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Review

Postoperative cognitive dysfunction in noncardiac surgery: A review

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ABSTRACT

Postoperative Cognitive Dysfunction (POCD) following noncardiac surgery is an underappreciated phenomenon. Researchers consistently find incidence rates around 25% in the first several weeks following noncardiac surgery in elderly patients, and the condition is associated with decreased quality of life, higher healthcare costs, and increased mortality. Despite the frequency and magnitude of its complications, POCD is seldom diagnosed outside of research settings. POCD is loosely defined as a decline in cognitive function following surgery, however, there is currently no consensus on diagnostic criteria for POCD. Proposed etiologies to explain POCD in noncardiac surgery have included the effects of centrally acting anesthetics, Alzheimer's pathology exacerbated perioperatively, changes in neuroreceptor function, and the effects of surgical trauma on cerebral endothelium. However, no single entity has garnered universal support as a single causative factor and the development of POCD likely involves a complicated interaction between patient- and procedure-related variables. Although inhaled anesthetics have been implicated in the development of POCD, any benefits seen with total intravenous anesthesia and regional techniques fade within the first postoperative week, regional cerebral oxygen saturation and processed encephalogram monitoring have produced contradictory findings, and no pharmaceutical adjunct or anesthetic technique has consistently decreased POCD rates. Therefore, the best evidence-based recommendations for preventing POCD are to reduce the inflammatory response to surgery through less invasive surgical approaches when possible and providing adequate analgesia to minimize the stress response. Those at risk for POCD should be provided candid counselling preoperatively so that cognitively demanding tasks can be accomplished before surgery and postoperative assistance arranged. Fortunately, POCD is usually self-limiting and cognitive performance improves during the first several months postoperatively, but there are no evidence-based treatment strategies to hasten recovery. The time has come for the perisurgical community to transition POCD from an entity confined to research settings with updated informed consents that note the possibility of post-operative cognitive decline, pre and post-operative cognitive testing for at-risk individuals, and routine referral for continuing care when post-operative deficits are identified.

Contents

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1. Introduction

Postoperative cognitive dysfunction (POCD) affects up to 25–40% of elderly, noncardiac surgery patients and is associated with decreased quality of life [1] increased exit from the workforce [2], and increased mortality within the first year of surgery [2–5]. As the number of major surgeries performed worldwide approaches 250 million per year [6] with as many as 33% of surgical patients over age 65 [7], POCD prevention is a growing global concern. This comprehensive review of POCD following noncardiac surgery includes information about the incidence, impact, and etiology of POCD as well as current evidence about risk reduction and prevention strategies. PubMed, the Cochrane Library, the Cumulative Index of Nursing and Allied Health Literature (CINAHL), and PsychINFO were searched with a combination of the terms postoperative cognitive dysfunction and postoperative cognitive decline as keywords and MeSH terms.

2. Definition

POCD is a subtle neurocognitive disorder characterized by a decline in cognitive performance following surgery and anesthesia [7]. POCD cannot be diagnosed unless the patient has undergone valid neuropsychological testing before and after surgery and postoperative testing should be conducted at least a week after surgery to allow the acute effects of surgery and anesthesia to dissipate [8]. There are no formal diagnostic criteria for POCD in either the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) or the tenth edition of the International Classification of Diseases (ICD-10) [4]. However, the DSM V does provide blanket guidance for diagnosing neurocognitive disorders: the disturbance cannot fit the criteria for delirium, dementia, or an amnestic disorder, and must be corroborated with neuropsychologic tests showing new deficits in at least two domains of cognitive function for a period of two weeks or more [7]. Currently, a wide variation in testing strategies is used by POCD researchers. Selected tests routinely examine changes in executive function, learning and memory, visuospatial function, and psychomotor function, though no particular test has been universally accepted [4]. No consensus exists for the appropriate threshold decrease in cognitive performance to identify POCD or the most appropriate time(s) to perform testing [4]. Researchers may compare strategies to prevent early, intermediate term, or persistent POCD, loosely defined as occurring from the first postoperative day to several weeks [9], lasting longer than six months [9], and longer than one year, respectively. These variations in testing strategies often prevent meta-analyses.

3. Impact

The overarching themes of POCD's negative impacts are reduced quality of recovery and increased cost. People with POCD experience a decreased ability to comply with discharge instructions and provide self-care which results in missed medication doses [10], an inability to seek medical care [2], poor nutritional status, and delayed wound healing [11]. Some people are compelled to leave the workforce prematurely leaving them dependent on social systems [2] and a positive association exists between POCD and mortality within the first year after noncardiac surgery [2,3]. Rarely, patients affected by persistent POCD never fully regain memory, intelligence, verbal ability, and sociability which impairs individuals' abilities to work and engage in social activities [12]. These unintended consequences cause both direct and indirect increases in health care costs [13].

4. Incidence

In 1955, P.D. Bedford presented the first large-scale study on the subject: in a retrospective review of 1193 elderly patients who received general anesthesia over a five-year period, 10% had temporary cognitive issues described as the inability to write a letter, go shopping independently, or read a book [14]. Eighteen people (1.5% of the sample) remained confused until their death [14]. Identifying these symptoms was based solely on subjective reports from the patient or a relative, was not confirmed with neurocognitive testing, and the investigation didn't follow a predetermined time-course. Regardless, Bedford's findings regarding incidence rates and symptomology are strikingly similar to those of his successors despite remarkable safety advancements in the intervening six decades [4].

The International Study of Postoperative Cognitive Dysfunction (ISPOCD1) was published in 1998 [15]. This large-scale observational study utilized neuropsychologic tests one week and three months postoperatively with a non-surgical control group for

comparison. Of 1218 surgical patients, 266 had POCD at one week (25.8%) and 94 had POCD at three months (9.9%), while only 3% of the control group tested positive for POCD at either time; $p < .0001$ and $p = .0037$, respectively [15].

Recent researchers report similar results. In a sample of 300 hip arthroplasty patients over age 60, 17.1% had POCD on postoperative day seven, 9.5% had POCD at three months, and 2.6% had POCD at one year [16]. In a prospective cohort study of 100 elderly patients undergoing major, noncardiac surgery (general, spinal, urologic, or thoracic cases), the incidence of POCD was 27% at three months [17]. In a study of 87 spinal surgery patients, POCD was detected in 23% of participants one week postoperatively [18]. In a sample of 355 noncardiac surgery patients over 60 years old, 41.4% had POCD at discharge from the hospital and 12.7% had not recovered by three months postoperatively [3]. In another large-scale observational study, POCD was detected in 162 of 776 (20.9%) noncardiac surgical patients one week postoperatively and 52 of 553 (9.4%) at three months [19]. Thus, evidence indicates the overall incidence of POCD in elderly, noncardiac surgery patients to be 17.1–41.4% in the first few week postoperatively, 9.4–12.7% after several months, and 2.6% or less at one year.

5. Etiology

Despite documented evidence of the phenomenon over 60 years ago, the exact mechanisms of POCD development are unclear. Proposed etiologies to explain POCD in noncardiac surgery have included the effects of centrally acting anesthetics, Alzheimer's pathology exacerbated perioperatively, and changes in neuroreceptor function, however, the effects of surgical trauma on cerebral endothelium likely provides the best explanation for the wide variation in surgical cases that cause POCD and associated risk factors [4]. Tissue damage causes the release of proinflammatory cytokines, such as tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), and inhibition of their anti-inflammatory counterparts, interleukin-4 (IL-4), interleukin-10 (IL-10), and transforming growth factor β (TGFβ) [20]. Cytokines communicate with the central nervous system (CNS) via vagal afferent stimulation or by directly entering the CNS [21]. Astrocytes and microglia then release additional proinflammatory mediators which disturb neuronal function, and if concentrations stay elevated for a sufficient length of time, the neuron dies [21]. Indeed, when healthy, young people had IL-6 infused intravenously to simulate the acute phase inflammatory response, they reported decreased self-assessed concentration and cognitive abilities [22].

Elevated concentrations of TNF-α, IL-6, IL-1β, IL-8, neuron specific enolase (NSE), S100-β protein, and C-reactive protein (CRP) are often elevated in POCD-affected study participants supporting an inflammation-POCD relationship [13]. A meta-analysis was undertaken to compare proinflammatory cytokine elevation across POCD trials: compared to POCD-unaffected participants, S-100β and IL-6 concentrations were the cytokines most commonly elevated in POCD-affected participants (standard mean difference for S-100β was 1.37, 95%CI 0.42–2.33, $p < .001$, and for IL-6 was 1.61. 95%CI 0.60–2.62, $p < .001$) [13]. Although frequently elevated, TNF-α, CRP, and IL-1β were not statistically correlated in this meta-analysis [13].

However, neuroinflammation doesn't account for age-related differences in POCD occurrence; after all, young people often have surgery with significant amounts of tissue damage yet rarely develop POCD. Theories developed to explain this fact revolve around the concept of limited reserve in the elderly brain, referred to as the failed resistance model [4,23]. An individual exposed to a stressor with adequate brain reserve may not be pushed beyond a critical threshold that allows detection of dysfunction, however, the same stressor may cause symptoms in another individual with less reserve [7,24]. Decreased white matter [25] immune dysregulation with hyperactive and prolonged microglial responses to stress [26], and more frequent comorbidities with ramifications for endothelial function (i.e., atherosclerosis, diabetes, and hypertension) [20] are more common in the elderly. Therefore, POCD can best be conceptualized as a condition that results from a brain primed by altered CNS responses to stress and a chronically compromised endothelium, becoming overwhelmed by proinflammatory cytokines from peripheral trauma.

6. Risk factors

6.1. Patient-related risk factors

Table 1 lists the most commonly reported risk factors for POCD development. Advanced age is unquestionably the most commonly identified contributor [3,15,27–31]. The elderly are more likely to be mentally or physically frail, exhibit altered pharmacokinetic profiles (reduced rates of drug clearance, prolonged half-lives, smaller muscle mass, increased adipose tissue), increased pharmacodynamic sensitivities, and suffer contributing comorbidities [32].

Preoperative mental capacity is another frequently observed risk factor for POCD development. Lower education attainment and lower preoperative neuropsychologic test scores indicate higher POCD risk [3,15,27]. In fact, the odds ratio for POCD development in participants who did versus did not finish high school in the influential ISPOCD1 was 0.6 (95%CI 0.4-0.9, $p = .002$) [15]. Mild cognitive impairment (MCI), a prodrome of Alzheimer's disease, has been associated with POCD occurrence, but the extent of the relationship between MCI, Alzheimer's, and POCD has not been fully elucidated [4]. Preexisting cognitive impairment (pre-CI) was shown to be a remarkably strong predictor of POCD in a prospective observational study of 300 patients undergoing elective total hip arthroplasty: POCD was diagnosed in double the percentage of participants with pre-CI at 7 and 30 days ($p = .012$ and .039, respectively), and ten times more frequently at 12 months ($p < .001$) [16]. Preoperative MMSE scores under 26 were predictive of POCD at 3 months in a series of 219 patients undergoing surgery for solid tumor removal (univariate analysis OR 6.3, 95%CI 2.4–17, $p < .001$, multivariate analysis OR 6.4, 95%CI 2.1–19, $p = .001$) [31].

Some have questioned if the development of postoperative delirium correlates with the subsequent development of POCD. In one large investigation of causative factors, postoperative delirium was associated with POCD at hospital discharge (1.5% versus 1.1%, $p = .046$), but not at the three-month mark (6.7% vs. 5.6%, $p = .373$) [3]. A more recent large-scale RCT reported postoperative delirium increased the odds of POCD development nearly 10-fold (OR 9.58, 95%CI 4.62–19.9, $p < .001$) [27]. In the case series of patients undergoing solid tumor removal, the development of postoperative delirium was associated with POCD at three months (univariate OR 8.7, 95%CI 3.3–23, $p < .001$; multivariate OR 5.3, 95%CI 1.8–16, $p = .002$) [31]. However, in a study of 1277 patients, postoperative delirium had no overall effect on POCD rates ($p = .3$) [19]. Thus, postoperative delirium's utility in predicting POCD development is unclear at present, although there is sufficient evidence to warrant increased vigilance for POCD in patients who have experienced postoperative delirium.

Comorbidities that alter the endothelial response to proinflammatory cytokines are known to increase POCD risk. A history of alcoholism was associated with POCD after cardiac surgery ($R^2 = 0.21$, $p = .001$) [33] as was cigarette use (OR 2.04, 95%CI 1.11–3.74, $p = .022$) [34]. There is evidence supporting previous stroke [35] and renal insufficiency [34] as risk factors. Metabolic

Table 1
Inferred risk factors for POCD development.

Patient-related	Procedure-related
Advanced age	Major surgery
Lower education level	Duration of anesthesia
Cognitive impairment at baseline (Pre-CI, MCI)	High blood loss
Alcohol and/or cigarette use	Length of hospitalization
Previous stroke	Repeat surgery
Cardiovascular disease	Post-op respiratory complications
DM/metabolic syndrome	SSI
Renal insufficiency	Appearance of POD
APO E4 gene	

Note: These risk factors are contentious and require further research.
Abbreviations: Pre-CI = preoperative cognitive impairment; MCI = mild cognitive impairment; DM = diabetes mellitus; APO = apolipoprotein; SSI = surgical site infection; POD = postoperative delirium.

syndrome significantly increased the rate of POCD in a cohort study of 60 noncardiac patients (43.3% versus 26.7%, $p < .02$) [36]. Several studies have evaluated the interaction of diabetes mellitus and POCD. In a prospective cohort study of 394 patients undergoing major noncardiac surgery, the odds ratio of POCD in patients with diabetes was 2.34 (95%CI 1.22–4.51, $p = .01$) [37]. In a recent meta-analysis of diabetes' influence on POCD, diabetes increased the odds of POCD development, though less than previous research (OR 1.26, 95%CI 1.12–1.42, $p < .001$), however, most of the participants were from cardiac surgery [38]. Despite the known inflammatory sequelae of obesity, a meta-analysis including 1432 participants did not find an obesity-POCD association (relative risk [RR] 1.27, 95%CI 0.95–1.70, $p = .10$) [39]. Hypercholesterolemia was not associated with increased POCD risk in a meta-analysis of 12 studies (RR 0.93, 95%CI 0.34–4.30, $p = .77$) [40].

A search for genetic contributors to POCD development has identified the apolipoprotein (APO) ε4 gene as a possible link. The APO ε4 gene is known to increase the risk of Alzheimer's disease, but its association with POCD is unclear [41]. A study of 2216 older patients found a strong association between APO ε4 during major surgery for cancer resection or fracture reduction in patients receiving isoflurane (OR 3.31, 95% CI 1.25–6.39, $p < .05$), but not in patients receiving propofol-based total intravenous anesthesia (TIVA) (OR 0.93, 95%CI 0.37–2.39, $p > .05$) [42]. The presence of the APO ε4 gene increased the risk of POCD nearly 5 fold (OR 4.74, 95% CI 1.09–22.19, $p = .041$) in a study of 69 elderly patients undergoing major, noncardiac surgery [41]. Despite these results, research findings inconsistently support an APO ε4 – POCD relationship, and no evidence-based conclusions can be made [41].

An individual's preoperative cognitive trajectory is an important risk factor for developing POCD. In fact, a growing body of evidence suggests that *persistent* POCD is altogether nonexistent [9]. For example, a comparison of 8503 middle-aged Dutch twins found insignificant differences in composite cognitive scores many years after one twin received major surgery and the other served as a control [43]. Another study found no long-standing cognitive differences in twins if one had coronary artery bypass and graft (CABG) [44]. Some researchers propose that a patient experiencing a subclinical cognitive decline preoperatively may suffer an acute and noticeable POCD that resolves in a matter of weeks, but due to a declining preoperative cognitive trajectory, never fully regain preoperative cognitive functioning [9]. This situation causes a *post hoc ergo propter hoc* (after this, therefore because of this) fallacy [9].

6.2. Procedural and anesthesia-related risk factors

Surgery and anesthesia comprise risk factors for POCD development independent of patient-related factors. It is common for patients to receive somewhere around a dozen drugs in the perioperative period. Drugs with central anticholinergic effects are known to diminish cognitive performance in the elderly [45–47], but RCTs conclude that POCD is not likely a manifestation of altered serum anticholinergic activity produced by anticholinergic medications [48,49]. Major, invasive procedures with long surgical times and clinically relevant blood loss are associated with higher POCD rates than less extensive, outpatient procedures [3,15,31,50]. Postoperative infection and postoperative respiratory complications are both associated with roughly twice the frequency of POCD (OR 2.17, 95%CI 1.5–3.15, $p = .001$ for infection, OR 1.69, 95%CI 1.01–2.89, $p = .02$ for respiratory complications) [27].

7. Prevention

7.1. Avoiding volatile anesthetics

Animal studies showing anesthetic-induced neuropathology have prompted researchers to evaluate whether avoiding volatile anesthetics can prevent POCD in humans. A recent RCT comparing volatile anesthesia to intravenous anesthesia in a sample of 90 patients recorded significantly higher scores on Montreal Cognitive Assessments (MoCA) and Mini-Mental Status Exams (MMSE) for the TIVA group on postoperative days one, three, and seven (p values for each time period: .003, .008, 0.013 for MOCA; 0.023, 0.015, 0.012 for MMSE) [51]. A much larger study (2000 participants) comparing volatile anesthetics to intravenous anesthesia found propofol-based anesthetics provided significant improvement on postoperative days one, two, and three, but the differences were insignificant by day ten [42]. In a sample of women undergoing laparoscopic cholecystectomies, participants in the sevoflurane group fared better up to four hours after surgery than those who received propofol-based anesthesia, but further follow up was not conducted [52]. A study of 92 elderly noncardiac surgical patients found no difference in POCD occurrence at one week: 12% in the propofol group compared to 15% in the sevoflurane group ($p = .72$) [53]. Thus, POCD rates in the early postoperative period may be lower with propofol-based anesthetics, but no study identified by this review established a link between volatile anesthesia and POCD beyond one week.

7.2. Avoiding general anesthesia

It has been proposed that avoiding general anesthesia when regional techniques are appropriate may reduce POCD occurrence. Meta-analyses conducted in 2010 and 2011 did not support the notion statistically (OR 1.34 for POCD after general anesthesia, 95% CI 0.93–1.95, $p = .26$) [54]; (standardized difference of means −0.08, 95%CI -0.17–0.01, $p = .094$) [55]. A systematic review included eight studies comparing POCD rates with general versus

regional anesthesia for total joint replacement surgery [56]. Of these studies, the three that conducted the first postoperative assessment within one week of surgery reported statistically better outcomes for regional anesthesia, however, there were no detectable differences beyond one week [56]. As was found in the prior comparison between volatile and intravenous anesthesia, any possible benefit to POCD development regional anesthesia may provide appears to be limited to the early postoperative period.

7.3. Cerebral monitoring

Monitors are available for intraoperative monitoring of processed electroencephalograms indicating the depth of anesthesia, such as the bispectral index (BIS) and cerebral state index (CSI), and regional cerebral oxygen saturation (rSO_2) with near-infrared spectroscopy, indicative of oxygen perfusion to the brain. Researchers have looked to these monitors for guidance on perioperative management to avoid POCD. BIS guided anesthetic monitoring has been occasionally found to improve POCD rates, though benefits are inconsistent [4,56]. The influence of BIS on POCD development was studied in a group of 77 patients undergoing general anesthesia for spinal, urologic, or noncardiac thoracic surgery [17]. Median BIS values were not statistically different for the participants who developed POCD compared to those who did not (46 compared 42, $p = .26$) [17]. However, longer lengths of time with BIS under 45 and with burst suppression were protective for POCD ($p = .01$ and .04, respectively) indicating deeper planes of anesthesia may be beneficial [17]. Similarly, in a study of 80 patients receiving TIVA for microvascular decompression of the facial nerve, individuals in deeper anesthetic planes (BIS 30–40) experienced less early POCD than those maintained in lighter planes (BIS 55–65): 10% compared to 27.5% ($p < .05$) [57]. Deeper planes of anesthesia may exert a protective benefit via decreased cerebral metabolism and decreased cerebral blood flow diverting inflammatory mediators away from the brain [27]. In a study of 70 noncardiac surgery patients, the mean CSI was 43 in those with POCD ($n = 9$) and 40 in those without ($n = 43$) after one week ($p = .41$) [58]. BIS guided lighter anesthetics produced lower rates of POCD at three months in a study of 902 noncardiac patients (10.2% compared to 14.7%, $p = .02$) [27]. These conflicting results preclude any evidence-based recommendations for processed encephalogram mediated methods of POCD prevention.

Like BIS, the effects of monitoring rSO_2 have not clearly been shown to improve rates of POCD. No differences in POCD rates were found with rSO_2 under 65% oxygen saturation in 77 noncardiac surgery patients ($p = .79$) [17]. However, several studies with small sample sizes support a relationship between POCD and low rSO_2. The length of time spent under 60% saturation in a study of 87 elderly patients undergoing spinal surgery was different between individuals who did and did not develop POCD: 215 min for the POCD group, 70 min in the non-POCD group ($p = .019$) [18]. Multivariate analysis found rSO_2 under 60% to be the only significant predictor of POCD in that study (OR 1.181 for every 30 min of rSO_2 under 60%, 95%CI 1.034–1.349) [18]. Cerebral oxygen saturation was decreased at all times in patients who developed POCD ($n = 9$) after hip fracture repair in a study of 69 participants [59]. A group of 43 patients undergoing surgical treatment of lumbar spondylosis was randomized into a rSO_2 monitoring group and a control group; after 30 days, the results of visual working memory N-back Tests were significantly different ($p = .013$ for time, and $p = .004$ for number of correct and incorrect answers) [60]. Zheng et al. [61] conclude that available evidence is currently insufficient to recommend near-infrared spectroscopy for POCD prevention in a systematic review of rSO_2 monitoring in cardiac surgery due in large part to methodological issues in published studies. Another meta-analysis found no significant differences in NIRS use when cardiac studies were excluded (RR 0.79, 95%CI 0.61–1.02, $p = .07$) [62]. Processed encephalogram and rSO2 used together may provide better protection than either alone [63], but these findings need to be replicated in future RCTs. In summary, regional cerebral perfusion monitoring holds some promise for POCD prevention but needs to be explored in larger sample sizes before recommendations can be definitively made.

7.4. Prehabilitation

There is a growing body of evidence demonstrating improved cognition after a program of modest physical activity in deconditioned, elderly people via stimulation of neurogenesis, enhanced synaptic plasticity, and systemic anti-inflammatory effects which may prove beneficial for POCD prevention [21]. An animal study found that a two-week period of preoperative environmental enrichment attenuated postoperative memory impairment and the neuroinflammatory response to surgery as measured by hippocampal levels of IL-1β and TNF-α [64]. An RCT with human subjects evaluated the effects of three one-hour training sessions with the method of *Loci*, a system of mentally associating concepts to familiar locations to improve recall [65]. The results are encouraging: 36.1% of the control group developed POCD compared with only 15.9% of the individuals who received the experimental training ($p = .007$) [65]. Prehabilitation for POCD prevention is a novel concept but will require substantial research efforts before it can be used in the clinical arena.

7.5. Pharmacologic strategies

Preventing POCD with the addition of a single pharmacologic agent associated with low cost and a high safety profile would be ideal, however, no such agent has been identified. Thiopental, propofol, nimodipine, monosialotetrahexosylganglioside (GM1 glycoside), lexipafant, glutamate, xenon, erythropoietin, remacemide, piracetam, magnesium, rivastigmine, pegorgotein, and 17β-estradiole have all been tried with no apparent benefit [66].

7.5.1. Steroids

Although the leading theoretic basis for POCD is an inflammatory response, glucocorticoid administration has been found to exacerbate POCD rather than prevent it. In the Dexamethasone for Cardiac Surgery (DECS) trial, 13.6% of participants who received 1 mg/kg of dexamethasone on induction developed POCD compared to 7.2% of controls at 1 month postoperatively (RR 1.87, 95%CI 0.90–3.88, $p = .09$) [67]. Three doses of dexamethasone (0.1 mg/kg, 0.2 mg/kg, and placebo) were trialed in 954 patients undergoing microvascular decompression for facial nerve spasms [68]. Differences between the placebo and 0.1 mg/kg groups were trivial ($p = .615$), but 0.2 mg/kg was found to be harmful ($p = .009$ compared to placebo) [68].

7.5.2. Opioids and multimodal strategies

No evidence-based recommendations can be made regarding opioid usage and POCD development in noncardiac surgery. Some researchers recommend employing strategies that minimize their need [56], and transitioning to oral pain medications as soon as possible [69]. Regardless of the method, adequate pain control should be considered to minimize the body's stress response [5], and if possible, pain should be treated preemptively [70].

7.5.3. Ketamine

Ketamine administration has shown cerebral protective and anti-inflammatory properties after cardiopulmonary bypass. For

instance, only 27% of patients given a 0.5 mg/kg bolus of ketamine on induction for coronary artery bypass and graft (CABG) or cardiac valvular surgery developed POCD compared to 81% in the placebo group ($p < .001$) [71]. Theoretical mechanisms for this protection include mitigating excitotoxic injury from glutamate-calcium overload, reducing neuronal cell loss, or a preconditioning effect from inactivation of N-methyl-D-aspartate receptors [71]. However, ketamine has not proven efficacious for POCD outside of the cardiothoracic suite; no difference was observed after 0.5 mg/kg on induction in elective, orthopedic cases ($p = .98$) [72]. Further investigation is warranted before ketamine's ability to thwart POCD development can be determined.

7.5.4. Lidocaine

Lidocaine has demonstrated neuroprotective qualities through deceleration of ischemic transmembrane ionic shifts, reduction in cerebral metabolic rate, and modulation of excitotoxin release [73]. Lidocaine has been tested with various bolus dosages followed by infusions of variable rates and durations to prevent POCD in cardiac surgery. A benefit was observed nine days postoperatively with a 1.5 mg/kg bolus followed by 4 mg/min until the end of surgery in a study of 118 cardiac patients ($p = .028$) [74]. A similar design produced significant results with a 1 mg/kg bolus followed by an infusion that was tapered over time for 48 h ($p = .025$ at 10 days, $p < .05$ at 10 weeks, and nonsignificant at six months) [75]. Two other similarly designed studies in cardiac patients did not produce significant findings, but the initial testing was performed at six weeks postoperatively in one [75], and ten weeks in the other [76]. Missed temporary cases of POCD in these studies is plausible, and if present, would make the results of the four studies with similar designs and populations homogenous. Outside the cardiothoracic suite, a 0.5 mg/kg bolus of lidocaine followed by 0.5 $mg*kg^{-1}*hour^{-1}$ until the end of surgery in 60 patients undergoing gastric tumor resections produced remarkable results: POCD was found in 33.3% of the control group compared to 6.7% of the lidocaine group two days postoperatively ($p < .05$) [77]. Given the existence of only one study outside the cardiothoracic suite (which had a small sample size and early postoperative testing), lidocaine cannot not yet be recommended to prevent POCD. However, given its low cost, high safety margin, and a handful of promising trials, lidocaine is an attractive candidate for an ideal POCD-prevention medication and merits future researchers' attention.

7.5.5. Dexmedetomidine

Perioperative dexmedetomidine administration has generated considerable interest in preventing postoperative cognitive derangements. Dexmedetomidine is usually used in clinical anesthesia for sedation without respiratory depression and to blunt sympathetic nervous system responses to painful stimuli, but a tempered inflammatory response has been reported in animal research [78]. A meta-analysis of 13 trials demonstrates intraoperative dexmedetomidine produces relative risks of 0.59 (95%CI 0.45–2.95, $p < .001$) on the first postoperative day and 0.66 (95%CI 0.45-0.98, $p = .04$) at any point after for early POCD development [12]. Perioperative infusions of dexmedetomidine coupled with parecoxib were able to preserve MMSE scores during the first week postoperatively compared to placebo (small but statistically significant differences for 152 total participants, $p < .5$ at 1, 2 and 3 days) [79]. However, a multicenter study of 404 patients undergoing major, noncardiac surgery found no differences in POCD at 3 and 6 months [80], implying that dexmedetomidine's capacity for POCD prevention may be limited to the early postoperative period.

7.5.6. Other medications

Participants who received piracetam, a CNS stimulant, preserved test scores far better than control-group participants after CABG (scores decreased about 40% more in the control group, $p < .005$) [81]. Parecoxib, a cyclooxygenase-2 (COX-2) inhibitor, was able to abate POCD development in a study of 134 patients undergoing total knee arthroplasty compared to controls: 16.7% versus 33.9% ($p < .05$) on postoperative day 7 [82]. A meta-analysis determined that ulistatin, a urinary trypsin inhibitor used for inflammatory disorders, was also able to curb POCD prevalence at 1 week postoperatively compared to controls (RR 0.37, 95%CI 0.23–0.61, $p < .0001$) [83]. Neither piracetam, parecoxib, nor ulistatin are available in the United States, but researchers could use these findings as a basis for investigating available nootropics, COX-2 inhibitors, and urinary trypsin inhibitors in noncardiac surgery.

Dobutamine exhibits central anti-inflammatory properties via hippocampal beta adrenergic mediated decreases in TNF-α, IL-6, and IL-10 [84]. Three infusion rates of dobutamine (2, 4, and 6 $mcg*kg^{-1}*min^{-1}$) were compared in 124 elderly people undergoing total hip arthroplasties under epidural anesthesia; MMSE scores were preserved in the 2 and 4 $mcg*kg^{-1}*min^{-1}$ groups ($p < .05$) [85]. Though promising, these results need to be replicated before POCD preventative capabilities can be attributed to dobutamine. Furthermore, the risk of creating a deficit in coronary oxygen supply and demand may hinder dobutamine's adoption as a first line agent for POCD prevention.

8. Treatment

Fortunately, POCD is usually self-limiting and symptoms lessen as inflammation is processed and CNS endothelial function returns to baseline [20,86]. Unfortunately, even less is known about POCD treatment than its pathology and prevention. Depression and anxiety may accompany perceived cognitive deteriorations following surgery [87,88]; standard screening and treatment for these conditions is justifiable even though no studies evaluating POCD recovery with depression or anxiety treatment were identified by this review. Potentiating factors such as pain, infection, and electrolyte imbalances should be addressed [89].

9. Nonpharmacologic recommendations

It is generally recommended that individuals at risk for POCD development be counseled prior to surgery [4]. This counselling would provide people with an opportunity to make important decisions preoperatively and arrange postoperative support for cognitively demanding tasks [4]. When possible, the surgical team should select shorter, less invasive procedures that can be done on an outpatient basis or with a short hospital stay [51]. Evidence-based prevention and treatment recommendations found throughout this review are summarized in Table 2.

10. Conclusion

Postoperative cognitive dysfunction is a significant, yet often unrecognized, complication to surgery and anesthesia. The condition is usually self-limiting, yet has been shown to increase healthcare cost, morbidity, and mortality. Though many have been tested, no single pharmacologic agent has proven ideal for POCD prevention and any cognitive improvement observed with regional or total intravenous anesthesia fade during the first postoperative week. Surgeons and anesthesia providers should be mindful of the risk factors for POCD development (Table 1) and utilize strategies to thwart its development (Table 2). Surgical and anesthetic consents should reflect a candid POCD-specific discussion for at-risk

Table 2
Inferred recommendations for POCD prevention and treatment.

General Considerations	
Optimize mental and physical status preoperatively	
Counsel patients at high risk	
Take measures to avoid postoperative delirium	
• Minimize fasting period	
• Maintain circadian rhythm	
• Avoid medications with central anticholinergic effects	
Use less invasive surgical techniques when possible	
Anesthetic Management	
Pharmacologic	-Dexmedetomidine 0.2–0.3 mcg/kg/hr → improved cognitive function in first week
TIVA vs volatile anesthetics	-Improved cognitive function in first week with TIVA
Regional vs GA	-Improved cognitive function in first week with regional
Treatment	
Rule out other causes of cognitive deterioration	
Investigate suspicious cases with neuropsychologic tests & depression/anxiety screening	
Consider SSRIs and/or other standard depression/anxiety treatment approaches.	
Supportive care	

Note: These risk factors are contentious and require further research.
Abbreviations: POCD = postoperative cognitive dysfunction; POD = postoperative delirium; mg/hr = milligrams per hour; mcg/kg/min = micrograms per kilogram per minute. GA = general anesthesia, TIVA = total intravenous anesthesia, SSRI = selective serotonin reuptake inhibitor.

individuals. Baseline neuropsychologic testing should be accomplished preoperatively for those at greatest risk and routine follow-ups should include evaluation of cognitive performance. In short, it is time for a paradigm shift in the standard of care for people at risk for POCD development: we must transition POCD from an entity confined to research settings and into mainstream, clinical practice.

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Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tacc.2018.08.003.

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