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# Perioperative neurocognitive disorders: Risk factors, mechanisms, and interventional strategies

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**Perioperative neurocognitive disorder (PND) is one of the most common perioperative complications in the older surgical population. However, its biomarkers and pathogenesis are largely undetermined, impeding further studies in developing new diagnostic strategies and establishing novel interventions for patients at high risk of PND. This review summarizes the risk factors, mechanisms, and current interventional strategies for PND, and aims to advance the development of innovative preventions and targeted treatments.**

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## Introduction

Perioperative neurocognitive disorder (PND) is one of the most common perioperative complications in the older surgical population, with the incidence ranging from 10% to 47% across different kinds of surgeries (1). PND was initially proposed by Bedford in 1995 and referred to a form of neurocognitive impairment (2). It affects multiple cognitive domains, including learning, memory, attention, executive function, and processing speed emerging after anesthesia and surgery (3). In 2018, the classification of PND was expanded to encompass cognitive decline diagnosed before surgery, any form of acute event (postoperative delirium), cognitive decline diagnosed up to 30 days after procedures (delayed neurocognitive recovery) and up to 12 months (postoperative neurocognitive disorder) (4).

However, PND may not always be transient or reversible, and increasing evidence has demonstrated both short-term and long-term poor prognoses in surgical patients who have developed PND (5). PND is associated with prolonged hospitalization (6), higher discharge rates to nursing homes, increased risk of mortality, and long-term cognitive deterioration (7, 8). Specifically, patients with postoperative delirium have a 39% increased mortality risk, and each additional delirium episode increases the risk of death by 10% (9). Moreover, postoperative delirium also contributes to a 3- to 4-fold increased risk of cognitive decline, with each episode elevating this risk by 20% (10). Additionally, Leighton *et al*. reported a 31% cumulative incidence of new dementia cases within 5 years among older patients with delirium (11). With the increase in population aging and the progress of surgery and anesthesiology, more geriatric patients are undergoing surgical procedures and the incidence of PND has dramatically increased (12). Annual healthcare expenditures attributable to postoperative delirium are estimated at $32.9 billion in the United States, imposing a heavy burden on the global social economy and public health services (13).

As a modifiable risk factor for dementia, PND presents a critical window for early interventions (14). However, the biomarkers and pathogenesis underlying PND remain largely undetermined, which impedes further studies in developing new diagnostic strategies, identifying high-risk population, and establishing targeted interventions for PND. Therefore, this review summarizes the risk factors, mechanisms, and current interventional strategies for PND, aiming to advance the development of innovative preventions and targeted treatments.

## Risk factors

The interaction of predisposing factors (e.g., advanced age, low educational levels, and history of physical and mental illnesses) and precipitating factors (e.g., anesthesia, surgery, and postoperative infections) significantly contributes to PND (15). Therefore, assessing and managing these risk factors is essential for screening high-risk individuals before surgery and improving short- and long-term postoperative outcomes. Predisposing and precipitating factors associated with PND are presented in Table 1.

### Predisposing factors

*Patient characteristics* Advanced age and low educational levels are well-documented risk factors for PND (16). Specifically, the incidence of PND in older patients ranges from 16.0% to 39.0%, significantly higher than the incidence of 5.6% in younger patients after cardiac surgery (8).

*Physical comorbidities* Patients with complex physical comorbidities have an increased risk of PND. Specifically, individuals with existing cerebrovascular diseases or neurological dysfunctions are particularly vulnerable to developing PND (17, 18). Among older patients aged 70 years and above with neurocognitive impairment, the incidence of postoperative delirium increases by 19% (19). In addition, patients with metabolic syndrome face a 1.85-fold higher risk of postoperative delirium (20). Sensory impairments, including hearing, vision, and olfactory damage, are significant risk factors for PND. For instance, hearing impairment doubles the odds of postoperative emergence agitation in older patients undergoing middle ear surgery (21). Therefore, routine screening and targeted interventions for sensory impairments would be critical for preventing or mitigating PND. Other predisposing factors include diabetes, end-stage renal failure, hypoalbuminemia, malignant neoplasm, and higher preoperative American Society of Anesthesiologists (ASA) classification (8, 18).

*Psychological factors* Psychological factors, such as preoperative depression, anxiety, and poor sleep quality, significantly contribute to the development of PND. Evidence has demonstrated that depression is an independent risk factor for postoperative delirium after elective spine surgery (22). Furthermore, preoperative depression increases the risk of delirium independent of existing cognitive impairment and cerebrovascular diseases (23). In addition, studies consistently suggest that severe anxious symptoms also increase the risk of postoperative cognitive

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**Table 1.** Predisposing and precipitating factors associated with perioperative neurocognitive disorder

| Predisposing factors | Precipitating factors |
|---|---|
| Advanced age | *Anesthesia factors:* |
| Low educational levels | Anesthetic drugs, e.g., sevoflurane and desflurane |
| Neurocognitive impairment, e.g., dementia | Anesthesia time and depth, e.g., prolonged general anesthesia |
| Cerebrovascular diseases | Anesthesia methods, e.g., general anesthesia and regional anesthesia |
| Cardiovascular disorders | *Surgical factors:* |
| Neurological dysfunctions | Longer operation time |
| Metabolic syndrome | More complex surgeries |
| Diabetes | Repeating surgeries |
| End-stage renal failure | Intraoperative blood loss |
| Hypoalbuminemia | Cerebral oxygen desaturation |
| Malignant neoplasm | *Postoperative complications:* |
| Higher ASA[a] classification | Infections |
| Mental illness, e.g., depression and anxiety | Persistent pain |
| Poor sleep quality | *Latrogenic and environmental factors:* |
| Sensory impairment, e.g., hearing, vision, and olfactory damage | ICU stays |
| Preoperative frailty | Physical restraint |

[a]ASA: American Society of Anesthesiologists.

deficits, such as executive function decline 3 months after oncological surgery (24, 25). These findings highlight the significance of carefully assessing and managing perioperative psychological factors in preventing PND.

### Precipitating factors

*Anesthesia factors* Choice of anesthetics may have some association with different risks of PND. A network meta-analysis compared different anesthetic drugs in preventing PND, and reported the incidence of PND for each anesthetic drug was dexmedetomidine (12.9%), ketamine (15.2%), propofol (16.8%), fentanyl (23.9%), midazolam (11.3%), sufentanil (6.3%), sevoflurane (24.0%), and desflurane (28.3%) (26). Results further demonstrate that dexmedetomidine and sufentanil have the greatest possibility to reduce the incidence of PND for older people undergoing noncardiac surgery. Moreover, prolonged general anesthesia (GA) (longer than 3 hours) is also associated with subjective cognitive and memory impairments after noncardiac surgery (8). Additionally, different anesthesia methods have certain influence on the development of PND. It has been reported that the delirium incidence for GA is 37.8%, much higher than that for regional anesthesia (RA) of 33.9% (27). Controversially, some other studies suggest that RA, including spinal and epidural anesthesia, cannot reduce the incidence of postoperative delirium, which might be due to its lack of sedative effects (28).

*Surgical factors* Longer and more complex surgeries increase the incidence and severity of PND probably due to cerebral embolism, hypoperfusion, and neuroinflammatory responses. Orthopedic surgeries, such as hip and knee replacements, and cardiac surgeries, particularly coronary artery bypass grafting with extracorporeal circulation, are high-risk procedures (29). Additionally, repeated surgeries increase the risk of early PND. Data from the UK Biobank reveal that a higher cumulative number of surgeries correlates with more significant neurocognitive dysfunction (30).

*Latrogenic and environmental factors* Latrogenic factors associated with anesthesia and surgery, such as intraoperative blood loss, cerebral oxygen desaturation, postoperative infections, and persistent pain, are linked to cognitive impairment in older patients (16, 31). Additionally, special environmental factors including ICU stays exceeding 2 days or being physically restrained also increase the likelihood of suffering postoperative short-term memory impairment and developing postoperative delirium (8).

### Risk factor assessments

This review provides a brief description of predisposing and precipitating factors associated with PND. Specifically, advanced age and cognitive impairment or dementia have been identified in most studies as risk factors of PND, while some other associations are not consistent across different clinical settings, such as racial categories, gender, hypotension, and hypoxemia (32).

Preoperative frailty assessment by using the Clinical Frailty Scale or the Edmonton Frailty Scale is beneficial for optimizing the anesthesia or surgery plans for high-risk individuals, and achieving targeted interventions or personalized treatments (33). Dodsworth *et al*. developed and validated an international preoperative risk assessment model (PIPRA algorithm) for postoperative delirium, which has been clinically used to optimize perioperative care and prioritize interventions for vulnerable patients (34). Accordingly, assessment-based interventions targeting preoperative conditions, such as poor sleep quality and depressive symptoms, and optimizing perioperative management, such as pain control, are effective strategies for reducing PND (8). Moreover, intraoperative measures, such as carefully adjusting anesthesia depth under electroencephalography (EEG) monitoring, may help prevent PND, but the randomized trials on these strategies have discordant findings (35). Studies reported that targeting a bispectral index (BIS)-guided anesthesia reading of 50 was associated with a lower incidence of postoperative delirium and cognitive impairment 1 year after surgery than targeting a BIS reading of 35 (36). However, other studies demonstrated that EEG-guided anesthetic administration did not decrease the incidence of postoperative delirium, compared with usual care, among older adults undergoing major surgeries (37, 38).

In general, PND is a clinically preventable condition. Systematic assessment of risk factors is important for optimizing perioperative treatment plans and implementing targeted interventions for PND.

## Mechanisms

PND has garnered increasing research attention as an important area of study in anesthesia, surgery, neuroscience, geriatrics, and aging. However, its pathological mechanisms remain incompletely understood, hindering efforts to identify high-risk individuals and develop novel interventions.

### Inflammation

Inflammation has been generally recognized as an important pathological mechanism of PND (39). Major surgeries usually induce an acute inflammatory response (40), characterized by elevated levels of inflammatory factors in blood and cerebrospinal fluid (CSF) (29). Both peripheral inflammatory responses (41, 42) and neuroinflammation (43, 44) play critical roles in the development of PND. Specifically, increased levels of interleukin-6 (IL-6) and interleukin-8 (IL-8) in CSF are strongly correlated with long-term cognitive decline (45), underscoring the critical

role of neuroinflammation in triggering neurocognitive changes. Meanwhile, peripheral inflammation associated with surgical trauma disrupts the permeability of blood–brain barrier (BBB) and results in peripheral macrophages infiltrating into the brain, contributing to excessive activation of microglia and astrocytes (46). This process triggers a neuroinflammatory cascade, leads to increased neuronal damage, and ultimately results in PND. However, biologics and nonsteroidal anti-inflammatory drugs (NSAIDs), which target inflammation, are not routinely administered due to their controversial clinical efficacy and potential side effects, such as impeding wound healing (47).

### Cerebral blood flow changes

Changes in cerebral blood flow contribute to the development of PND. A multicenter study reports that perioperative covert strokes increase the risk of perioperative delirium by 6% and cognitive decline 1 year after noncardiac surgery by 13% (48). Several studies indicate that cerebral blood flow fluctuations during operation may be attributed to the disrupted cerebral autoregulation mechanisms (49), and may be associated with the onset of delirium (50). In addition, monitoring cerebral oxygenation during surgery has been shown to reduce postoperative cognitive complications (51). Accordingly, tailored blood pressure management based on cerebral autoregulation may offer a promising strategy to improve the clinical outcomes of PND (52).

### Neurotransmitter alterations

Neurotransmitter homeostasis is necessary for maintaining normal cognitive function. Anesthetics and surgical trauma would disrupt the balance of neurotransmitters and thus impair cognitive performance. The balance between $\gamma$-aminobutyric acid (GABA) and glutamate has been implicated in the development of postoperative delirium and cognitive dysfunction (53–55). Excessive glutamatergic neurotransmission can cause excitotoxic neuronal damage. Studies have demonstrated that ketamine may prevent PND by inhibiting calcium influx in glutamate-activated neurons through N-methyl-D-aspartate (NMDA) receptor antagonism (56). These findings highlight the need for further research to validate the role of anesthesia type, anesthetic option, anesthesia dosage and duration in promoting cognitive recovery after surgery.

### Tau protein phosphorylation

Hyperphosphorylated tau (pTau) has been considered a classical biomarker of PND and Alzheimer disease (57–59). Elevated levels of pTau in CSF are key indicators of neurocognitive decline and remain unaffected by the anesthetic effects of propofol or isoflurane (60, 61). However, the clinical application of CSF pTau is limited due to being invasive or expensive, particularly in large-scale early-stage screening. Therefore, there is an urgent need to establish a noninvasive and less expensive biomarker to identify high-risk individuals and initiate interventions at an early stage.

Recently, peripheral tau protein has emerged as a potential biomarker for PND. Studies demonstrate that the levels of plasma tau protein after anesthesia and surgery are significantly increased, although the specific pathophysiological mechanisms remain unclear (62). Increased levels of total tau and pTau181 correlate with the occurrence and severity of postoperative delirium among patients undergoing cardiac surgery (63). Notably, preoperative plasma pTau217 and pTau181 could accurately predict the development of postoperative delirium in the older surgical population, with an area under the receiver operator characteristic (ROC) curve of 0.969 and 0.885, respectively (57). Animal studies further confirm that reducing blood pTau217 levels alleviates PND-like behavior, reinforcing its pivotal role in disease pathogenesis (64).

Despite its promise, the clinical application of peripheral tau protein as a biomarker faces great challenges due to its rapid fluctuation, low molecular weight, and limited sensitivity of traditional detection methods (65, 66). Advances in proteomics, such as nanoneedle technology with ultra-high sensitivity (fg/mL level) and computer chip analysis, could enable high-throughput detection suitable for large-scale research and early screening (57, 67). Overall, peripheral tau and pTau offer new insights into the pathophysiology of PND and represent a potential target for intervention.

### Interactions of multiple mechanisms

This review summarizes classical mechanisms of PND, including inflammation, cerebral blood flow, neurotransmitters, and tau hyperphosphorylation. However, many episodes of PND are multifactorial, and it is unlikely that any single pattern of biological factors underlies all instances of PND. A prospective observational study showed that an increase in plasma tau after surgery was associated with elevated IL-8 and interleukin-10 (IL-10) levels among delirious patients (68). Animal studies further indicated that tau phosphorylation might cause IL-6 elevation, leading to mitochondrial dysfunction, synaptic loss and cognitive impairment in young mice following sevoflurane anesthesia (69). Specifically, tau or pTau could traffic from neurons to microglia via vesicles, leading to IL-6 generation and cognitive impairment (70). In addition, evidence also demonstrated that inflammation associated with anesthesia and surgery could cause BBB disruption and cerebral blood flow abnormalities, ultimately resulting in neuronal damage and PND-like behaviors (71).

Overall, current evidence provides a particular perspective on understanding the interconnections of PND pathological mechanisms, which may be used to inform the study of PND pathophysiology and its treatment. Most importantly, it encourages clinicians to understand, identify and treat PND from a view of multiple physiological pathways, instead of a one-size-fits-all approach.

## Management strategies

Due to the complex pathological mechanisms of PND, there are currently no targeted therapeutic approaches available in clinical practice. For patients experiencing delirium symptoms, antipsychotic drugs or benzodiazepines are often administered for sedation. However, these treatments lack consistent efficacy and may lead to long-term cognitive decline (72). In recent years, emerging pharmacological and nonpharmacological interventions have shown potential for preventing and treating PND.

### Pharmacological interventions

*Dexmedetomidine* Dexmedetomidine, a highly selective $\alpha^2$-adrenoceptor agonist, has shown certain neuroprotective effects. Recent clinical trials of older patients admitted to ICUs after noncardiac surgery suggested that low-dose dexmedetomidine significantly decreased the incidence of postoperative delirium by 14% during the first postoperative 7 days (73). Yu and colleagues conducted a meta-analysis of 14 randomized controlled trials including 1626 patients of 60 years or older, and found that dexmedetomidine was associated with a reduced risk of PND in older patients receiving surgeries with GA (74). Dexmedetomidine may be a potential preventative measure for PND, and future research should focus on determining the optimal timing and dosage for its therapeutic application.

*NSAIDs* Perioperative pain and inflammation management is essential for preventing PND. A meta-analysis of eight studies showed that NSAIDs could relieve postoperative pain and reduce the incidence of postoperative delirium from 19% to 11% (75). Another meta-analysis of eight studies consistently found that perioperative intravenous Parecoxib reduced PND incidence and improved Mini-Mental State Examination scores (76).

*Cognitive enhancers* Drugs such as donepezil, memantine, and rivastigmine, commonly used for AD, have been investigated for PND. Preclinical studies suggest that donepezil alleviates central cholinergic impairment and improves learning and memory deficits in aged mice (77). However, clinical studies have shown inconsistent results, and there is currently no robust evidence supporting the administration of cognitive enhancers for PND treatment.

*WS635* WS635, a nonimmunosuppressive inhibitor of cyclophilin D and mitochondrial function enhancement (78, 79), shows potential in preventing or treating PND. WS635 could reduce pTau217 concentrations in the blood of mice potentially via enhancing the mitochondrial function of B cells (64). Studies in animal models have demonstrated that WS635 attenuates cognitive deficits induced by anesthesia/surgery and restores postsynaptic density 95 (PSD-95), synaptophysin, and ATP levels in brain tissue (80). On January 1, 2023, the FDA has approved WS635 to proceed a phase Ib/II clinical study of postoperative delirium. However, since the

current data are still preclinical, the clinical efficacy of WS635 for preventing PND should be further validated with large-scale trials.

### Nonpharmacological strategies

*Sleep promotion* Disturbances in the sleep-wake cycle are common in PND. Interventions such as low-dose dexmedetomidine infusion (73), melatonin administration (81), and environmental modifications (e.g., earplugs, eye masks, and soothing music) have been proven effective in promoting sleep (82). A meta-analysis of 13 randomized controlled trials found that sleep interventions reduced postoperative delirium risk by approximately 50% (83). Accordingly, actively addressing perioperative sleep disturbances may significantly improve cognitive outcomes.

*Sensory stimulation* Evidence has indicated that reduced preoperative olfactory discrimination and thresholds, persisting for at least 1 week postoperatively, have been observed in patients with PND. In animal studies, 21 days of olfactory stimulation mitigated the anesthesia/surgery-induced learning and memory deficits, reduced synaptic markers in the hippocampus, and alleviated PND-like behavior in mice (84). As a safe and convenient intervention, olfactory stimulation warrants further clinical exploration. Specifically, Shen *et al*. have registered the first clinical trial to validate the efficacy of perioperative olfactory stimulation on preventing PND in the geriatric surgical population (85). In addition, multisensory stimulation involving auditory and visual inputs has been shown to alleviate Alzheimer-associated pathology and improve cognitive function (86). Music interventions activate brain regions related to memory, cognitive function, and emotions, reducing the risk of delirium by approximately 50% in ICU patients (87, 88). Virtual reality (VR) integrating auditory and visual stimuli is beneficial for relieving pain and anxiety, which may enhance cognitive function (89, 90). However, large-scale randomized controlled trials are needed to validate the clinical effects of VR on preventing PND.

*Psychosocial support* Adequate psychosocial support positively impacts patients' emotions, cognitive performance, and long-term surgical prognoses. Specifically, supportive group psychotherapy can alleviate anxiety and depression and improve postoperative quality of life in patients with lung cancer undergoing gamma knife surgery (91). Furthermore, preoperative cognitive training can significantly mitigate the decline of early postoperative cognitive function 1 week after major gastrointestinal surgery in older patients (92). Recent research suggests that implementing a modified Hospital Elder Life Program (HELP), which emphasizes cognitive stimulation activities such as discussing current events or engaging in word games, has led to a significant reduction in delirium incidence (93). Multidisciplinary collaboration among surgical teams, anesthesiologists, and psychiatrists is essential for providing psychological support and reducing the incidence of PND.

*Physical stimulation* Recently, noninvasive brain stimulation techniques, such as repeated transcranial magnetic stimulation and transcranial direct current stimulation (tDCS), have been demonstrated to improve cognitive function (94, 95). Previous studies with tDCS sessions applied over the dorsolateral prefrontal cortex have shown a significant decrease in the incidence of postoperative delirium among older patients undergoing surgery (96). However, there are no clear guidelines for determining the most effective specific parameters and standardized stimulation protocols, which need to be confirmed by multicenter studies in the future.

### Multimodal interventions and treatments

This section outlined potential pharmacologic and nonpharmacologic management strategies. According to the latest guideline, dexmedetomidine, NSAIDs, and sleep promotion strategies were supported by moderate certainty of evidence, whereas olfactory or virtual reality interventions remain at a more exploratory stage (97). However, it is obvious that the development of PND is multifactorial, so multimodal interventions are recommended, including treatment for physical diseases, as well as medication, psychotherapy, and physiotherapy.

## Conclusions

This review provides a comprehensive evaluation of the risk factors, mechanisms, and management strategies of PND. First, both precipitating and predisposing factors have been emphasized, as screening high-risk populations and optimizing management based on these perioperative risk factors could mitigate the incidence and severity of PND. Second, PND mechanisms including neuroinflammation, changes in cerebral blood flow, neurotransmitter imbalances, and tau phosphorylation have been elaborated. Levels of phosphorylated tau proteins in blood are highlighted due to their critical role in pathogenesis and novel insights for PND targeted treatment. In particular, plasma pTau levels determined by nanoneedles require less sample volume (2–5 μL), have higher sensitivity and lower per-assay cost, as compared to traditional existing methods, facilitating their translational application in clinical practice. At last, pharmacological and nonpharmacological interventions are discussed, inspiring clinicians to early identify high-risk patients and to advocate multimodal approaches for improving PND outcomes. Despite the significant consequences and costs associated with PND, the accurate diagnosis and effective treatments remain to be determined. In the future, research into developing standardized assessment frameworks, large-scale biomarker validation, and multicenter trials of multimodal interventions for PND should be priorities, which will contribute to reducing the global burden of dementia.

## Author contributions

YS outlined the specific issues reviewed in this paper, designed the study concept, and obtained funding. ZS prepared the first draft of the manuscript, provided critical revision for important intellectual content, and obtained funding. The manuscript has been read and approved by all the authors. All authors take full responsibility for all data, tables and text, and approve the content and submission of the study. No related work is under consideration elsewhere. Corresponding author: YS takes full responsibility for any aspect of the work and for the submission process.

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## Author disclosures

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