Cognitive Decline after Critical Illness

Severe cognitive decline and cognitive dysfunction has been attributed to patients' stay in the cardiovascular intensive care unit (ICU) in several studies. The prevalence rate of long-term cognitive impairment reported after critical illness varies widely in studies, with prevalence rates ranging from 4 to 62%. Long-term adverse functional disability, after discharge from an ICU, was first reported in ARDS survivors. Hospitalization for noncritical illness increases the risk of incident dementia by 50% while critical illness may double this risk. In-hospital delirium is associated with adverse global cognitive function 3 and 12 months after discharge, independent of known risk factors, especially if the duration of in-hospital delirium is longer. A retrospective data analysis of more than 10,000 ICU survivors found a nearly 50% higher risk of subsequent dementia, than in matched controls, within 3 years.

Cognitive decline is an independent marker of adverse outcomes in patients with heart failure. A nearly 80% prevalence of neurocognitive disorder (NCD) was reported in patients with acute decompensation. Factors thought to contribute to NCD are hypertension, atrial fibrillation, stroke, and impaired hemodynamics. Cerebral hypoperfusion, disruption of the blood–brain barrier (BBB), and oxidative stress are considered to be responsible. Neuroimaging in such patients reveal hyperintense white matter, lacunar infarcts, and brain volume loss. Global cognitive decline has been reported to occur significantly faster after newly diagnosed heart failure than their peers, in the absence of a documented neurological event or concomitant atrial fibrillation. Though this decline is more pronounced at older ages, it is evident in all patients between 70 and 90 years. The rate of cognitive decline is not related to a reduction in ejection fraction.

Several patients admitted to cardiac ICU have a prolonged ICU stay and/or have severe multiorgan involvement, making them prone to NCD. Advances in critical care have improved patient survival, but...
the quality of life after that has not improved significantly. After recovery from the illness, many patients have impaired cognition and functional status, which results in the necessity for institutional/supported care, regular medical support, rehabilitation support, and loss/sheltered employment. Patients commonly have memory, attention, mental processing, visual-spatial, and motor execution deficits.

The risk factors pre-ICU-admission and post-ICU-admission,[4] which make the patient susceptible to develop NCD after the ICU stay are listed in Table 1. Hospital data of patients aged >65 years, without baseline dementia, revealed a 50% higher risk of dementia in patients admitted for noncritical illness and a 100% higher risk in those admitted for critical illness.[6] The “Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in Intensive Care Unit (BRAIN-ICU)” Survivors study reported that 32% of survivors had impaired activities of daily living (ADL) at 3 months which persisted even at 1 year. 26% of the BRAIN-ICU survivors had restrictions in instrumental ADL at 3 months which remained so at 1 year in 23% of them.[12] Long-term data evaluation of 743 patients, who required mechanical ventilation during critical illness, revealed that only 53% of survivors returned to functional baseline at 5 years.[13]

Apart from being associated with poor clinical outcomes, prolonged mechanical ventilation, more ICU days, and more radiological investigations for mental status assessment, deep ICU sedation is associated with an increased likelihood of patients developing delirium.[14,15] A recent randomized control trial (RCT) reported that early goal-directed mobilization reduces the incidence of ICU delirium and increased ICU delirium-free days.[16] The MENDs RCT indicated ICU outcome benefits with the use of dexmedetomidine for ICU sedation.[17] On the other hand, several studies have demonstrated increased incidence/duration of delirium and sleep deprivation in ICU patients with the use of benzodiazepines.[17,18] Figure 1 displays a flow chart summarizing important aspects of long-term cognitive decline after ICU admission.

Inadequate sleep and its disruption during hospitalization adversely impact patient outcomes. Polysomnographic studies have revealed extreme sleep deprivation, sleep fragmentation, and altered sleep patterns in ICU.[19] Acute withdrawal from long-term benzodiazepines/opioid sedation may result in severe sleep disruption.[20] Poor sleep hygiene results in delirium and cognitive dysfunction.[21] Perioperative sleep deprivation has been shown to induce microglia activation in the hippocampus and increase the expression of proinflammatory cytokines in the brain to induce neuroinflammatory changes.[22] Table 2 lists the strategies recommended to prevent delirium in ICUs.

The pathogenesis of long-term cognitive and functional impairment is complex and multifactorial. Neuroimaging studies of patients have identified morphological changes like cerebral atrophy and white matter disruption. In case delirium persists at 3-month follow-up, it is associated with NCD for up to 12 months after discharge.[5,23] Prolonged ICU delirium is associated with early white matter changes of the corpus callosum and anterior limb of the internal capsule. In later stages, integrity decreases, and there is increased diffusion in periventricular, frontal, and temporal white matter.[24,25] The above indicates that the acute brain dysfunction possibly leads to structural neurological changes causing long-term cognition deficit.[4]

### Table 1: Risk factors identified which make the patient susceptible for neurocognitive dysfunction after intensive care stay

| Pre-admission Risk Factors | Post-admission Risk Factors |
|----------------------------|-----------------------------|
| Advanced age               | Longer duration of delirium |
| Poor educational status    | Prolonged mechanical ventilation |
| Prior cognitive impairment | Severe sepsis               |
| Significant comorbidity    | Delirium after CPB          |

### Table 2: Strategies to prevent delirium in intensive care units (Adapted from Rengel KF, et al. Anesth Analg 2019;128:772-80)[4]

- Minimize delirium
  - Avoid benzodiazepines
  - Avoid anticholinergics
  - Short-acting sedatives such as dexmedetomidine or propofol
  - Light sedation
  - Reorientation
  - Sleep hygiene
  - Use Non-pharmaceutical interventions

- Utilization of liberation and animation bundle

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**Figure 1: Important elements in the development of delirium after ICU admission (Adapted from Rengel KF, et al. Anesth Analg 2019;128:772-80)**[4]
Potential Contributors to Perioperative Neurological Dysfunction

Role of intraoperative hypotension

Cerebral insults may result from cerebral tissue hypoxia. Intraoperative systemic hypoxemia and hypotension result in brain tissue hypoxia. A study in the early 1990s, however, reported no association between intra- and postoperative hypotension and postoperative cognitive dysfunction (POCD). Intraoperative hypoxemia is a relatively rare today, but intraoperative hypotension/relative hypotension is frequent in elderly and hypertensive patients. Incidence of hypotension during anesthesia has been reported to be higher in the group that developed dementia, but adjusted for other variables, it was not associated with increased dementia risk. A recent RCT, on patients ≥75 years of age, the protocol required prevention of relative hypotension in the study group. The anesthesiologist maintained a target blood pressure at 90% of baseline mean arterial pressure (MAP), rather than an arbitrary MAP value. With the MAP maintained in the patient’s cerebral autoregulation range, the regional cerebral oxygen saturation in the target group was similar to the no-intervention group. The target group also spent less time with low/high depths of anaesthesia as inhaled agent concentrations were not changed to manipulate blood pressure. Z-score evaluation, by a number of neuropsychological tests, found no correlation between intraoperative hypotension and cognitive function, indicating that intraoperative hypotension plays no significant role in the development of POCD and postoperative delirium.

Role of altered homeostasis

Altered homeostasis is known to cause POCD. A meta-analysis of 14 studies found a 1.26-times higher risk of POCD in diabetic patients as compared with diabetes-free patients. Poor glycemic control, with intraoperative blood sugar levels >200 mg/100 mL, has been reported to impair cognitive function in nondiabetic patients 6 weeks after surgery in patients. Hyperglycemia downregulates the glucose transporter on capillaries to retard glucose influx into brain tissue while hypoglycemia up-regulates it to promote glucose influx.

Data suggest that it may be equally important to avoid both hypo- and hyperglycemia to avoid PND. There is ample evidence implicating diabetes to cause oxidative and proinflammatory stress on the brain vasculature and the BBB with activation of the receptor for advanced glycation end-products (RAGE). RAGE activation impairs endothelial nitric oxide bioavailability, increases adhesion molecules expression, and promotes the release of inflammatory factors.

Both hyper- and hyponatremia may lead to PND. Chronic hyponatremia in humans may cause cognitive impairment, but impairments are reversible with correction of the condition. Hypotonocity in hyponatremia may cause astrocyte swelling and induce the release of osmolytes, such as glutamate, in order to regulate brain volume and thereby cause neuronal abnormalities or injury. Lower extracellular sodium levels are also thought to increase markers of oxidative stress. Hypernatremia (143–153 mmol/L) is also associated with cognitive decline indicating a U- or J-shape association between serum sodium level and cognitive function.

Temperature management plays a major role in POCD. Hypothermic CPB decreases cerebral blood flow and cerebral metabolic rate of oxygen (CMRO₂), which disrupts the BBB. Hypothermia is neuroprotective as it weakens the neuroinflammatory response, impedes free radical formation, and reduces apoptosis. However, rapid rewarming after hypothermic CPB can cause cerebral hyperthermia by disrupting autoregulation mechanisms and lead to cerebral edema. The resulting rise in intracranial pressure impairs perfusion/oxygenation and can lead to POCD. Administration of inhaled anesthetics in a setting of hypothermia has been shown to enhance tau phosphorylation in animal studies leading to memory deficits. Hyperthermia increases CMRO₂, which results in worse neurocognitive outcomes and is associated with increased mortality risk.

Pain-related cognitive dysfunction

Many clinical studies strongly indicate impairment of multiple cognitive functions in patients with chronic pain. On the other hand, there are also studies disagreeing to an association between chronic pain and impaired cognitive function. A recent study, comparing patients with chronic pain with controls, concluded that pain negatively impacts cognition, mainly in the domains of memory and attention, and this relationship is age-dependent. Moriarty et al. have suggested a model based on vying for limited resources, neuroplasticity, and dysregulated neurochemistry to explain the genesis of PND due to pain.

Pathogenesis

Based on Alzheimer pathology

Mechanisms involved in the development of PND may include anaesthetic-induced acceleration of Alzheimer pathology in the gamma-amino-butryric acid.
(GABA) receptors; anaesthetic-induced disruption of gamma-oscillation patterns responsible for amyloid-β clearance; and direct neuronal or glial cell damage. Several histopathological features seen in patients with PND are similar to those seen in patients of Alzheimer’s disease. Alzheimer’s disease pathology classically presents as extracellular deposition of Aβ-amyloid protein plaques, intracellular tau proteins tangles, and inflammation of neuronal cells which is followed by neuronal death.

Biomarkers of neuronal injury, neurofilament light and tau, have been shown to increase after general anaesthesia and surgery. Increased cerebrospinal fluid (CSF) β-amyloid protein and tau proteins levels have been demonstrated in patients developing PND. Changes in these markers, glial cell integrity, and integrity of BBB were also noticed in the CSF of patients after spinal blockade with propofol sedation. Positron emission tomography has also revealed an association of β-amyloid protein deposits with cognitive deficits 6 weeks after cardiac surgery.

**Based on neuroinflammation and oxidative stress**

Data from multiple studies suggest inflammation as the pathogenic mechanism for POCD. Sepsis and surgery are both proinflammatory conditions, which promote the production of cytokines such as tumor necrosis factor-α (TNF-α) and interleukins (IL) like IL-1, IL-6, and IL-10. These cytokines play a significant role in the genesis of POCD, and their high levels can also produce diminished cognitive function. Impaired memory has been demonstrated in patients with high IL-6 and this cognitive impairment persisted 1 month after surgery in patients with high IL-6 levels. Patients with elevated levels of IL 6 and IL-10 have poor 48-month cognitive performance. Peng et al. in a meta-analysis have shown that elevated inflammatory markers, particularly IL-6, were associated with PND.

Endothelial cells, pericytes, and astrocytic end-feet together ensure proper BBB formation, which protects against potentially harmful peripheral molecules. The existence of the BBB and limited lymphatic drainage protects the brain from inflammatory factors, but significant inflammatory states may breach the BBB. Elevated levels of peripheral inflammatory cytokines may disrupt the BBB, and this breach may initiate neuroinflammation. The high-mobility group box-1 chromatin protein (HMGB1) plays a vital role in inflammatory pathways. Elevated cytokines and oxidative stress promote the release and activation of HMGB1 after surgery.

The hippocampus plays a significant role in the brain to assimilate new memories, learning, and emotions. The hippocampus contains a large number of proinflammatory cytokine receptors with a high density of IL receptors. Increased expression of IL in the hippocampus, associated with cognitive decline, has been demonstrated after minor surgery in mice indicating a role of surgery-induced neuroinflammation in cognitive impairment.

The microglia are innate immune cells of the central nervous system (CNS), which are functionally similar to macrophages. Microglia are motile cells that continuously monitor the brain microenvironment and facilitate the synaptic activity, pruning, and remodeling. Microglia regulate cell–cell and cell–matrix interactions and also release multiple proinflammatory, immunoregulatory and oxidative factors. In Alzheimer’s disease, activated microglia have been shown to produce large amounts of cytokines, leading to neuronal dysfunction and death. After surgery adenosine triphosphate (ATP), alarmins, and cytokines, leak from an injury site or their levels may rise in response to systemic inflammation. These mediators enter the brain and activate the microglia to produce cytokines.

Astrocytes are the principal glial cells in the CNS. The astrocyte protein S100β (S100 calcium binding protein β) plays a crucial role in most homeostatic and damage/infection-associated processes. Elevated peripheral cytokines cause neuronal apoptosis and cerebral edema by inducing an inflammatory cascade which induces the centrally located microglia to produce proinflammatory cytokines, oxygen-derived free radicals, and by recruiting monocytes to the brain. S100β released from injured astrocytes spills into the extracellular space, and their elevated serum levels indicate BBB injury. Cytokines bind to the BBB promoting adhesion of cells, permeability and cytokine transfer across the barrier. Acute BBB interruption has been observed, after cardiac surgery, in gadolinium-enhanced magnetic resonance imaging which correlated with subsequent neurological impairments.

Surgery induces elevations of both CSF and serum S100β levels, and this has been shown to correlate with neuropathological processes. An association between serum S100β and impaired cognitive function after various surgery types has been demonstrated, and studies with narrower definitions of POCD have replicated these findings. Elevated E-selectin is a biomarker of endothelial injury. Elevated levels of S100B and E-selectin is associated with worse cognitive function at 3 and 12 months after critical illness. Inflammatory changes associated with critical illness and surgery may induce a cycle of neuroinflammation, leading to apoptosis and atrophy.

POCD is associated with neuronal apoptosis. Microglia induce production and release of reactive oxygen species, which has deleterious effects on brain architecture and neuronal function. Oxidative stress leads to an increase in pro-apoptotic proteins with a concomitant decrease in anti-apoptotic proteins levels in the hippocampus and frontal cortex. Brain tissue has low amounts of antioxidants and is vulnerable to oxidative stress. Microglia express

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antioxidant brain glutathione and its circulating level have been proposed to be a predictive biomarkers of cognitive decline in patients with neurodegenerative disease.\cite{79}

Surgical stress induces a rise in brain nicotinamide adenine dinucleotide phosphate (NADPH) oxidase levels, a key oxidative stress regulator, and this rise correlates with behavioral changes in mice.\cite{80} Superoxide dismutase and malondialdehyde are classical indices reflecting systemic redox homeostasis.\cite{81} The impairment of superoxide dismutase and malondialdehyde, enzymes that catalyze the conversion of the superoxide radicals into hydrogen peroxide or oxygen, has been linked to oxidative stress and neurocognitive deficits.\cite{82}

A flow chart summarizing the major steps in the pathogenesis of cognitive decline after surgery and anaesthesia, based on the neuroinflammation and oxidative stress, is displayed in Figure 2.

**Based on breakdown in CNS synaptic network**

Multiple “functionally connected” brain networks play essential roles in specific cognitive processes. Delirium is a failure to integrate and process information, and it has been hypothesized to represent an acute breakdown in brain network connectivity.\cite{83} We have observed (unpublished) that, in delirious patients, delirium settles after regional blockade in patients with hip fractures indicating that the brain possibly misinterprets pain sensation due to faulty connectivity. In cardiac surgery patients, postoperative global cognitive dysfunction was found to correlate with decreased functional connectivity in critical regions of the brain’s default mode network. Changes in hippocampal neurogenesis and BDNF, seen after cardiac surgery and persisting for weeks after that, are signs of impaired neuronal plasticity.\cite{84}

Cognitive reserve relates to the resilience of the brain to an insult or pathology. Individual differences in cognitive processes or neural networks allow some people to deal with stress better than others. The available synapses and anatomical variability of the neural networks both play an essential role. Default mode network functional connectivity disruptions may underlie PND. Education helps form more neuron synapses and thus fortifies the defense against brain injury. A higher level of education thus possibly offers some protection against POCD as more significant neuronal damage, of a larger number of neurons, is needed to reach the threshold of cognitive decline.\cite{85}

Functional MRI can measure correlated activity patterns between brain regions (functional connectivity). In cardiac surgical patients, the degree of global cognitive dysfunction was found to correlate with the expanse of decreased functional connectivity in the posterior cingulate cortex and the right superior frontal gyrus, critical regions of the brain’s default mode network.\cite{86} Decreased default mode network functional connectivity has also been reported after orthopedic surgery.\cite{87}

Electroencephalogram (EEG) recordings have been used to identify brain connectivity patterns that may be associated with postoperative delirium and/or POCD. Elderly cardiac surgery patients with PND display decreased postoperative EEG alpha band (8–13 Hz) power and connectivity in EEG under general anaesthesia.\cite{88} Patients have significant decreases in alpha band power. Low intraoperative alpha band power has also been correlated with lower preoperative baseline cognitive function.\cite{89}

**Based on GABA receptor theory**

The anxiolytic effects of GABA$_A$ receptor agonists are thought to result from their facilitation of neuronal uptake of chloride ion.\cite{90} Intravenous and inhaled general anaesthetics are positive modulators of synaptic and extra-synaptic GABA$_A$ receptors enabling them to enhance GABA-mediated opening

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**Figure 2: Pathogenesis based of Neuroinflammation and Oxidative Stress. IL - Interleukin; TNF - Tumour Necrosis Factor; CNS - Central Nervous System; S100β - S100 calcium binding protein β**
Best Practices to Prevent PND

Cardiac surgery protocols should ensure proper postoperative cognitive function with the early return of the patient to presurgical functional status and independent living. The potential benefit of the surgery on an elderly, against its potential harm, including PND, must critically be evaluated before any significant intervention. The cognitive function must be evaluated preoperatively. As POCD is more frequent and severe after extensive surgery, perioperative complications must be avoided. Minimally invasive surgery may offer benefits as the procedure is less extensive, and the inflammatory response limited. Several drugs used to facilitate anaesthesia and prevent perioperative adverse effects and pain of surgery/anaesthesia have been implicated for promoting PND. These drugs should be used with caution in the elderly. The medications with this stigma are listed as Table 3. Perioperative anaesthetic protocols to reduce PND need to be employed which include strategies such as avoidance of benzodiazepines, anticholinergics, meperidine; improving sleep hygiene; early mobilization; preventing sensory deprivation; encouraging interaction with family; cognitive stimulation therapies; and aerobic exercise. Use of short-acting anaesthetic drugs is recommended as the duration of cognitive impairment is shorter with them. A large number of investigations have shown that benzodiazepine administration is associated with a risk of neurological dysfunction and a need for prolonged mechanical ventilation.

The MENDS randomized trial found that dexmedetomidine use for targeted sedation was associated with a 60% lower risk of delirium/coma and more days alive as compared to lorazepam. A similar benefit of recused incidence of delirium has been demonstrated with dexmedetomidine sedation vis-a-vis midazolam in the SEDCOM study. With evidence that GABA suppression protects against neurological dysfunction, propofol and dexmedetomidine are increasingly used for procedural and ICU sedation.

Therapies Evaluated for Prevention and Treatment of PND

Many non-pharmacologic, interdisciplinary and multicomponent programs, targeting different mechanisms, have been tried for delirium prevention. Therapies targeting cytokine secretion by immune cells may be useful in POCD. The therapies tried are:

**COX-II inhibitors:** Cyclo-oxygenase (COX) inhibitors, such as parecoxib and celecoxib, reduce activation of microglia and the neuroinflammation following that. They were, therefore, tried for Alzheimer’s disease but a Cochrane review and meta-analysis found no evidence to suggest any significant benefit.

**Statins:** A systematic review and meta-analysis reported a 29% reduction in the incidence of long-term dementia, compared to controls, with the use of statins for both short and long-term cognitive function. However, their use for cognitive change is controversial, with a recent Cochrane review negating this benefit.

**Pregabalin:** Pregabalin was hypothesized to alter the release of neurotransmitters in the hippocampus by

Table 3: Medications used by Anesthesiologists which can have adverse impact of neurological outcome of patients

| Adverse effect | Culprit drugs |
|----------------|---------------|
| Central anticholinergic effects | First-generation antihistamines |
| | Phenothiazine-type antihelminetics |
| | Antispasmodics/anticholinergics |
| | Skeletal muscle relaxants |
| Risk of cognitive impairment and delirium | Benzodiazepines |
| | Corticosteroids |
| | H2-receptor antagonists |
| | Antipsychotics (1st and 2nd generation) |
| Extrapyramidal effects | Metoclopramide |
| Neurotoxic effects | Meperidine |

Intravenous and Inhalational Anaesthetics

- Release of systemic proinflammatory cytokines
- Positive modulation of GABA receptors
- Activation of extra-synaptic GABA receptors
- Chloride ion influx
- Neuronal inhibition/depression - Hypnosis
- Perioperative neurocognitive disorder

Figure 3: Pathogenesis based on the gamma-aminobutyric-acid receptor theory. GABA- gamma-amino-butyric-acid.
moderating microglia activation and restricting cytokine release.\textsuperscript{[101]} Evidence for cognitive preservation is, however, not well established with acute confusional state and disturbance of attention reported as a risk of pregabalin use.\textsuperscript{[102]}

**Dexmedetomidine:** Current evidence suggests that dexmedetomidine protects against cognitive decline in the early postoperative period. Two meta-analyses have shown that it was superior to controls for reducing the risk of postoperative delirium in ICU.\textsuperscript{[103,104]}

**Lidocaine:** There is evidence of a significant reduction in inflammatory markers IL-1\(\beta\), IL-6, IL-8; TNF-\(\alpha\), and c-reactive proteins along with cognitive protection, after intraoperative lidocaine administration.\textsuperscript{[105]} A recent RCT, however, has demonstrated that intravenous lidocaine administered perioperatively in cardiac surgery did not reduce cognitive decline at 6 weeks.\textsuperscript{[106]}

**Ketamine:** There is evidence that ketamine moderates inflammatory macrophage activation and production of cytokines like IL-1\(\beta\), IL-6 and TNF-\(\alpha\).\textsuperscript{[107]} However, studies have demonstrated conflicting results regarding its protective cognitive effect.\textsuperscript{[108,109]}

**Minocycline:** Minocycline is a tetracycline antibiotic with anti-inflammatory and microglial inhibitory properties. It reduces the excitotoxicity resultant from increased glutamate production and subsequent production of mitochondrial reactive oxygen species and resulting neurodegeneration.\textsuperscript{[110]}

**N-acetyl cysteine:** It is a precursor for glutathione which acts to reduce markers of inflammation, suppresses mitochondrial dysfunction, reduces oxidative stress and reverses the behavioral deficits resultant from glutathione depletion.\textsuperscript{[111,112]} It targets many of the cellular processes implicated in cognitive dysfunction. Several recent studies provide evidence for the its procognitive effects and highlight the potential of N-acetyl cysteine in overcoming inflammation and oxidative stress.\textsuperscript{[113]}

**Deferoxamine:** Deferoxamine treatment was found to reduce cytokine production in microglia cultures by preventing the release of TNF-\(\alpha\), IL-1\(\beta\), and IL-6. Deferoxamine reduces oxidative stress by downregulation of NADPH oxidase subunits and p38-mitogen-activated protein kinase responsible for oxidative stress signaling after surgical trauma as a target to treat POCD.\textsuperscript{[114]}

**Conclusion**

With the age scale of the patient population tilting to the geriatric end of the spectrum, PND has become a significant cause of morbidity and mortality in older adults. PND is today perhaps the most investigated health problem internationally. A random search on Pubmed displayed more than 5500 publications on the subject in the last 5 years. A large number of pharmacologic strategies are under investigation to prevent/treat PND, but they need long-term efficacy evaluations.

Inconsistencies and shortcomings, in the screening methodology, currently hinder the diagnosis/recognition of patients with PND. The Network for Investigation of Delirium: Unifying Scientists (NIDUS) was created to support a collaborative network for delirium research to determine the cause, mechanisms, outcomes, diagnosis, prevention, and treat delirium in older adults.\textsuperscript{[115]} The evaluation of anaesthetics on cognitive outcome also seems to be difficult as they have been demonstrated to be potentially neurotoxic and also to be neuroprotective for ischemia-reperfusion injury.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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