional distinction concerns cerebrovascular injury. In NeuroVISION, postoperative magnetic resonance imaging identified covert stroke in 7% of 1,114 older adults undergoing elective inpatient noncardiac surgery. Covert stroke was associated with a higher risk of cognitive decline at one year. This finding indicates that some postoperative cognitive deterioration may involve discrete ischemic injury despite the absence of recognized focal symptoms. Delirium, covert stroke, and postoperative neurocognitive disorder are therefore overlapping clinical concerns rather than interchangeable labels, and studies targeting one outcome may leave another pathway unaffected [8].

2.3 Baseline vulnerability and reliable clinical assessment

Risk is determined by the interaction between an individual's baseline reserve and the burden of perioperative insults. Preexisting cognitive impairment, prior delirium, functional dependency, frailty, sensory impairment, and cerebrovascular disease should influence the intensity of preventive care. Cognitive screening adds information that may not be apparent from routine conversation or educational attainment. Culley and colleagues showed that poor performance on a brief preoperative cognitive screen was associated with adverse postoperative outcomes in older orthopedic patients. Screening should trigger further assessment and tailored support rather than be treated as an autonomous diagnosis or a reason to withhold beneficial surgery [9].

Delirium surveillance requires an explicit assessment process. The Confusion Assessment Method operationalized acute onset or fluctuation, inattention, disorganized thinking, and altered consciousness into a practical diagnostic algorithm. The 4AT provides another rapid approach for detecting possible delirium in routine care. Neither tool eliminates the need for clinical evaluation, and a normal assessment at one time point cannot exclude a fluctuating disorder. Staff must recognize hypoactive presentations, in which quiet withdrawal, slowed responses, or reduced engagement may be mistaken for fatigue or satisfactory postoperative rest [10, 11].

Baseline documentation is also essential for discharge planning. A family member may identify a meaningful loss of concentration or medication-management ability despite a score that remains within a conventional screening range. Conversely, a low score obtained during severe pain or immediately after sedation may overestimate persistent impairment. A useful assessment pathway records baseline cognition, functional independence, sensory needs, and the person most able to describe changes. Postoperative reassessment should then address attention, arousal, function, and recovery over time rather than rely on an isolated test result. This approach improves the interpretability of both clinical decisions and research outcomes.

3 Neuroinflammation and the Vulnerable Brain

3.1 Surgical injury and peripheral immune signaling

Surgery generates an inflammatory response even in the absence of infection. Tissue damage releases endogenous danger signals, activates innate immune pathways, and stimulates cytokine production. In experimental surgical models, tumor necrosis factor signaling can initiate a downstream inflammatory cascade associated with hippocampal inflammation and memory impairment. Terrando and colleagues demonstrated that interrupting this pathway attenuated postoperative cognitive changes in mice, providing intervention-based evidence that inflammatory signaling can participate causally in the experimental phenotype. The finding establishes a biological mechanism in a defined model; it does not establish that routine cytokine inhibition prevents clinical delirium [12].

High-mobility group box 1 protein provides an upstream link between tissue injury and immune activation. Vacas and colleagues implicated this damage-associated molecular signal in recruitment of bone marrow-derived macrophages and postoperative memory decline. Complementary experiments showed that depletion of these macrophages reduced hippocampal inflammation and memory dysfunction after tibial fracture. Together, these studies suggest that peripheral immune-cell trafficking can connect an extracranial surgical insult with altered brain function. Their translational importance lies in identifying potential targets and temporal sequences, although experimental depletion or blockade is not equivalent to a safe perioperative treatment for patients [13, 14].

Inflammatory signaling must also be understood as a component of normal tissue repair. An appropriate response helps contain injury and coordinate recovery; pathological consequences may arise from excessive activation, prolonged signaling, or inadequate resolution. Strategies that broadly suppress inflammation could therefore interfere with beneficial processes. The more useful therapeutic question is whether a susceptible subgroup has a specific, modifiable failure of inflammatory regulation. Answering that question requires biomarkers that distinguish risk, mechanism, and treatment responsiveness, together with clinical outcomes that demonstrate benefit rather than a change in circulating cytokine concentrations alone.

3.2 Blood–brain barrier dysfunction and communication with the brain

The blood–brain barrier is an active interface rather than an impermeable partition. Endothelial integrity, tight junctions, pericyte support, astrocytic signaling, and transport mechanisms influence how systemic physiological changes affect neural tissue. In a mouse surgical model, peripheral inflammatory activation disrupted barrier integrity and facilitated macrophage migration into the hippocampus. Activation of a cholinergic inflammation-resolving pathway reduced these changes and prevented memory impairment. These experiments linked immune activation, barrier dysfunction, cellular recruitment, and behavioral change within the same model, supporting a coherent mechanism rather than a simple association between blood cytokines and cognition [15].

Several routes may contribute to immune-to-brain communication, including endothelial signaling, altered barrier permeability, immune-cell recruitment, and neural pathways. The relative contribution of each route probably differs between procedures and patients. Barrier dysfunction may interact with vascular disease, metabolic stress, and preexisting neurodegeneration, but the presence and magnitude of those interactions in an individual patient cannot currently be inferred from routine perioperative measurements. The mechanistic literature therefore supports a network of potential pathways rather than a single obligatory sequence that explains every episode of postoperative confusion [16].

Human investigations provide an important, more cautious bridge to these experiments. Hirsch and colleagues documented postoperative changes in plasma and cerebrospinal fluid inflammatory mediators after orthopedic surgery. Such findings demonstrate that a peripheral operation can be accompanied by changes in the central inflammatory environment. However, small samples, variable sampling schedules, and imperfect correspondence between biochemical changes and clinical syndromes restrict causal interpretation. A cytokine increase may indicate a response to surgery without identifying the patients who will develop delirium or explaining whether the marker is a driver, a compensatory response, or a correlate of another process [17].

3.3 Microglial responses and disruption of cognitive networks

Microglia participate in immune surveillance, synaptic maintenance, and responses to injury. Their activity cannot be reduced to a permanently harmful state, nor does every increase in an inflammatory marker imply neuronal destruction. In a mouse model, perioperative depletion of microglia using colony-stimulating factor 1 receptor inhibition attenuated hippocampal inflammatory changes and postoperative memory impairment. This intervention supports a functional contribution of microglia to the experimental phenotype. It also illustrates a translational challenge: a manipulation that demonstrates biological necessity in a model may be unsuitable as a preventive intervention in patients [18].

The cognitive expression of inflammatory disturbance may involve altered synaptic plasticity, neurotransmission, network coordination, and metabolic support. Acute attentional failure is likely to reflect distributed network dysfunction rather than an isolated hippocampal lesion, whereas many animal studies emphasize hippocampal-dependent memory tasks. This mismatch matters. Fear conditioning or spatial-memory performance after surgery cannot reproduce the fluctuating attention, altered arousal, medical complexity, and functional consequences that define human delirium. Mechanistic findings should therefore inform hypotheses

about clinical syndromes without being presented as direct proof that the same pathway dominates all perioperative neurocognitive disorders [16, 18].

Human inflammatory profiles also show temporal complexity. In older patients undergoing major elective surgery, Vasunilashorn and colleagues identified associations between perioperative cytokine patterns and delirium. The value of these observations is their integration with a carefully characterized surgical cohort and repeated assessment. Nevertheless, association does not supply a validated diagnostic threshold or identify a drug-responsive phenotype. Differences in sampling time, underlying disease, surgical burden, and delirium ascertainment can alter the apparent relationship. Molecular studies become more clinically informative when they specify whether a marker predicts vulnerability before surgery, tracks the acute syndrome, or relates to recovery afterward [19].

3.4 Neuronal injury and limits of biomarker interpretation

Neurofilament light offers a complementary perspective because it reflects neuroaxonal injury rather than inflammation alone. Casey and colleagues found that postoperative delirium was associated with a greater perioperative increase in plasma neurofilament light in a surgical biomarker cohort. The association provides biological plausibility for a relationship between acute delirium and neuronal injury. It does not resolve whether injury precedes delirium, results from processes producing delirium, or accompanies a shared underlying vulnerability. Baseline neurodegeneration, vascular disease, renal function, and sampling interval can complicate interpretation of a circulating biomarker [20].

At present, no routinely available inflammatory or neuronal-injury assay can replace clinical delirium assessment or establish that an asymptomatic postoperative patient needs a specific neuroprotective drug. Biomarker changes should also not be treated as validated substitutes for cognition or independent function. A treatment may suppress a cytokine response while leaving the patient's recovery unchanged; another may improve attention without materially altering the measured marker. Trials need to demonstrate both target engagement and clinically relevant benefit before a biomarker-defined treatment pathway can be recommended. The proposed interaction between immune activation, vascular stress, and cognitive vulnerability is illustrated in Figure 1. The diagram intentionally treats these processes as converging influences. It distinguishes an explanatory model, supported to different degrees by experimental and observational evidence, from a diagnostic algorithm. This distinction prevents mechanistic detail from conveying more certainty than the clinical evidence permits.

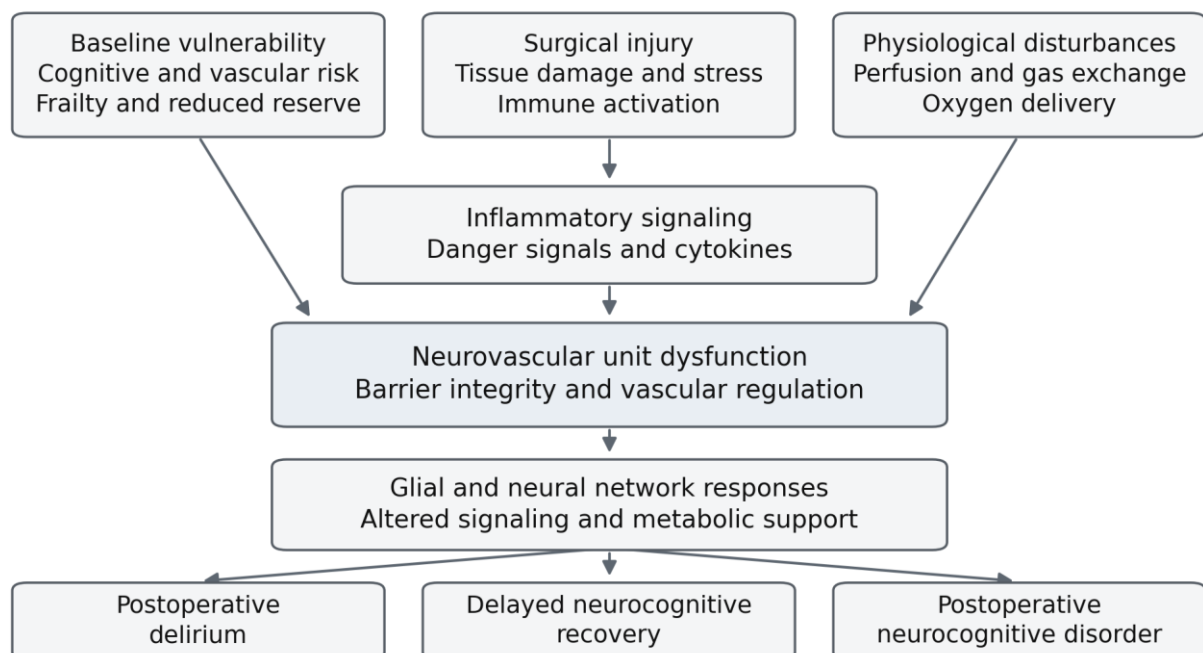


Figure 1. Converging immune and vascular pathways in perioperative cognitive dysfunction.

Inflammation, baseline vulnerability, and disturbed oxygen delivery may converge on neurovascular and neural pathways. The schematic combines experimental mechanisms and human associations; arrows do not establish causality in every patient or equivalence between the three clinical outcomes [12, 13, 14, 15, 17, 18, 19, 20].

4 Cerebral Autoregulation and Perioperative Perfusion

4.1 Physiological principles and the limits of fixed pressure thresholds

Cerebral blood flow depends on perfusion pressure, vascular resistance, metabolic demand, arterial gases, and neurovascular signaling. Autoregulation describes the cerebrovascular response that buffers changes in perfusion pressure; carbon dioxide reactivity and neurovascular coupling describe related but distinct regulatory functions. These mechanisms interact, and none should be interpreted independently of the patient's

physiological state. Cerebral perfusion pressure is commonly approximated by mean arterial pressure minus intracranial pressure when intracranial pressure exceeds downstream venous pressure. In most non-neurosurgical patients intracranial pressure is not measured, making systemic arterial pressure a practical but incomplete indicator of cerebral perfusion [21].

The familiar depiction of a broad, flat autoregulatory plateau can be misleading when treated as a universal bedside rule. Human cerebral blood flow is not guaranteed to remain constant across a fixed mean arterial pressure range. Responses depend on the magnitude and speed of a pressure change, carbon dioxide tension, vascular health, and other regulatory influences. Consequently, a pressure tolerated by one patient may not be appropriate for another. Chronic hypertension, aging, and cerebrovascular disease should prompt consideration of altered vascular reserve, although they do not allow a clinician to calculate an individual's lower autoregulatory limit from a diagnostic label alone [21, 22].

Autoregulation is also dynamic during surgery. Anesthetic agents, changes in ventilation, hemodilution, cardiopulmonary bypass, temperature, and surgical positioning can modify the relationship between pressure and measured cerebral signals. A pressure estimate derived under one set of conditions may therefore require reassessment after a major physiological transition. The clinically relevant question is whether monitoring can identify a useful treatment target and whether maintaining that target improves outcomes. Demonstrating an autoregulatory correlation or estimating an optimal pressure is an intermediate step, rather than evidence of successful neuroprotection.

4.2 Measuring autoregulation and interpreting cerebral oximetry

Transcranial Doppler measures cerebral arterial flow velocity, while near-infrared spectroscopy estimates regional cerebral oxygen saturation. Correlation-based approaches assess how slow changes in these signals relate to arterial pressure. When flow is effectively buffered, pressure and cerebral flow-related signals may show limited correlation; increasingly pressure-passive behavior can produce a more positive relationship. Brady and colleagues demonstrated the feasibility of continuous near-infrared spectroscopy-based autoregulation monitoring during cardiopulmonary bypass and compared it with transcranial Doppler assessment. The work supported clinical feasibility, although the methods do not measure identical physiological quantities [23].

Each modality has limitations. Doppler velocity is an imperfect surrogate for flow when arterial diameter changes, and adequate acoustic windows or stable probe positioning may be difficult to maintain. Near-infrared spectroscopy samples a limited superficial region and is influenced by hemoglobin concentration, arterial oxygenation, venous blood distribution, extracranial tissue, sensor characteristics, and the device algorithm. An isolated low saturation therefore does not identify a unique cause. Signal quality and the broader physiological context must be reviewed before increasing pressure, oxygen concentration, or cardiac output in response [23, 24].

Cerebral oximetry nevertheless provides a potentially useful warning when interpreted as part of a structured assessment. A substantial change may prompt review of ventilation, oxygenation, hemoglobin, perfusion, head position, venous drainage, and surgical events. Correcting an evident abnormality is physiologically sensible, but the ability to normalize a saturation value should not be equated with preventing delirium or long-term cognitive decline. The Cochrane assessment of perioperative near-infrared spectroscopy found insufficient certainty to establish consistent patient-important neurological benefit. Differences in patient populations, devices, intervention thresholds, and treatment algorithms remain central to interpretation [24].

4.3 Clinical trials of individualized perfusion management

The most direct supportive evidence for autoregulation-guided pressure management comes from cardiac surgery. In a nested randomized study of 199 evaluable older patients, delirium occurred in 38% of patients assigned to a cardiopulmonary bypass pressure strategy guided by the individual lower limit of autoregulation, compared with 53% receiving usual care, after excluding patients with coma. This result provides a clinically relevant proof of concept. Its interpretation requires attention to the selected high-risk population, single-center setting, nested design, and the fact that the intervention specifically targeted bypass perfusion rather than all phases of perioperative care [25].

The parent randomized trial enrolled 460 patients and evaluated a broader composite of clinical stroke, new magnetic resonance imaging-detected ischemic injury, or cognitive decline. Autoregulation-guided management did not significantly reduce that primary composite outcome, although clinically detected delirium and a memory measure favored the intervention. Complete data for all components were available in a smaller subset. The nested delirium analysis and parent trial therefore provide related findings from overlapping participants and must not be counted as independent replications. Together, they support further investigation while limiting claims of established prevention of global neurological injury [26].

The evidence from noncardiac surgery further cautions against equating higher pressure with better cognitive protection. In the 2,603-patient cogPOISE-3 substudy, a hypotension-avoidance strategy incorporating an intraoperative mean arterial pressure target of at least 80 mmHg did not reduce delirium compared with a hypertension-avoidance strategy using a target of at least 60 mmHg. Delirium occurred in 7.3% and 7.0%, respectively. There was also no demonstrated benefit for the prespecified one-year cognitive outcome. Follow-up cognitive testing was available in only 701 patients, and the intervention also involved perioperative

antihypertensive medication management. The trial tested two management strategies rather than two isolated pressure values [27].

Individualized pressure management can still improve other perioperative outcomes. INPRESS found less postoperative organ dysfunction with a strategy maintaining systolic pressure close to the patient's reference value in high-risk major surgery. That result supports the broader importance of hemodynamic management, but its composite endpoint should not be represented as proof of prevention of postoperative neurocognitive disorder. Likewise, the established associations between hypotension and myocardial or renal injury justify prompt assessment and treatment without establishing a single cerebral threshold applicable to every patient [28, 29].

4.4 Integrating pressure with oxygen delivery and surgical context

Blood pressure is only one determinant of oxygen delivery. An apparently satisfactory arterial pressure may coexist with low cardiac output, substantial anemia, hypoxemia, or impaired regional perfusion. Conversely, treating every transient pressure decline with vasoconstriction without assessing its cause may fail to address reduced flow or inadequate circulating volume. A practical approach considers the duration and magnitude of the abnormality, recent anesthetic changes, bleeding, cardiac function, ventilation, and the patient's baseline vascular disease. The response should be directed to the identified physiological problem, with reassessment after treatment.

Ventilation deserves particular attention because carbon dioxide strongly influences cerebral vascular tone. Unnecessary hypocapnia may reduce cerebral blood flow, while marked hypercapnia can create other physiological difficulties and cannot be prescribed as a general cognitive-protection strategy. Normocapnia is a reasonable starting principle for most patients, adjusted when the clinical situation requires otherwise. Adequate oxygenation and avoidance of major temperature or metabolic disturbances are similarly foundational, but supraphysiological oxygen administration, aggressive glucose normalization, or induced hypothermia have not been established as routine methods to prevent postoperative neurocognitive disorders in general surgical care [22, 30].

The most defensible interpretation of autoregulation evidence is therefore selective and contextual. Patients undergoing cardiopulmonary bypass or procedures with substantial perfusion risk may be appropriate candidates for advanced monitoring where expertise and a defined response algorithm exist. Routine noncardiac practice should emphasize reliable blood pressure measurement, timely recognition of sustained hypotension, assessment of oxygen delivery, and individualized treatment. Wider adoption of autoregulation-guided care requires reproducible monitoring, transparent handling of uninterpretable data, and multicenter trials demonstrating cognitive or functional benefit.

5 Strategies to Prevent Postoperative Neurocognitive Disorders

5.1 Preoperative preparation and shared planning

Prevention begins by identifying the patients most likely to benefit from additional support. A brief cognitive assessment, delirium history, review of functional independence, and evaluation of sensory needs establish a useful baseline. Medication reconciliation should consider anticholinergic burden, sedatives, and potential withdrawal syndromes. Correctable contributors such as dehydration, infection, uncontrolled pain, malnutrition, or sleep disturbance should be addressed when feasible. The American Geriatrics Society guideline and the perioperative quality consensus support a multidisciplinary approach rather than a preventive prescription based solely on chronological age. The 2025 American Society of Anesthesiologists advisory conditionally supports expanded preoperative evaluation, including cognitive and frailty assessment, with multidisciplinary changes in care when impairment is identified [30, 31, 32].

Risk communication should be specific enough to guide preparation. Patients and families should understand that acute fluctuating confusion can occur, that baseline cognitive problems increase concern, and that persistent changes warrant reassessment. A practical plan can identify who will provide collateral history, bring hearing aids and glasses, support orientation, and assist with medications after discharge. Such planning also supports interpretation of postoperative symptoms: recognizing a new change requires knowing the person's usual function. Preventive discussions should be integrated with the anticipated benefits of surgery and the patient's goals for recovery.

Cognitive prehabilitation is promising but should be presented with appropriate restraint. In the Neurobics randomized trial, delirium occurred in 14.4% of the intervention group and 23.0% of controls, but the primary intention-to-treat comparison did not reach conventional statistical significance. A post hoc analysis excluding patients who did no cognitive exercise favored the intervention. This pattern supports further research into adherence, activity selection, and feasible training duration; it does not establish a universal cognitive exercise prescription. The exclusion of patients with preexisting cognitive dysfunction also limits direct extrapolation to the group with greatest baseline vulnerability [33].

5.2 Anesthetic depth and electroencephalographic monitoring

Excessive anesthetic exposure is a plausible modifiable contributor to disturbed recovery, and electroencephalography can reveal cortical suppression that is not evident from hemodynamics. An early randomized study by Chan and colleagues reported less delirium and less cognitive dysfunction at three months with bispectral index guidance. The treatment also reduced anesthetic exposure, offering a plausible clinical mechanism. However, evidence from a successful monitoring strategy cannot be interpreted independently of

the population, the comparator, or the care delivered alongside monitoring. Demonstrating a favorable outcome in one trial does not establish that the same effect will occur when the intervention is added to a different contemporary care pathway [34].

Subsequent studies have not produced a uniform result. ENGAGES randomized 1,232 older surgical patients and found that an electroencephalography-guided strategy reduced anesthetic concentration and suppression exposure without reducing delirium; the observed rates were 26.0% with guidance and 23.0% with usual care. ENGAGES-Canada similarly found virtually identical delirium incidence after cardiac surgery, 18.15% and 18.10%, despite less volatile anesthetic exposure and less electroencephalographic suppression in the guided group. These trials demonstrate that improving the targeted electroencephalographic exposure alone may be insufficient to change delirium risk [35, 36].

In contrast, the BALANCED delirium substudy found less delirium when anesthesia was targeted to a bispectral index of 50 rather than 35, with rates of 19% and 28%. The comparison involved deliberately different depth targets, whereas ENGAGES evaluated a guidance strategy against contemporary usual care. Treatment contrast, patient characteristics, surgery, cointerventions, and baseline vulnerability can therefore explain part of the apparent inconsistency. The finding supports avoiding unnecessarily deep anesthesia, but it does not validate a single processed index target as a universal cognitive-protection threshold or establish that suppression is always a causal mediator [37].

Sedation during regional anesthesia requires the same attention to dose and patient response. STRIDE found no significant overall delirium reduction with lighter rather than heavier propofol sedation during hip-fracture repair, although a prespecified analysis suggested an interaction with comorbidity. Such subgroup findings require cautious interpretation. In practice, raw electroencephalographic patterns, suppression, age-related sensitivity, clinical requirements, and awareness prevention should be considered together. Monitoring can support individualized dosing and detect unexpected responses; claims that it reliably prevents delirium in all older adults exceed the available randomized evidence [38].

5.3 Anesthetic technique and effective analgesia

Regional anesthesia should not be selected solely on the assumption that avoiding general anesthesia prevents postoperative delirium. In REGAIN, involving 1,600 patients undergoing hip-fracture surgery, delirium occurred in 20.5% of assessed patients assigned to spinal anesthesia and 19.7% assigned to general anesthesia. RAGA also found no significant difference between regional anesthesia without sedation and general anesthesia, with delirium rates of 6.2% and 5.1%. The differences in absolute incidence between the trials illustrate the effects of population, care setting, and ascertainment. Together, they do not support regional anesthesia as a universally superior delirium-prevention strategy [39, 40].

Anesthetic agent selection may nevertheless matter within particular settings. A multicenter trial in older adults undergoing major cancer surgery found delirium in 8.4% of patients receiving propofol-based anesthesia and 12.4% receiving sevoflurane-based anesthesia. Much of the difference occurred early after surgery, and the trial did not establish a corresponding improvement in longer-term cognition. Its findings can inform individualized decisions in comparable patients, but they should not be generalized into a claim that propofol prevents postoperative neurocognitive disorder across surgical specialties. Consistent depth, perfusion, analgesia, and postoperative care remain important regardless of the maintenance agent [41].

Pain management involves competing risks. Severe pain can worsen sleep, mobility, stress, and attention, while excessive opioid or sedative exposure can impair arousal and ventilation. The objective is effective analgesia with the least burdensome regimen appropriate to the procedure and patient, using regional techniques and nonopioid medications when suitable. In a large trial of major thoracic and abdominal surgery, combined epidural-general anesthesia with postoperative epidural analgesia reduced delirium compared with general anesthesia and intravenous analgesia, but increased hypotension. The intervention combined anesthetic and analgesic components, so its effect cannot be attributed to neuraxial anesthesia alone [42].

5.4 Dexmedetomidine and the interpretation of pharmacological prevention

Dexmedetomidine has attracted particular interest because its sedative and sympatholytic effects can reduce exposure to other agents and may influence sleep and inflammatory signaling. A placebo-controlled trial of 700 older patients admitted to intensive care after noncardiac surgery found substantially less delirium with a low-dose postoperative infusion. In cardiac surgical patients requiring postoperative sedation, Djaiani and colleagues found less delirium with dexmedetomidine than with propofol. These studies support a preventive role in defined populations, while also showing that timing, comparator, dose, and the surrounding care pathway are integral to the intervention [43, 44].

Other trials have been neutral. Deiner and colleagues found no reduction in delirium with an intraoperative dexmedetomidine infusion continued briefly into recovery after major elective noncardiac surgery. DECADE likewise did not show a delirium benefit from a perioperative regimen in cardiac surgery. These findings do not negate every positive trial, but they prevent the drug from being treated as an intervention with a constant effect independent of context. A sedative substitution strategy after surgery and an additional infusion beginning before incision may modify different exposures and produce different benefit-harm balances [45, 46].

A 2026 network meta-analysis including 158 randomized trials and 41,084 participants provides a more current synthesis. Dexmedetomidine reduced the odds of postoperative delirium, including after exclusion of trials at high risk of bias, with an odds ratio of 0.46 and a 95% credible interval of 0.36–0.57. Hypotension and

bradycardia were more frequent. Most interventions did not improve longer-term cognition, mortality, quality of life, or length of stay. Accordingly, delirium prevention is a reasonable basis for selective consideration of dexmedetomidine, but evidence of reduced delirium should not be described as established prevention of persistent postoperative neurocognitive disorder [47].

Guideline interpretation has evolved alongside the evidence. The 2024 European guideline did not endorse routine pharmacological prophylaxis and emphasized balancing dexmedetomidine's potential benefit against bradycardia and hypotension. The 2025 American Society of Anesthesiologists advisory conditionally supports considering dexmedetomidine in older inpatients, while acknowledging cardiovascular adverse effects and uncertainty about the most appropriate regimen. These positions reflect different evidence reviews and recommendation frameworks rather than a universally accepted dosing protocol [3, 32].

Clinical decisions should weigh anticipated delirium risk against cardiovascular reserve, conduction disease, concurrent medication effects, and the availability of appropriate monitoring. Regimens should follow a defined local protocol and an individualized indication, rather than be transferred uncritically from a trial with different patients or timing. Dexmedetomidine should supplement a comprehensive prevention pathway. Its use does not replace pain assessment, evaluation of physiological instability, mobilization, orientation, or investigation of a new neurological change.

5.5 Medication stewardship and interventions with uncertain benefit

Avoidance of unnecessary centrally acting medication remains a sensible component of care, particularly when several agents impair attention or arousal. However, the strength of evidence depends on the setting. In the large B-Free cluster randomized crossover trial, an institutional policy restricting intraoperative benzodiazepines during cardiac surgery did not significantly reduce delirium in the intention-to-treat analysis. The finding cautions against attributing a large preventive effect to benzodiazepine restriction alone. It does not justify indiscriminate sedative use, and it does not address every indication, dose, duration, or postoperative exposure. Established dependence and withdrawal risk also require a separate clinical plan [48].

Ketamine illustrates why mechanistic plausibility and opioid-sparing effects cannot establish cognitive benefit. The PODCAST trial did not demonstrate prevention of postoperative delirium with a single intraoperative subanesthetic dose and found more hallucinations and nightmares. A drug may still have an appropriate analgesic indication, but that indication should be distinguished from prophylaxis against delirium. Similarly, antipsychotics should not be introduced routinely as if they were established agents for preserving postoperative cognition [31, 49].

The 2026 pharmacological synthesis identified possible benefits for corticosteroids, melatonin receptor agonists, parecoxib, intranasal insulin, and olanzapine, but the certainty and applicability of these signals varied, and some depended on small or isolated evidence networks. These findings support confirmatory trials with adequate adverse-event assessment. They do not establish a standard preventive combination. Experimental approaches directed at inflammatory signaling or immune resolution likewise require human evidence demonstrating that the benefits exceed risks to hemodynamics, infection control, tissue repair, and overall recovery [15, 47].

The principal randomized evidence and its practical limitations are compared in Table 2. The table presents study-specific results rather than a pooled estimate. Absolute event rates should not be compared across rows as though the populations, assessment methods, and underlying care were equivalent.

Table 2. Selected randomized evidence informing perioperative brain protection

Intervention and setting	Principal finding	Interpretation
Autoregulation-guided bypass pressure, nested cardiac trial [25]	Delirium 38% versus 53% with usual care	Promising selected-population finding; overlaps the parent trial.
Autoregulation-guided pressure, parent cardiac trial [26]	Primary neurological composite not reduced	Delirium signal does not establish broad neurological protection.
cogPOISE-3 blood pressure strategies [27]	Delirium 7.3% versus 7.0%	Higher-target strategy did not improve neurocognitive outcomes.
ENGAGES electroencephalographic guidance [35]	Delirium 26.0% versus 23.0%	Less suppression did not translate into less delirium.
ENGAGES-Canada guidance after cardiac surgery [36]	Delirium 18.15% versus 18.10%	No delirium benefit despite physiological treatment separation.
BALANCED depth substudy [37]	Delirium 19% at BIS 50 versus 28% at BIS 35	Avoidance of deliberately deeper anesthesia benefited this population.

Intervention and setting	Principal finding	Interpretation
REGAIN spinal versus general anesthesia [39]	Delirium 20.5% versus 19.7%	Spinal anesthesia was not superior for this outcome.
Propofol versus sevoflurane in cancer surgery [41]	Delirium 8.4% versus 12.4%	Setting-specific benefit; persistent cognitive protection unproven.
Neurobics cognitive prehabilitation [33]	Delirium 14.4% versus 23.0%; primary P = .08	Promising signal; primary analysis was not statistically significant.
Modified Hospital Elder Life Program [50]	Delirium 6.6% versus 15.1%	Supports a structured postoperative care intervention.

BIS, bispectral index. Percentages use each publication's evaluable outcome population. The Brown and Hogue reports include overlapping participants. Individual trial results do not provide a universal expected treatment effect.

5.6 Multicomponent prevention and postoperative surveillance

Multicomponent care directly addresses the fact that delirium usually emerges from several interacting vulnerabilities. The original Hospital Elder Life Program-based intervention targeted cognitive impairment, sleep deprivation, immobility, visual impairment, hearing impairment, and dehydration in hospitalized older patients. This foundational study was a controlled, matched intervention rather than a conventional individually randomized surgical trial. Subsequent meta-analysis supported lower delirium incidence with multicomponent nonpharmacological interventions, although included settings and designs varied. These findings provide a coherent basis for combining modest, feasible measures rather than expecting one exposure to explain the entire syndrome [51, 52].

Surgical trials support application of this approach. Chen and colleagues reported less delirium with a modified Hospital Elder Life Program after abdominal surgery. A tailored family-involved program also reduced delirium and supported functional outcomes in older surgical patients. The multicenter PAWEL study found benefit from a multidisciplinary prevention program overall, with differences between surgical subgroups and no demonstrated benefit in its cardiac subgroup. These studies show that structured care can improve outcomes, while also emphasizing the importance of local implementation, patient selection, staffing, and the actual intervention delivered [50, 53, 54].

At the bedside, prevention should include regular orientation, access to glasses and hearing aids, daytime engagement, appropriate lighting, sleep protection, hydration, nutrition, early mobilization, pain control, and avoidance of unnecessary devices or medication. The measures should be individualized: mobility requires assessment of surgical restrictions and hemodynamic tolerance, and nighttime care should consolidate interruptions without delaying necessary treatment. Families can support reassurance and recognition of change, but responsibility for prevention must remain with the clinical team rather than depend on a relative being continuously available.

Delirium assessment should begin in recovery when feasible and continue regularly through the period of risk, with reassessment after any clinical change. A positive screen should prompt evaluation of oxygenation and ventilation, perfusion, infection, pain, urinary retention, constipation, glucose or electrolyte disturbance, medication effects, and withdrawal. Focal deficits, unexpectedly depressed consciousness, seizures, or a concerning trajectory require assessment for alternative neurological causes. Management of severe agitation may sometimes require short-term medication when nonpharmacological measures fail and immediate safety is threatened, but sedation should not substitute for identifying the cause of the acute brain dysfunction [3, 55].

An integrated pathway, proposed as a practical synthesis rather than a separately validated bundle, is presented in Table 3 and Figure 2. Its purpose is to make responsibilities and reassessment explicit across transitions of care. Local implementation should specify who assesses risk, who delivers each component, and how missed assessments or unresolved cognitive changes are escalated.

Table 3. Practical perioperative pathway for patients at increased neurocognitive risk

Phase	Priority actions	Documentation and reassessment
Before surgery	Establish cognition and function; review medications; address reversible illness; involve patient and family	Record baseline, sensory needs, prior delirium, and recovery goals.
During anesthesia	Individualize dose; assess pressure and oxygen delivery; manage ventilation, temperature, and analgesia	Document sustained physiological abnormalities and treatment response.

Phase	Priority actions	Documentation and reassessment
Recovery and ward care	Assess delirium; orient; support sleep, mobility, hydration, nutrition, and sensory function	Record assessment completion, positive findings, precipitants, and care delivery.
New delirium or deterioration	Evaluate reversible medical causes and alternative neurological diagnoses	Escalate according to severity and document the response and trajectory.
Discharge and follow-up	Communicate delirium history; assess support and medication safety; reassess persistent symptoms	Arrange clinical review and appropriate cognitive or functional evaluation.

Author synthesis informed by peer-reviewed perioperative brain-health and delirium guidance [2, 3, 30, 31, 55]. The pathway is not an independently validated intervention or a substitute for individualized clinical assessment.

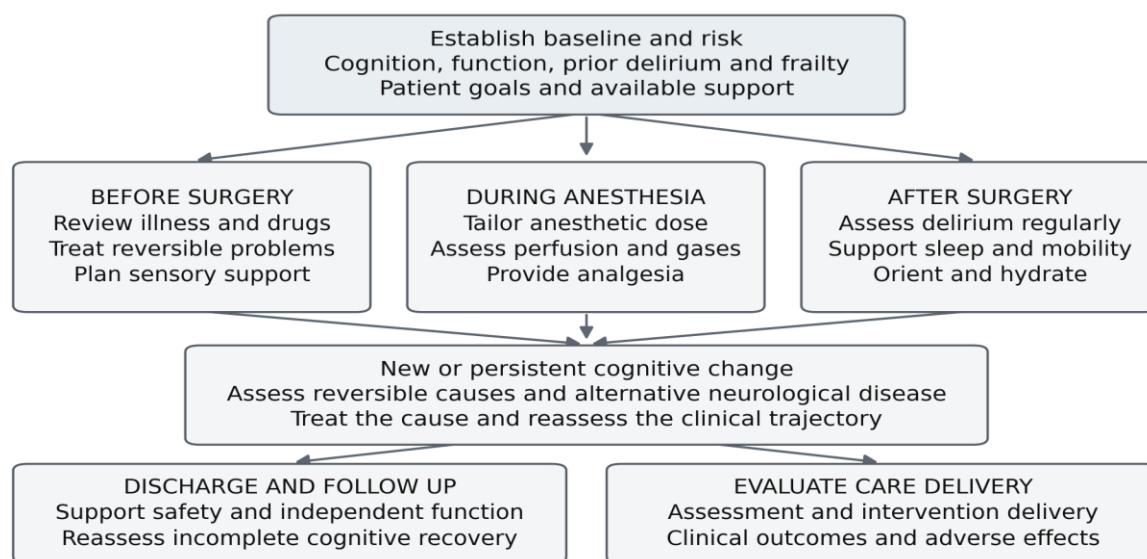


Figure 2. A coordinated pathway for perioperative brain protection. Baseline assessment informs care before, during, and after surgery. New cognitive change triggers assessment for reversible causes and alternative neurological pathology. Discharge planning and follow-up address incomplete recovery. The pathway distinguishes clinical outcomes from monitoring and process measures [2, 30, 31, 55].

5.7 Implementation, persistent impairment, and future research

An effective prevention program requires more than publishing a checklist. Delirium detection depends on staff training, assessment completion, collateral history, and a response to positive findings. A program that appears to reduce delirium while substantially reducing screening may merely detect fewer cases. Likewise, documenting an order for mobilization does not establish that the patient mobilized. Implementation assessment should therefore examine intervention delivery, assessment coverage, clinical outcomes, adverse effects, and resource requirements. Process measures and patient outcomes should be analyzed separately so that apparent adherence is not confused with demonstrated benefit.

Patients with substantial baseline cognitive impairment require particular attention when prevention programs are evaluated. An intervention may reduce avoidable exposures without overcoming the full burden of vulnerability, and a persistent delirium rate does not by itself demonstrate failure of care. Evaluation should account for case mix, intervention delivery, assessment completeness, and competing clinical events. Comparing institutions without those considerations can produce misleading conclusions. The relevant question is whether a defined pathway improves outcomes relative to credible usual care in the population actually receiving it.

Persistent impairment requires a distinct follow-up pathway. Delirium at discharge, ongoing medication effects, depression, sleep disorders, unresolved medical illness, stroke, and previously unrecognized neurocognitive disease can all contribute to poor recovery. Patients and families should receive clear information about the episode and the need for reassessment if cognition or independent function remains impaired. Brief screening can identify concern, but a diagnosis of postoperative mild or major neurocognitive disorder may require more detailed testing and functional evaluation. The clinical goal is to establish the cause and consequences of the change, while arranging support that preserves safety and independence.

Future trials should test mechanism-informed interventions without replacing clinical outcomes with molecular surrogates. Inflammatory phenotypes, vascular reserve, preoperative cognition, and electroencephalographic responses may help identify subgroups with different treatment effects. Such enrichment must be prospectively specified and externally validated rather than inferred from small favorable subgroups. Autoregulation studies need transparent reporting of signal quality, treatment feasibility, pressure exposure, and cointerventions. Pharmacological trials should compare clearly defined regimens and report bradycardia, hypotension, oversedation, and other clinically relevant harms alongside delirium incidence.

Longer-term studies should incorporate repeated cognitive assessment, patient or informant concern, everyday function, quality of life, and living situation. Baseline measurements, appropriate handling of practice effects, and assessment of preexisting decline improve interpretation. Attrition deserves particular attention because death, illness, and disability may selectively remove the most vulnerable participants from follow-up. The limited one-year testing in cogPOISE-3 illustrates the difficulty of drawing firm cognitive conclusions from incomplete data [27]. Demonstrating less delirium remains valuable, but establishing sustained neurocognitive protection requires a trial specifically designed and adequately followed for that outcome.

6. CONCLUSION

Perioperative brain protection requires attention to the interaction between baseline cognitive vulnerability, surgical inflammation, cerebral perfusion, anesthetic exposure, and postoperative recovery. Experimental studies provide persuasive mechanisms through which peripheral injury can influence barrier integrity, immune-cell signaling, glial activity, and memory. Human studies support related associations but have not yet produced a routinely actionable molecular treatment strategy. Autoregulation-guided perfusion management is promising in selected cardiac surgical patients, while the broader evidence does not support a universal higher blood pressure target for preventing neurocognitive complications.

Clinical prevention should combine early risk identification, individualized anesthesia and physiological management, effective analgesia, systematic delirium assessment, and reliable delivery of multicomponent supportive care. Dexmedetomidine can reduce delirium in appropriate settings, but cardiovascular adverse effects and differences between regimens require deliberate selection. Electroencephalographic monitoring and regional anesthesia should be judged according to their specific indications and trial evidence. The central unresolved challenge is demonstrating that prevention of acute delirium translates into sustained preservation of cognition and independent function. Progress will depend on precise outcome definitions, mechanistically informed trials, and follow-up that captures recovery as patients experience it.

REFERENCES

1. Evered L, Silbert B, Knopman DS, Scott DA, DeKosky ST, Rasmussen LS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery-2018. *Br J Anaesth*. 2018;121(5):1005-1012. doi:10.1016/j.bja.2017.11.087.
2. Berger M, Schenning KJ, Brown CH 4th, Deiner SG, Whittington RA, Eckenhoﬀ RG, et al. Best Practices for Postoperative Brain Health: Recommendations From the Fifth International Perioperative Neurotoxicity Working Group. *Anesth Analg*. 2018;127(6):1406-1413. doi:10.1213/ANE.0000000000003841.
3. Aldecoa C, Bettelli G, Bilotta F, Sanders RD, Aceto P, Audisio R, et al. Update of the European Society of Anaesthesiology and Intensive Care Medicine evidence-based and consensus-based guideline on postoperative delirium in adult patients. *Eur J Anaesthesiol*. 2024;41(2):81-108. doi:10.1097/EJA.0000000000001876.
4. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, Canet J, et al. Long-term postoperative cognitive dysfunction in the elderly: ISPOCD1 study. *Lancet*. 1998;351(9106):857-861. doi:10.1016/s0140-6736(97)07382-0.
5. Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, et al. Cognitive trajectories after postoperative delirium. *N Engl J Med*. 2012;367(1):30-39. doi:10.1056/NEJMoa1112923.
6. Inouye SK, Marcantonio ER, Kosar CM, Tommet D, Schmitt EM, Trivison TG, et al. The short-term and long-term relationship between delirium and cognitive trajectory in older surgical patients. *Alzheimers Dement*. 2016;12(7):766-775. doi:10.1016/j.jalz.2016.03.005.
7. Kong H, Xu LM, Wang DX. Perioperative neurocognitive disorders: A narrative review focusing on diagnosis, prevention, and treatment. *CNS Neurosci Ther*. 2022;28(8):1147-1167. doi:10.1111/cns.13873.
8. NeuroVISION Investigators. Perioperative covert stroke in patients undergoing non-cardiac surgery (NeuroVISION): a prospective cohort study. *Lancet*. 2019;394(10203):1022-1029. doi:10.1016/S0140-6736(19)31795-7.
9. Culley DJ, Flaherty D, Fahey MC, Rudolph JL, Javedan H, Huang CC, et al. Poor Performance on a Preoperative Cognitive Screening Test Predicts Postoperative Complications in Older Orthopedic Surgical Patients. *Anesthesiology*. 2017;127(5):765-774. doi:10.1097/ALN.0000000000001859.
10. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med*. 1990;113(12):941-948. doi:10.7326/0003-4819-113-12-941.

11. Bellelli G, Morandi A, Davis DHJ, Mazzola P, Turco R, Gentile S, et al. Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. *Age Ageing*. 2014;43(4):496-502. doi:10.1093/ageing/afu021.
12. Terrando N, Monaco C, Ma D, Foxwell BMJ, Feldmann M, Maze M. Tumor necrosis factor-alpha triggers a cytokine cascade yielding postoperative cognitive decline. *Proc Natl Acad Sci U S A*. 2010;107(47):20518-20522. doi:10.1073/pnas.1014557107.
13. Vacas S, Degos V, Tracey KJ, Maze M. High-mobility group box 1 protein initiates postoperative cognitive decline by engaging bone marrow-derived macrophages. *Anesthesiology*. 2014;120(5):1160-1167. doi:10.1097/ALN.0000000000000045.
14. Degos V, Vacas S, Han Z, van Rooijen N, Gressens P, Su H, et al. Depletion of bone marrow-derived macrophages perturbs the innate immune response to surgery and reduces postoperative memory dysfunction. *Anesthesiology*. 2013;118(3):527-536. doi:10.1097/ALN.0b013e3182834d94.
15. Terrando N, Eriksson LI, Ryu JK, Yang T, Monaco C, Feldmann M, et al. Resolving postoperative neuroinflammation and cognitive decline. *Ann Neurol*. 2011;70(6):986-995. doi:10.1002/ana.22664.
16. Subramaniyan S, Terrando N. Neuroinflammation and Perioperative Neurocognitive Disorders. *Anesth Analg*. 2019;128(4):781-788. doi:10.1213/ANE.00000000000004053.
17. Hirsch J, Vacas S, Terrando N, Yuan M, Sands LP, Kramer J, et al. Perioperative cerebrospinal fluid and plasma inflammatory markers after orthopedic surgery. *J Neuroinflammation*. 2016;13(1):211. doi:10.1186/s12974-016-0681-9.
18. Feng X, Valdearcos M, Uchida Y, Lutrin D, Maze M, Koliwad SK. Microglia mediate postoperative hippocampal inflammation and cognitive decline in mice. *JCI Insight*. 2017;2(7):e91229. doi:10.1172/jci.insight.91229.
19. Vasunilashorn SM, Ngo L, Inouye SK, Libermann TA, Jones RN, Alsop DC, et al. Cytokines and Postoperative Delirium in Older Patients Undergoing Major Elective Surgery. *J Gerontol A Biol Sci Med Sci*. 2015;70(10):1289-1295. doi:10.1093/gerona/glv083.
20. Casey CP, Lindroth H, Mohanty R, Farahbakhsh Z, Ballweg T, Twadell S, et al. Postoperative delirium is associated with increased plasma neurofilament light. *Brain*. 2020;143(1):47-54. doi:10.1093/brain/awz354.
21. Claassen JAH, Thijssen DHJ, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. *Physiol Rev*. 2021;101(4):1487-1559. doi:10.1152/physrev.00022.2020.
22. Willie CK, Tzeng YC, Fisher JA, Ainslie PN. Integrative regulation of human brain blood flow. *J Physiol*. 2014;592(5):841-859. doi:10.1113/jphysiol.2013.268953.
23. Brady K, Joshi B, Zweifel C, Smielewski P, Czosnyka M, Easley RB, et al. Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. *Stroke*. 2010;41(9):1951-1956. doi:10.1161/STROKEAHA.109.575159.
24. Yu Y, Zhang K, Zhang L, Zong H, Meng L, Han R. Cerebral near-infrared spectroscopy (NIRS) for perioperative monitoring of brain oxygenation in children and adults. *Cochrane Database Syst Rev*. 2018;(1):CD010947. doi:10.1002/14651858.CD010947.pub2.
25. Brown CH 4th, Neufeld KJ, Tian J, Probert J, LaFlam A, Max L, et al. Effect of Targeting Mean Arterial Pressure During Cardiopulmonary Bypass by Monitoring Cerebral Autoregulation on Postsurgical Delirium Among Older Patients: A Nested Randomized Clinical Trial. *JAMA Surg*. 2019;154(9):819-826. doi:10.1001/jamasurg.2019.1163.
26. Hogue CW, Brown CH 4th, Hori D, Ono M, Nomura Y, Balmert LC, et al. Personalized Blood Pressure Management During Cardiac Surgery With Cerebral Autoregulation Monitoring: A Randomized Trial. *Semin Thorac Cardiovasc Surg*. 2021;33(2):429-438. doi:10.1053/j.semthor.2020.09.032.
27. Marcucci M, Chan MTV, Painter TW, Efremov S, Aguado HJ, Astrakov SV, et al. Effects of a Hypotension-Avoidance Versus a Hypertension-Avoidance Strategy on Neurocognitive Outcomes After Noncardiac Surgery. *Ann Intern Med*. 2025;178(7):909-920. doi:10.7326/ANNALS-24-02841.
28. Futier E, Lefrant JY, Guinot PG, Godet T, Lorne E, Cuvillon P, et al. Effect of Individualized vs Standard Blood Pressure Management Strategies on Postoperative Organ Dysfunction Among High-Risk Patients Undergoing Major Surgery: A Randomized Clinical Trial. *JAMA*. 2017;318(14):1346-1357. doi:10.1001/jama.2017.14172.
29. Sessler DI, Bloomstone JA, Aronson S, Berry C, Gan TJ, Kellum JA, et al. Perioperative Quality Initiative consensus statement on intraoperative blood pressure, risk and outcomes for elective surgery. *Br J Anaesth*. 2019;122(5):563-574. doi:10.1016/j.bja.2019.01.013.
30. Hughes CG, Boncyk CS, Culley DJ, Fleisher LA, Leung JM, McDonagh DL, et al. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Postoperative Delirium Prevention. *Anesth Analg*. 2020;130(6):1572-1590. doi:10.1213/ANE.00000000000004641.
31. American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. American Geriatrics Society abstracted clinical practice guideline for postoperative delirium in older adults. *J Am Geriatr Soc*. 2015;63(1):142-150. doi:10.1111/jgs.13281.

32. Sieber F, McIsaac DI, Deiner S, Azefor T, Berger M, Hughes C, et al. 2025 American Society of Anesthesiologists Practice Advisory for Perioperative Care of Older Adults Scheduled for Inpatient Surgery. *Anesthesiology*. 2025;142(1):22-51. doi:10.1097/ALN.0000000000005172.
33. Humeidan ML, Reyes JPC, Mavarez-Martinez A, Roeth C, Nguyen CM, Sheridan E, et al. Effect of Cognitive Prehabilitation on the Incidence of Postoperative Delirium Among Older Adults Undergoing Major Noncardiac Surgery: The Neurobics Randomized Clinical Trial. *JAMA Surg*. 2021;156(2):148-156. doi:10.1001/jamasurg.2020.4371.
34. Chan MTV, Cheng BCP, Lee TMC, Gin T; CODA Trial Group. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol*. 2013;25(1):33-42. doi:10.1097/ANA.0b013e3182712fba.
35. Wildes TS, Mickle AM, Ben Abdallah A, Maybrier HR, Oberhaus J, Budelier TP, et al. Effect of Electroencephalography-Guided Anesthetic Administration on Postoperative Delirium Among Older Adults Undergoing Major Surgery: The ENGAGES Randomized Clinical Trial. *JAMA*. 2019;321(5):473-483. doi:10.1001/jama.2018.22005.
36. Deschamps A, Ben Abdallah A, Jacobsohn E, Saha T, Djaiani G, El-Gabalawy R, et al. Electroencephalography-Guided Anesthesia and Delirium in Older Adults After Cardiac Surgery: The ENGAGES-Canada Randomized Clinical Trial. *JAMA*. 2024;332(2):112-123. doi:10.1001/jama.2024.8144.
37. Evered LA, Chan MTV, Han R, Chu MHM, Cheng BP, Scott DA, et al. Anaesthetic depth and delirium after major surgery: a randomised clinical trial. *Br J Anaesth*. 2021;127(5):704-712. doi:10.1016/j.bja.2021.07.021.
38. Sieber FE, Neufeld KJ, Gottschalk A, Bigelow GE, Oh ES, Rosenberg PB, et al. Effect of Depth of Sedation in Older Patients Undergoing Hip Fracture Repair on Postoperative Delirium: The STRIDE Randomized Clinical Trial. *JAMA Surg*. 2018;153(11):987-995. doi:10.1001/jamasurg.2018.2602.
39. Neuman MD, Feng R, Carson JL, Gaskins LJ, Dillane D, Sessler DI, et al. Spinal Anesthesia or General Anesthesia for Hip Surgery in Older Adults. *N Engl J Med*. 2021;385(22):2025-2035. doi:10.1056/NEJMoa2113514.
40. Li T, Li J, Yuan L, Wu J, Jiang C, Daniels J, et al. Effect of Regional vs General Anesthesia on Incidence of Postoperative Delirium in Older Patients Undergoing Hip Fracture Surgery: The RAGA Randomized Trial. *JAMA*. 2022;327(1):50-58. doi:10.1001/jama.2021.22647.
41. Cao SJ, Zhang Y, Zhang YX, Zhao W, Pan LH, Sun XD, et al. Delirium in older patients given propofol or sevoflurane anaesthesia for major cancer surgery: a multicentre randomised trial. *Br J Anaesth*. 2023;131(2):253-265. doi:10.1016/j.bja.2023.04.024.
42. Li YW, Li HJ, Li HJ, Zhao BJ, Guo XY, Feng Y, et al. Delirium in Older Patients after Combined Epidural-General Anesthesia or General Anesthesia for Major Surgery: A Randomized Trial. *Anesthesiology*. 2021;135(2):218-232. doi:10.1097/ALN.0000000000003834.
43. Su X, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2016;388(10054):1893-1902. doi:10.1016/S0140-6736(16)30580-3.
44. Djaiani G, Silverton N, Fedorko L, Carroll J, Styra R, Rao V, et al. Dexmedetomidine versus Propofol Sedation Reduces Delirium after Cardiac Surgery: A Randomized Controlled Trial. *Anesthesiology*. 2016;124(2):362-368. doi:10.1097/ALN.0000000000000951.
45. Deiner S, Luo X, Lin HM, Sessler DI, Saager L, Sieber FE, et al. Intraoperative Infusion of Dexmedetomidine for Prevention of Postoperative Delirium and Cognitive Dysfunction in Elderly Patients Undergoing Major Elective Noncardiac Surgery: A Randomized Clinical Trial. *JAMA Surg*. 2017;152(8):e171505. doi:10.1001/jamasurg.2017.1505.
46. Turan A, Duncan A, Leung S, Karimi N, Fang J, Mao G, et al. Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): a randomised placebo-controlled trial. *Lancet*. 2020;396(10245):177-185. doi:10.1016/S0140-6736(20)30631-0.
47. Luney M, Holdsworth L, Hagana A, Kaminskaite V, Qiu L, Berner J, et al. Effectiveness of drug interventions to prevent delirium after surgery for older adults: systematic review and network meta-analysis of randomised controlled trials. *BMJ*. 2026;392:e085539. doi:10.1136/bmj-2025-085539.
48. Spence J, Devereaux PJ, Lee SF, D'Aragon F, Avidan MS, Whitlock RP, et al. Benzodiazepine-Free Cardiac Anesthesia for Reduction of Postoperative Delirium: A Cluster Randomized Crossover Trial. *JAMA Surg*. 2025;160(3):286-294. doi:10.1001/jamasurg.2024.6602.
49. Avidan MS, Maybrier HR, Ben Abdallah A, Jacobsohn E, Vlisides PE, Pryor KO, et al. Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. *Lancet*. 2017;390(10091):267-275. doi:10.1016/S0140-6736(17)31467-8.
50. Chen CCH, Li HC, Liang JT, Lai IR, Purnomo JDT, Yang YT, et al. Effect of a Modified Hospital Elder Life Program on Delirium and Length of Hospital Stay in Patients Undergoing Abdominal Surgery: A Cluster Randomized Clinical Trial. *JAMA Surg*. 2017;152(9):827-834. doi:10.1001/jamasurg.2017.1083.

51. Inouye SK, Bogardus ST Jr, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med.* 1999;340(9):669-676. doi:10.1056/NEJM199903043400901.
52. Hsieh TT, Yue J, Oh E, Puella M, Dowal S, Trivison T, et al. Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis. *JAMA Intern Med.* 2015;175(4):512-520. doi:10.1001/jamainternmed.2014.7779.
53. Wang YY, Yue JR, Xie DM, Carter P, Li QL, Gartaganis SL, et al. Effect of the Tailored, Family-Involved Hospital Elder Life Program on Postoperative Delirium and Function in Older Adults: A Randomized Clinical Trial. *JAMA Intern Med.* 2020;180(1):17-25. doi:10.1001/jamainternmed.2019.4446.
54. Deeken F, Sanchez A, Rapp MA, Denkinger M, Brefka S, Spank J, et al. Outcomes of a Delirium Prevention Program in Older Persons After Elective Surgery: A Stepped-Wedge Cluster Randomized Clinical Trial. *JAMA Surg.* 2022;157(2):e216370. doi:10.1001/jamasurg.2021.6370.
55. Marcantonio ER. Delirium in Hospitalized Older Adults. *N Engl J Med.* 2017;377(15):1456-1466. doi:10.1056/NEJMcp1605501.