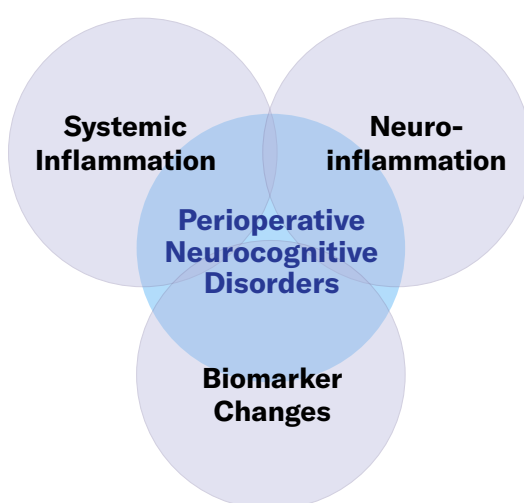


# Can Anesthesiologists Prevent Perioperative Neurocognitive Decline? A Review of the Literature

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Individuals over the age of 65 make up the largest proportion of patients seeking surgical care. Advanced age and underlying cognitive disorders are risk factors for the development of cognitive impairment, the most common complication in this age group. Perioperative neurocognitive disorders (PNDs) comprise a variety of transient or longer-lasting impairments in cognition, memory, executive function, and behavior. Delirium is the most common, with an incidence of 26%-53%. Postoperative cognitive dysfunction is estimated at 10% at three months. In addition to age, cardiac and orthopedic surgeries place patients at higher risk of cognitive decline (*Anesth Analg* 2019;128:781-88). Impacted patients have increased risk of mortality and lower quality of life (*Anesthesiology* 2008;108:18-30; *Stroke* 2001;32:2874-81). As a result, ongoing research has sought to elucidate the pathophysiology of these disorders as well as possible preventative measures, providing guidance to anesthesiologists and surgeons on how to take care of an aging population.

Emerging evidence on PND is unveiling not only who is affected and why, but also the biochemical pathway by which the brain is impacted by anesthesia and surgery, providing an opportunity to potentially mitigate the development of cognitive decline. Changes in biomarkers, such as B-amyloid protein and tau found in Alzheimer's disease, have been implicated in the development of cognitive dysfunction following anesthesia and surgery. Lower CSF beta-amyloid was associated with postoperative cognitive decline at three months in patients at least 60 years old receiving spinal and general anesthesia for elective total hip replacement



**Figure:** Multiple biochemical pathways contribute to the development of perioperative neurocognitive disorders, including systemic inflammation, neuroinflammation, and biomarker changes.

surgery (*Anesthesiology* 2016;124:353-61). Systemic inflammation and neuroinflammation play important roles, as well. Activation of microglia and astrocytes has been shown to be associated with cognitive decline after surgery (*Anesth Analg* 2019;128:781-88). Systemic inflammation leads to disruption in the blood brain barrier, allowing inflammatory substances access to the CNS (Figure) (*Anesth Analg* 2019;128:781-88). Pretreating mice with anti-TNF-alpha before orthopedic surgery mitigated memory impairment (*Proc Natl Acad Sci U S A* 2010;107:20518-22). Interestingly, giving dexamethasone intraoperatively during cardiac surgery did not reduce the incidence of postoperative neurocognitive decline (*Anesthesiology* 2014;121:492-500). Rather, targeting specific anti-inflammatory pathways following surgery could activate an anti-inflammatory cascade. For example, omega-3 fatty acids are important anti-inflammatory

mediators and could play a role in reducing inflammation and incidence of cognitive decline (*Anesth Analg* 2019;128:781-88). However, more research is necessary to determine specific targets of inflammation to prevent PND.

Choice of anesthetic agent could potentially play a role in development of PND. There is debate in the literature whether an intravenous (I.V.) versus a volatile anesthetic contributes to cognitive dysfunction. Recently, a large randomized controlled trial comparing patients 65-90 years old who received propofol total intravenous anesthesia (TIVA) to sevoflurane inhalational anesthesia resulted in significantly lower incidence of delirium with propofol, specifically on postoperative day one, but not on days two through seven (*Br J Anaesth* 2023;131:253-65). However, another recent study conducted in cardiac valvular surgery patients showed no difference in incidence of delirium between TIVA and inhalational anesthesia (*Anesth Analg* 2023;136:60-9). More studies are needed, investigating not only delirium but other PNDs, to determine whether anesthetic choice reduces cognitive decline. Similarly, it is not clear whether other anesthetic agents contribute to PND. A systemic review and meta-analysis of 34 randomized controlled trials found that perioperative benzodiazepines did not increase the risk of delirium. Interestingly, studies comparing benzodiazepines to dexmedetomidine showed reduced risk of delirium with dexmedetomidine administration, raising the question of whether dexmedetomidine has a neuroprotective effect or reduces the likelihood that patients screen positive for delirium (*Br J Anaesth* 2023;131:302-13).

Measuring anesthetic depth as a means of preventing PND has gained attention and has been the focus of multiple studies. A sub-study of a large international trial in patients aged 60 or older comparing bispectral index (BIS) readings of 35 to 50 found that targeting BIS readings of 35 resulted in significantly higher incidence of delirium, while the parent trial



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found no difference in adverse outcomes or one-year mortality with deeper anesthesia (*Lancet* 2019;394:1907-14). Targeting BIS readings of 40 to 60 reduced delirium incidence and postoperative cognitive decline at three months compared to usual care in patients 60 years and older (Table) (*J Neurosurg Anesthesiol* 2013;25:33-42). Both this study and the sub-study included patients from some of the same hospitals. Interestingly, in the sub-study, the results were mostly driven by sites in Asia, with significant reduction in delirium incidence with lighter anesthesia, while the incidence of delirium was not much different between lighter and deeper anesthesia in sites outside of Asia (*Br J Anaesth* 2021;127:667-71). Potentially, certain populations could be at greater risk of delirium postoperatively due to genetic or ethnic differences.

More research is needed to determine which factors, such as anesthetic choice and depth of anesthesia, contribute to PND. As evidence suggests, some patient populations could be at higher risk of delirium, and further studies are needed to determine what predisposes these patients to PND. Targeting specific inflammatory pathways could also prevent the occurrence of cognitive decline. For now, the evidence at least supports delivering lighter anesthesia to elderly patients. Anesthesiologists need to be aware of who is at risk of PND and tailor their anesthetic appropriately based on the available evidence. ■

Intraoperative Management	Effect on PND Development
TIVA versus inhalational anesthesia	TIVA <i>potentially</i> reduces delirium on POD 1
Intraoperative benzodiazepines	None
Dexmedetomidine	<i>Potentially</i> reduces delirium
Targeting lighter anesthesia	Reduces incidence of delirium

**Table:** Based on review of the literature, several intraoperative management strategies could reduce the incidence of perioperative neurocognitive disorders.