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Postoperative delirium: Addressing the rising scourge in healthcare

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Abstract

The rising global life expectancy comes with challenges relating to the increasing elderly population, including delirium which those with background cognitive deficits are especially prone to. Advances in anaesthesia and surgery have contributed to a rapidly increasing number of surgeries in the elderly. Postoperative delirium with its worrisome prognosis is a common complication of surgery in the elderly; yet widely under-diagnosed, and under-treated. The use of validated tools to detect delirium, and preoperative cognitive impairment which is a core risk and prognostic factor is key to risk stratification, prevention and treatment. Management of postoperative delirium is anchored on prevention through optimization of modifiable risk factors, early detection using validated tools and care directed at reducing its severity and duration when it occurs. This is best achieved by individualized care through multi-component interventions involving the anaesthesiologist, surgeon, geriatrician, psychiatrist, physiotherapist, nursing services and the patient's family. However, It is imperative to state that while the key principles of multi-component intervention apply broadly, the specific components of each regimen may vary widely. Despite existing international guidelines on the management of postoperative delirium, wide knowledge and practice gap is still prevalent.

Key words: Elderly; surgery; delirium; cognitive impairment; anaesthesia

Introduction

The United Nations population estimates indicate that by 2050, 16% of the global population will be 65years or older (with Japan and parts of Europe having as high as 40%); compared to 9% in 2019.[1] This changing demography is a major social transformation with implications for healthcare. In reality, the demand for healthcare services by the elderly is disproportionately beyond the foregoing statistics, as represented by the 65% acute hospital admissions in England and Wales.[2] Postoperative delirium (POD) is acute brain dysfunction that manifests as acute onset of fluctuating altered consciousness, inattention and disorganized thinking following surgery. Postoperative delirium is common in the elderly but widely under-diagnosed, while the diagnosed cases are poorly treated. Prevention through the optimization of modifiable risk factors is key in the management. The reported incidence of POD varies widely and could range from 3.6% to 45%[3,4] depending on the sample patient population, method of observation and delirium instrument deployed for the assessment. The Incident rate of 1.5% has been reported following total joint replacement surgery based on retrospective review of routine nursing assessment chart,[5] while 51% rate was reported among patients that underwent elective cardiac surgery who were assessed twice daily during the first five postoperative days using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU);[6] lending credence to the influence of different methodologies on the quoted incidence rates in the literature. Owing to its fluctuating nature enhanced detection of delirium requires multiple

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daily assessments.[7] However, with the near absence of literature on postoperative delirium in Africa how this scourge is being addressed in the region can only be imagined. Hence the purpose of this review is to acquaint perioperative practitioners with practice recommendations relating to this serious complication, and for which poor awareness and sub-optimal care have been near-universal.

Materials and methods:

Design: This is an unsystematic narrative review of several clinical and educational issues relating to postoperative delirium in the elderly, rather than a narrowly focused review of a research question typical of systematic reviews. It has been synthesized from previously published literature in order to illuminate the various aspects of clinical and knowledge gaps which inform the objective of this review. Consequently, no rating or grading of evidence was used.

Search Strategy: Online search was conducted on two databases; PUBMED and Cochrane Database of Systematic Reviews. The PUBMED database was searched using the term ….. 'delirium elderly' for the period spanning 1990 to December 2020; and 9117 articles were turned in; with the observed exponential increase in the articles over the period supposedly reflecting the surge in interest regarding delirium in the elderly within the research community. The search term 'postoperative delirium studies in Cochrane evidence' was used to explore the Cochrane Database of Systematic Reviews. Further hand searches of the references of retrieved literature were also conducted.

Eligibility criteria: Only studies of human subjects with available English language full texts, published in peer reviewed journals were considered, and retrieved. The study was limited to adult and elderly populations, as such studies considering delirium in children were excluded.

Consequences of POD

Whereas the episode of postoperative delirium is transient, it is a harbinger of wide-ranging consequences; including an independent association with higher morbidity and mortality rates in diverse surgical settings. The patients with POD have an increased length of stay in the hospital with attendant increase in healthcare costs,[8,9] and they are more prone to postoperative complications.[10,11] The development of POD presages a cascade of deterioration in physical and cognitive function, with increased deaths. Following POD return to the functional state prior to the surgery is less likely[8,12] while both short-term and long-term mortality have been shown to be significantly higher.[8,12,13] Patients who developed POD are at increased risk of fresh onset and more rapid deterioration of pre-existing cognitive impairment, with a progressive and irreversible decline in mental functions.[14-16]

Risk factors for POD

A constellation of preoperative, intraoperative, postoperative, patient and surgical factors have been implicated in the development of postoperative delirium, but among them advanced age and poor preoperative cognitive status rank high.[17-20] Other associated factors include; poor functional status, co-morbidities, American society of anesthesiology (ASA) grade, polypharmacy, malnutrition, alcohol use, lower education, perioperative anaemia or blood transfusion, history of diabetes, perioperative use of anticholinergics, opioids and benzodiazepines, perioperative hypotension or hypoxia, perioperative dehydration or electrolyte imbalance, increased surgery duration, perioperative pain or hypoxia, night time surgeries, pain, sleep deprivation and urethral catheter in-situ. Patients admitted into the ICU after surgery are at increased risk of POD due to the patients' isolation, strange environment, sleep disturbance, device attachments and lack of family support. Mechanical ventilation and the duration of ICU stay have equally been found to be risk factors for delirium.[21]

Prognostic indicators in POD

Postoperative delirium can be classified based on psychomotor features as; hyperactive, hypoactive, or mixed.[22] The hypoactive form which carries the worst prognosis is less dramatic and most often unrecognized, yet is the most common.[23,24] Formal assessment and recognition of motor subtypes of delirium in patients with POD aids in creating awareness, and relating better with the respective

adverse event profile. Patients with severe delirium, or long-lasting delirium also have worse outcomes.[25,26] Another determinant of prognosis in patients with POD is co-morbid dementia. Investigation of the impact of delirium superimposed on dementia among elderly Italian patients by Bellelli et al. found that the mortality in this subgroup was increased over two-fold compared to those with dementia alone, with delirium alone, or with neither dementia nor delirium;[27] further highlighting the grave impact of pre-existing cognitive impairment, not only on delirium incidence but as a predictor of worse outcome in delirious patients. Similarly, a Brazilian study conducted to evaluate the combined effect of dementia and delirium on elderly individuals posted in-hospital mortality of 8% for patients without delirium or dementia, 12% for patients with dementia alone, 29% for patients with delirium alone, and 32% for 'Delirium Superimposed on Dementia' (DSD) patients.[28] Other factors such as advanced age and low baseline functional status have also been implicated as indicators of poorer prognosis in elderly patients with delirium.[29] Recent evidence also suggests that pharmacological intervention with antipsychotics alone, or in combination with benzodiazepines is associated with longer length of hospital stay, mortality and institutionalized care post-discharge.[30]

Preoperative cognitive assessment in older adults

Cognitive deficit is a frequent morbidity in older adults with a recent report indicating a prevalence rate of 33.3% in a community-based study conducted in Cameroon, Central Africa.[31] A very high prevalence of cognitive impairment (51.9%) was observed among elderly patients during preoperative evaluation for elective cancer surgery in Romania, with a considerably higher figures being noted with respect to the very elderly segment of this population; reflecting increasing prevalence with age.[32] Ageing is associated with a global decrease in physiologic reserve, including a decline in cognitive reserve related to chronic neuroinflammation "inflammaging"[33,34] - a mechanism of age-related susceptibility to cognitive decline that has also found expression in animal model.[35] Baseline cognitive deficit, frequently present in the elderly has consistently been shown to be a major risk factor for postoperative delirium. We had earlier been informed that delirium is associated with accelerated cognitive decline, long-term functional impairment and other poor outcomes. Other studies have revealed that baseline cognitive status independently predicts mortality following surgery in the elderly, even after adjustment for confounders such as age, ASA grade and functional status; and despite similarity in postoperative complication rates and hospital length of stay.[36,37] These considerations provide sufficient ground for routine formal assessment of cognitive status during clinical assessment of elderly patients for anaesthesia and surgery. Current European and American guidelines on the preoperative evaluation of elderly patients have recognized this.[38,39] While it is acknowledged that many among the battery of tools currently deployed for detecting cognitive impairment are inclined to cultural and educational bias the Mini Mental Status Exam (MMSE) is still adjudged the criterion-standard, and is most frequently used. This, in spite of its low points in sensitivity[40] and very poor performance among elderly patients with poor educational and socio-economic background.[41,42] However, the short blessed test (SBT)[43] also termed the short Orientation-Memory-Concentration test which is a very brief, rapid and simpler tool without copyright protection has demonstrated comparable performance to the MMSE in detecting cognitive impairment in the elderly.[44,45] Thus it presents an attractive alternative to the MMSE and can be administered by non-psychiatry-trained personnel and on less-educated, or visually impaired elderly patients. The challenge posed by the lack of suitable instrument with optimal performance in detecting cognitive impairment in resource-poor countries with limited health personnel and uneducated elderly patients is a major one, as these regions account for the majority of patients with cognitive impairment.[46] This concern has also been raised recently by Magklara et al.[47] For elderly patients in whom cognitive deficits have been detected current evidence does not support pharmacological interventions in the management.[48] Instead, non-pharmacological interventions through lifestyle modification offer better prospects, and encompass

physical, mental and social activities tailored to the needs and ability of the individual patient. Among these are physical exercises, mental exercises (cognitive training and rehabilitation), mobility training, sensory stimulation with visual and hearing aids, sleep hygiene, proper nutrition and hydration, smoking and alcohol control.[49,50]

Delirium detection tools

Psychiatrists' evaluation based on the DSM-V Diagnostic and Statistical Manual for Mental Disorders is currently regarded as the gold standard method for diagnosing delirium.[51] The inherent expertise and time requirements however limit its utility for the ubiquitous and fleeting nature of the scourge that is POD in the clinical setting. Consequently, brief and easy tools are preferred. Among the common tools deployed in detecting POD are; the Confusion Assessment Method (CAM), Confusion Assessment Method for Intensive Care Unit (CAM-ICU), Nursing Delirium Symptom Checklist (NuDESC), the Neelon and Champagne (NEECHAM) Confusion scale, the Delirium Observation Screening (DOS) scale, and the 4 A's test (4AT). However, a comparative study conducted by Neufeld et al. concluded that neither the CAM-ICU nor the NuDESC had satisfactory sensitivity, despite their high specificity for POD.[52] The NEECHAM confusion scale and the DOS scale (like the CAM-ICU and the NuDESC), are popular tools for delirium detection among nurse-raters; but time consumption and difficulty of use make the former less attractive for routine clinical application.[53,54] The 4AT is a brief screening tool recently developed for delirium screening in acute care, but which has been validated with good test properties for use in POD detection.[55] The 'Confusion assessment method' (CAM)[56] is regarded as the best offering among the bedside tools for detecting POD in the elderly; on account of its simplicity, speed, versatility , validity and reliability.[57-59] While the CAM was designed for use by nonpsychiatry-trained physicians, the importance of training in its use has been emphasized in the work of Ryan et al.[60]

Clinical interventions

Non-pharmacological clinical interventions to prevent and treat POD have been receiving some modest attention and several of these have been successfully implemented in hospitalized patients. While many of these had been isolated uni-component therapies[61,62] multi-component measures are preferred in view of the plurality of risk factors implicated in POD. The meta-analysis conducted by Hshieh et al. using 14 interventional studies to evaluate the effectiveness of multi-component non-pharmacologic delirium prevention interventions in reducing delirium attests to the effectiveness of this approach.[63] Economic analysis of these prevention strategies has also proven that they are hugely cost-effectiveness in surgical,[64] medical[65] and ICU settings.[66]

Enhanced Recovery After Surgery (ERAS) program

Since its introduction for abdominal surgery patients over two decades ago, ERAS has been adapted to surgical specialties that have predominant elderly population such as arthroplasty and oncology. Conceived to enhance recovery, reduce morbidity and length of stay in surgical patients through optimization of perioperative care, ERAS has become increasingly attractive to both patients and care providers. Evaluation of elderly patients undergoing fast-track surgery program has revealed that POD could contribute significantly to increased length of stay in the ERAS program and mitigate against its objective.[67] Hospitalization has several inherent attributes that predispose elderly patients to development of delirium.[68,69] However there is substantial evidence suggesting that ERAS is associated with less POD than traditional care.[70] This should not be a surprise though, since the multidisciplinary, multimodal and individualized patient optimization that is the sine qua non for delirium prevention is implicitly implemented in the enhanced recovery pathway of ERAS. Delirium prevention thus qualifies as one of the quality metrics for ERAS programs in the elderly. ERAS may have also presented a platform for implementing many of the preventive interventions for postoperative delirium. Prehabilitation with its three main pillars of physical, nutritional, and psychological optimization of patients, as distinct from traditional medical optimization of comorbid conditions has evidence base in improving surgical outcome, and has also found accommodation in the ERAS model.[71]

Table1. Hospital elder life program (HELP), and its modifications. (Part one)

Study/year/ country	Intervention Components	Impact	Comment
Inouye et al. [72]/1999 USA	6 targeted interventions: cognitive impairment, sleep deprivation, immobility, dehydration, vision or hearing impairment.	Reduced delirium (9.9% versus 15.0%). Reduced total number of days with delirium (105 versus. 161), p=0.02). Reduced number of delirium episodes (62 versus 90), p=0.03.	Implemented by Geriatric nurse specialist, Elder Life Specialists, therapeutic-recreation specialist, physical-therapy consultant, trained volunteers and geriatrician. Medical ward.
Boockvar et al. [73]/2016 USA	6 targeted interventions: Orientation, mobilization, nutrition, hydration, sleep, delirium-risk medication alert.	Reduced hospital transfer and mortality in the nursing home	Implemented by Certified Nursing Assistant, with in-house nursing team, physician and a geriatrician program director. Nursing home.
Chen et al. [74]/2017 Taiwan	3 targeted interventions: orienting communication, oral and nutritional assistance, and early mobilization	Reduced relative risk of 0.44 in the modified HELP group (95% CI, 0.23-0.83), p =0.008.	Implemented by modified HELP nurse. Surgical ward, postoperatively.
Wang et al. [75]/2019 China	11 targeted interventions:3 universal interventions (Orientation, cognitive stimulation, early mobilization) plus 8 targeted patient-specific interventions(pain,sleep, hypoxia, nutrition, dehyration/constipation, Vision/Hearing,Hypoxia, Catheter Associated UTI Prevention, Multiple medications)	Reduced delirium incidence; 2.6% versus 19.4%. RR (95% CI); 0.14 (0.05-0.38), p <0.001 Severe delirium is less (1.5% versus 9.6%), p=0.008	Implemented by family member, assisted by family-paid caregivers; under nurse guidance. Surgical ward, postoperatively.

Table1. Hospital elder life program (HELP), and its modifications. (Part two)

Huson et al. [76]/2016 Canada	6 targeted interventions: cognitive impairment, sleep protocol (limited), early mobility protocol (modified), dehydration, vision or hearing impairment.	Larger reduction in delirium prevalence from admission to discharge for patients who received the HELP.	Implemented by trained volunteers; in collaboration with Elder Life Specialist, nursing, therapy, and administrative staff members. Post-acute facility.
Vidan et al. [77]/2009 Spain	7 targeted interventions: orientation, sensory impairment, sleep, mobilization, hydration, nutrition, drug use	Lower incidence of delirium, p=0.005.	Geriatric unit and internal medicine unit.
Ochiai et al. [78]/2020 Japan	5 targeted interventions: orientation, sleep, early rehabilitation, provision of glasses, hearing aids, and dentures, termination of continuous infusion.	Reduction in delirium was not statistically significant; p=0.06.	Acute medical ward.
Gorski et al. [79]/2017 Poland	7 targeted interventions: Orientation and cognitive stimulation, addressing psychosocial distress, mobilization, dehydration, nutrition, provision of visual and hearing aids, improving sleep.	Less antipsychotic medications with intervention (16.9% versus 32.3%). No difference in the number of delirium episodes (13.8% versus 18.5%).	Intervention implemented by trained volunteers, in medical wards.
Zaubler et al. [80]/2013 USA	6 targeted interventions: Daily visits, therapeutic activities, feeding, hydration, sleep, and vision/hearing impairment.	40% reduction in delirium, p=0.019. Reduction in patients days with delirium, p = 0.005.	Medical ward, in a community hospital.

The Hospital Elder Life Program (HELP)

A model of the multi-component bundle therapy for preventing POD tagged "The Hospital Elder Life Program (HELP)" was structured over two decades ago by Inuoye et al.[72] and has received wide acclaim. However it must be emphasized that the multidisciplinary team and the six risk factors targeted in the HELP (cognitive impairment, sleep deprivation, immobility, visual and hearing impairment, and dehydration) are by no means exhaustive and several modifications have been effectively adapted to suit diverse patient populations and settings[73-80] (Table 1). Several other preoperative, intraoperative and postoperative risk factors are amenable to environmental and supportive modification by multidisciplinary teams through; medication review, nutrition review, correcting preoperative anaemia and electrolyte derangement, encouraging visits by family, music, avoiding prolonged fasting and unnecessary invasive procedures, optimal opioid-sparing pain management, encouraging daytime surgery, with provision of appropriate lighting and clock to facilitate orientation and sleep.

Anaesthesia perspectives

The anaesthesiologists implement a handful of interventions addressing the modifiable risk factors for POD. In view of the pre-eminence of cognitive deficits in predicting POD and outcome, including mortality in geriatric surgical patients, it is apposite that anaesthesiologists conduct mandatory cognitive assessment in this patient population in order to situate overall preoperative fitness and risk appreciation properly. This is in addition to the traditional American Society of Anesthesiologists (ASA) grading which considers the patients physical status only, but not cognitive status. Other measures include preoperative polypharmacy review, prevention of prolonged fasting and dehydration, perioperative hypoxia, hypothermia and hypotension, avoidance of anticholinergic drugs and dehydration, optimal perioperative pain management with opioid-sparing multimodal analgesia. An anaesthesia-based program implementing some of these multi-component interventions (early surgery, oxygen therapy, and control of peri-operative hypotension) has been credited with markedly reducing POD incidence, duration and severity.[81] Titration of anaesthetics and cerebral monitoring of anaesthetic depth in surgical patients undergoing sedation or general anaesthesia facilitated by processed EEG have long been part of anaesthetic practice. Earlier comparative studies using Bispectral index (BIS) or auditory evoked potentials (AEP) monitoring had shown that titration of anaesthetics with these non-invasive devices led to reduced anaesthetic exposure with improved recovery profile and patient satisfaction, compared to routine clinical monitoring.[82,83] Subsequently, interest in POD prevention through anaesthetic-sparing has festered, with several meta-analysis studies and Cochrane reviews attesting to POD reduction accruable to cerebral monitoring in patients undergoing general anaesthesia.[84-86] However, its approval for this indication has so far remained contentious.[87,88] Sedation is extensively used for procedures in the operating room and ICU to improve patient comfort and cooperation. Still, the role of cerebral monitoring in preventing delirium has been over-represented in patients undergoing general anaesthesia. Nevertheless, information from the few available studies on BIS monitoring of sedation suggests that it could also have a beneficial impact on reducing POD.[89,90] Thus cerebral monitoring during anaesthesia and sedation could be considered a worthy option for avoiding unduly high exposure to anaesthetics in patients at high risk of delirium. Current guidelines do not recommend any technique of anaesthesia (general versus local anaesthesia), anaesthetic agent or pharmacological prophylaxis for the prevention of POD. While there is preponderance of evidence conferring superiority on regional techniques of anaesthesia over general anaesthesia in respect of deep vein thrombosis, blood loss and respiratory complications, among other outcomes; there is no such evidence to support a technique over the other regarding POD.[91] However, large scale, multicentre randomized controlled trials are ongoing and may provide further insight regarding the impact of anaesthetic technique on POD.[92] Similarly, the route of administering postoperative analgesia does not seem to impact the development of POD.[93] Despite of the popularity of the neuroinflammation hypothesis of POD,[94,95] meta-analysis of several works evaluating the role of anti-inflammatory adjuncts such as dexamethasone in preventing

POD drew blank.[96] While the use of pharmacological prophylaxis for the prevention of POD is not recommended by current guidelines, the recent meta-analysis by Ciu et al. attests to the better safety profile of dexmedetomidine regarding POD, compared to other drugs used for perioperative sedation.[97] In the ICU setting where delirium incidence is highest dexmedetomidine-based sedation has displayed similar trends.[98,99] Optimization of pain control using multimodal strategies such as acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), pregabalin, gabapentin, dexmedetomidine, local infiltration anaesthesia and nerve blocks have also been credited with remarkable opioid-sparing benefits and satisfactory pain control that benefits patients at risk of POD.

From the foregoing, and his pivotal role in the multiple initiatives at enhancing safety and better surgical outcomes for the elderly such as prehabilitation[100] and ERAS,[101] the anaesthesiologist has substantial potential in influencing the course of POD in older adults.

Pharmacological prophylaxis

Pharmacological prophylaxis per se is currently not recommended for POD prevention. However, following the reported efficacy of dexmedetomidine prophylaxis in several studies.[102-104] interest in this drug is increasing despite some contradictions and queries regarding the evidence for it.[105,106] The use on low dose of intraoperative ketamine to prevent POD had gained some attention, but a recent meta-analysis which utilized 6 RCTs did not yield convincing evidence.[107] Furthermore, the Prevention of Delirium and Complications Associated with Surgical Treatments [PODCAST] study revealed that prophylactic administration of ketamine was not superior to normal saline placebo in preventing POD, rather it was associated with greater incidence of postoperative hallucinations and nightmares.[108] Currently, available evidence does not recommend the use of antipsychotics for the prevention or treatment of delirium.[109] Comparative investigation of prophylactic use of haloperidol versus normal saline placebo among intensive care unit (ICU) patients with high delirium risk had also found no significant difference between the two regarding the incidence of delirium, and other outcomes associated with it.[110] In the systematic review and meta-analysis conducted by Igwe et al. to evaluate pharmacological interventions for reducing POD in elderly patients it was also concluded that the use of haloperidol for this indication was no better than a placebo.[111] The risk of harm from antipsychotics is substantial in the elderly despite the questionable benefit of the therapy. Their use has also been implicated as prognostic of worse outcome in delirious older adults. Antipsychotics and other psychotropic medications have instead been implicated with accelerated functional and cognitive decline.[112]

Delirium treatment

The goal of treatment in patients who have developed POD is to reduce its severity and duration, by identifying and addressing the contributing factors. Non-pharmacological multi-component interventions are equally applicable in the treatment of delirious patients, as they are with the prevention; and have recorded some success.[113] Pharmacological intervention may only be indicated to manage delirious patients with severe agitation who are at risk of harming themselves or others. Antipsychotics even for this indication have been regarded as mere chemical restraints by Inuoye et al.[114] They may also be considered when delirium persists despite the implementation of all relevant non-pharmacological measures. In such instances titrated low-dose antipsychotics are recommended. Haloperidol is often preferred despite its association with QT interval elongation, but chlorpromazine and atypical antipsychotics such as risperidone, clozapine or olanzapine may be used. Chlorpromazine and atypical antipsychotics are less likely than haloperidol to cause extrapyramidal motor effects. Both chlorpromazine and clozapine have marked anticholinergic effects, with sedation and orthostatic hypotension; and may lead to falls, deep vein thrombosis episodes, constipation, and urinary retention in elderly patients with prostatic hypertrophy. Therapy with clozapine also carries greater risk of agranulocytosis, myocarditis and seizures. Considerations for these side effects and safety in the elderly tend to determine the choice of antipsychotic agent more than efficacy, as most have good efficacy in controlling agitated delirious

patients. These adverse effects of antipsychotics in the elderly compel their use at minimal effective doses for brief periods and wide expert opinion recommends tapering off of antipsychotics as soon as the delirium resolves. Despite the caveat on the use of antipsychotics there are still disconcerting reports of their overwhelming use in most delirious geriatric patients, irrespective of the motor subtype,[115,116] and in preference to non-pharmacological multi-component interventions. Similar abuse has also been observed with regard to the continuation of antipsychotics at discharge, in patients who had commenced it in the ICU for treatment of delirium.[117] Similarly, misuse of benzodiazepines which are known risk factors for the development of POD is widespread in the treatment of POD. This is unfortunate, as they may only be indicated for managing agitation associated with drug withdrawal such as benzodiazepines, and alcohol. The suboptimal care of the elderly patients regarding POD is not surprising with the pervading background of knowledge deficit regarding the scourge.[118,119] This, in spite of recent effort at establishing international guidelines on POD.[120–122]

Limitations

This review is short on elaborating the various pathophysiologic mechanisms that have been hypothesized for the evolution of POD. This was actually intended, in order to keep within the declared objective of the study. It would further be acknowledged that owing to the lack of explicit benchmark for the selection of the source articles used for the synthesis, subjectivity and bias may not be entirely ruled out. In the same vein, the review unlike a systematic review had no focused research question being interrogated, and applied no explicit methodology in the synthesis. These shortcomings are necessarily inherent in this type of study design and guided by the stated objective.

Conclusion

Postoperative delirium is a common complication that exerts enormous burden on patients, their families, and healthcare resources. Clinicians are likely to encounter delirium frequently in elderly surgical patients, and its management should be considered in all stages of the surgical care pathway. Addressing the knowledge and practice gap regarding multi-component preventive and treatment interventions is crucial, while prompt detection of delirium using validated tools is key to changing the narrative of poor care provided to the elderly. The SBT and CAM are valid and reliable easy-to-use tools that every physician irrespective of background can use during routine assessment of elderly patients. Anaesthesia-based multi-component interventions have great potential among the broad options in the prevention and treatment of POD in surgical patients.

References

1. Population Division. World Population Prospects 2019. Available at https://population.un.org/wpp/. Accessed: January 20, 2021.
2. Cornwell J, Levenson R, Sonola L, Poteliakhoff E. Continuity of Care for Older Hospital Patients: A Call for Action. London: King's Fund; 2012. Available at; https://www.kingsfund.org.uk/sites/default/files/field/field_publication_file/continuity-of-care-for-older-hospital-patients-mar-2012.pdf. Accessed January 31, 2021.
3. Pipanmekaporn T, Chittawatanarat K, Chaiwat O, Thawitsri T, Wacharasint P, Kongsayreepong S. Incidence and risk factors of delirium in multi-center Thai surgical intensive care units: a prospective cohort study. J Intensive Care. 2015;3:53.
4. Shi CM, Wang DX, Chen KS, Gu XE. Incidence and risk factors of delirium in critically ill patients after non-cardiac surgery. Chin Med J (Engl). 2010;123:993-9.
5. Huang J, Sprung J, Weingarten TN. Delirium following total joint replacement surgery. Bosn J Basic Med Sci. 2019;19:81-5.
6. Mu DL, Wang DX, Li LH, Shan GJ, Li J, Yu QJ, et al. High serum cortisol level is associated with increased risk of delirium after coronary artery bypass graft surgery: a prospective cohort study. Crit Care. 2010;14:R238.
7. de Freitas SA, Wong E, Lee JY, Reppas-Rindlisbacher C, Gabor C, Curkovic A, et al. The Effect of Multiple Assessments on Delirium Detection: a Pilot Study. Can Geriatr J. 2020;23:277-82.

8. Edelstein DM, Aharonoff GB, Karp A, Capla EL, Zuckerman JD, Koval KJ. Effect of Postoperative Delirium on Outcome after Hip Fracture, Clinical Orthopaedics and Related Research: 2004;422:195-200
9. Leslie DL, Marcantonio ER, Zhang Y, Leo-Summers L, Inouye SK. One-year health care costs associated with delirium in the elderly population. Arch Intern Med. 2008;168:27-32.
10. Mangusan RF, Hooper V, Denslow SA, Travis L. OUTCOMES ASSOCIATED WITH POSTOPERATIVE DELIRIUM AFTER CARDIAC SURGERY. Am. J. Crit. Care 2015;24:156-63
11. Moreira A, Antunes MV, Norton M, Moreira JF, Abelha F. Complications in postoperative delirium patients in a post anesthesia care unit. Eur. J. Anaesthesiol. 2013;30:11.
12. Abelha FJ, Luís C, Veiga D, Parente D, Fernandes V, Santos P, et al. Outcome and quality of life in patients with postoperative delirium during an ICU stay following major surgery. Crit Care. 2013:17: R257.
13. Moskowitz EE, Overbey DM, Jones TS, Jones EL, Arcomano TR, Moore JT, et al. Post-operative delirium is associated with increased 5-year mortality. Am J Surg. 2017;214:1036-8.
14. Sprung J, Roberts RO, Weingarten TN, Nunes Cavalcante A, Knopman DS, Petersen RC, et al. Postoperative delirium in elderly patients is associated with subsequent cognitive impairment. Br J Anaesth. 2017;119:316-23.
15. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. JAMA. 2010;304:443-51.
16. Krogseth M, Watne LO, Juliebø V, Skovlund E, Engedal K, Frihagen F, et al. Delirium is a risk factor for further cognitive decline in cognitively impaired hip fracture patients. Arch Gerontol Geriatr. 2016;64:38-44.
17. Adogwa O, Elsamadicy AA, Vuong VD, Fialkoff J, Cheng J, Karikari IO, et al. Association between baseline cognitive impairment and postoperative delirium in elderly patients undergoing surgery for adult spinal deformity. J Neurosurg Spine. 2018;28:103-8.
18. Kazmierski J, Kowman M, Banach M, Fendler W, Okonski P, Banys A, et al.; IPDACS Study. Incidence and predictors of delirium after cardiac surgery: Results from The IPDACS Study. J Psychosom Res. 2010 ;69:179-85.
19. Rizk P, Morris W, Oladeji P, Huo M. Review of Postoperative Delirium in Geriatric Patients Undergoing Hip Surgery. Geriatr Orthop Surg Rehabil. 2016;7:100-5.
20. Iamaroon A, Wongviriyawong T, Sura-arunsumrit P, Wiwatnodom N, Rewuri N, Chaiwat O. Incidence of and risk factors for postoperative delirium in older adult patients undergoing noncardiac surgery: a prospective study. BMC Geriatr. 2020;20:40.
21. Tsutura R, Nakahara T, Miyauchi T, Kutsuna S, Ogino Y, Yamamoto T, et al. Prevalence and associated factors for delirium in critically ill patients at a Japanese intensive care unit. Gen Hosp Psychiatry. 2010;32:607-11.
22. Robinson TN, Raeburn CD, Tran ZV, Brenner LA, Moss M. Motor subtypes of postoperative delirium in older adults. Arch Surg. 2011; 146:295-300.
23. Avelino-Silva TJ, Campora F, Curiati JAE, Jacob-Filho W. Prognostic effects of delirium motor subtypes in hospitalized older adults: A prospective cohort study. PLoS One. 2018;13:e0191092.
24. Kiely DK, Jones RN, Bergmann MA, Marcantonio ER. Association between psychomotor activity delirium subtypes and mortality among newly admitted post-acute facility patients. J Gerontol A Biol Sci Med Sci. 2007;62:174-9.
25. Rosgen BK, Krewulak KD, Stelfox HT, Ely EW, Davidson JE, Fiest KM. The association of delirium severity with patient and health system outcomes in hospitalised patients: a systematic review. Age Ageing 2020;49:549–57.
26. Lee KH, Ha YC, Lee YK, Kang H, Koo KH. Frequency, risk factors, and prognosis of prolonged delirium in elderly patients after hip fracture surgery. Clin Orthop Relat Res. 2011;469:2612-20.
27. Bellelli G, Frisoni GB, Turco R, Lucchi E, Magnifico F, Trabucchi M. Delirium superimposed on dementia predicts 12-month survival in elderly patients discharged from a

postacute rehabilitation facility. J Gerontol A Biol Sci Med Sci. 2007;62:1306-9.
28. Avelino-Silva TJ, Campora F, Curiati JA, Jacob-Filho W. Association between delirium superimposed on dementia and mortality in hospitalized older adults: A prospective cohort study. PLoS Med. 2017;14:e1002264.
29. Dasgupta M, Brymer C. Prognosis of delirium in hospitalized elderly: worse than we thought. Int J Geriatr Psychiatry. 2014;29:497-505.
30. Egberts A, Alan H, Ziere G, Mattace-Raso FUS. Antipsychotics and Lorazepam During Delirium: Are We Harming Older Patients? A Real-Life Data Study. Drugs Aging. 2021;38:53-62.
31. Tianyi FL, Agbor VN, Njamnshi AK, Atashili J. Factors Associated with the Prevalence of Cognitive Impairment in a Rural Elderly Cameroonian Population: A Community-Based Study in Sub-Saharan Africa. Dement Geriatr Cogn Disord. 2019;47:104-13.
32. Ristescu AI, Pintilie G, Moscalu M, Rusu D, Grigoras I. Preoperative Cognitive Impairment and the Prevalence of Postoperative Delirium in Elderly Cancer Patients-A Prospective Observational Study. Diagnostics (Basel). 2021;11:275.
33. Luo A, Yan J, Tang X, Zhao Y, Zhou B, Li S. Postoperative cognitive dysfunction in the aged: the collision of neuroinflammaging with perioperative neuroinflammation. Inflammopharmacology. 2019;27:27-37.
34. Lin T, Liu A, Perez E, Rainer RD, Febo M, Cruz-Almeida Y, et al. Systemic Inflammation Mediates Age-Related Cognitive Deficits. Front. Aging Neurosci. 2018;10:236.
35. d'Avila JC, Siqueira LD, Mazeraud A, Azevedo EP, Foguel D, Castro-Faria-Neto HC, et al. Age-related cognitive impairment is associated with long-term neuroinflammation and oxidative stress in a mouse model of episodic systemic inflammation. J Neuroinflammation 2018;15:28.
36. Chen D, Chen J, Yang H, Liang X, Xie Y, Li S, et al. Mini-Cog to predict postoperative mortality in geriatric elective surgical patients under general anesthesia: a prospective cohort study. Minerva Anestesiol. 2019;85:1193-200.
37. Robinson TN, Wu DS, Pointer LF, Dunn CL, Moss M. Preoperative cognitive dysfunction is related to adverse postoperative outcomes in the elderly. J Am Coll Surg. 2012;215:12-7; discussion 17-18.
38. De Hert S, Staender S, Fritsch G, Hinkelbein J, Afshari A, Bettelli G, et al. Pre-operative evaluation of adults undergoing elective noncardiac surgery: Updated guideline from the European Society of Anaesthesiology. Eur J Anaesthesiol. 2018;35:407-65.
39. Chow WB, Rosenthal RA, Merkow RP, Ko CY, Esnaola NF; American College of Surgeons National Surgical Quality Improvement Program; American Geriatrics Society. Optimal preoperative assessment of the geriatric surgical patient: a best practices guideline from the American College of Surgeons National Surgical Quality Improvement Program and the American Geriatrics Society. J Am Coll Surg. 2012;215:453-66.
40. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. J Am Geriatr Soc. 2005;53:695-9.
41. Scazufca M, Almeida OP, Vallada HP, Tasse WA, Menezes PR. Limitations of the Mini-Mental State Examination for screening dementia in a community with low socioeconomic status: results from the Sao Paulo Ageing & Health Study. Eur Arch Psychiatry Clin Neurosci. 2009;259:8-15.
42. Anthony JC, LeResche L, Niaz U, von Korff MR, Folstein MF. Limits of the 'Mini-Mental State' as a screening test for dementia and delirium among hospital patients. Psychol Med. 1982;12:397-408.
43. Katzman R, Brown T, Fuld P, Peck A, Schechter R, Schimmel H. Validation of a short Orientation-Memory-Concentration Test of cognitive impairment. Am J Psychiatry. 1983; 140:734-9.
44. Carpenter CR, Bassett ER, Fischer GM, Shirshekan J, Galvin JE, Morris JC. Four sensitive screening tools to detect cognitive dysfunction in geriatric emergency department patients: brief Alzheimer's Screen, Short Blessed Test, Ottawa 3DY, and the caregiver-completed AD8. Acad Emerg Med.

2011;18:374-84.
45. Tuijl JP, Scholte EM, de Craen AJ, van der Mast RC. Screening for cognitive impairment in older general hospital patients: comparison of the Six-Item Cognitive Impairment Test with the Mini-Mental State Examination. Int J Geriatr Psychiatry. 2012;27:755-62.
46. Dementia: a public health priority. Geneva: World Health Organization; 2012. Available at: https://www.who.int/mental_health/publications/dementia_report_2012/en/. Accessed March 11,2021.
47. Magklara E, Stephan BCM, Robinson L. Current approaches to dementia screening and case finding in low- and middle-income countries: Research update and recommendations. Int J Geriatr Psychiatry. 2019;34:3-7
48. Daviglus ML, Bell CC, Berrettini W, Bowen PE, Connolly ES Jr, Cox NJ, et al. NIH state-of-the-science conference statement: Preventing Alzheimer's disease and cognitive decline. NIH Consens State Sci Statements. 2010;27:1-30.
49. Yorozuya K, Kubo Y, Tomiyama N, Yamane S. Hanaoka H. A Systematic Review of Multimodal Non-Pharmacological Interventions for Cognitive Function in Older People with Dementia in Nursing Homes. Dement Geriatr Cogn Disord 2019;48:1–16.
50. Karssemeijer EGA, Aaronson JA, Bossers WJ, Smits T, Olde Rikkert MGM, Kessels RPC. Positive effects of combined cognitive and physical exercise training on cognitive function in older adults with mild cognitive impairment or dementia: A meta-analysis. Ageing Res Rev. 2017 ;40:75-83.
51. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders: DSM-V®. American Psychiatric Association, 5th Edn. Washington, DC: American Psychiatric Association Publishing, 2013.
52. Neufeld KJ, Leoutsakos JS, Sieber FE, Joshi D, Wanamaker BL, Rios-Robles J, et al. Evaluation of two delirium screening tools for detecting post-operative delirium in the elderly. Br J Anaesth. 2013;111:612-8.
53. Poikajärvi S, Salanterä S, Katajisto J, Junttila K. Validation of Finnish Neecham Confusion Scale and Nursing Delirium Screening Scale using Confusion Assessment Method algorithm as a comparison scale. BMC Nurs. 2017;16:7.
54. Gemert van LA, Schuurmans MJ. The Neecham Confusion Scale and the Delirium Observation Screening Scale: capacity to discriminate and ease of use in clinical practice. BMC Nurs. 2007;6:3.
55. Saller T, MacLullich AMJ, Schäfer ST, Crispin A, Neitzert R, Schüle C, et al. Screening for delirium after surgery: validation of the 4 A's test (4AT) in the post-anaesthesia care unit. Anaesthesia . 2019;74:1260-6.
56. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med. 1990; 113:941-8.
57. Wong CL, Holroyd-Leduc J, Simel DL, Straus SE. Does this patient have delirium?: value of bedside instruments. JAMA. 2010;304:779-86.
58. Grover S, Kate N. Assessment scales for delirium: A review. World J Psychiatry. 2012;2:58-70.
59. Neufeld KJ, Leoutsakos JS, Sieber FE, Joshi D, Wanamaker BL, Rios-Robles J, Needham DM. Evaluation of two delirium screening tools for detecting post-operative delirium in the elderly. Br J Anaesth. 2013;111:612-8.
60. Ryan K, Leonard M, Guerin S, Donnelly S, Conroy M, Meagher D. Validation of the confusion assessment method in the palliative care setting. Palliat Med. 2009;23:40-5.
61. Mudge AM, Giebel AJ, Cutler AJ. Exercising body and mind: an integrated approach to functional independence in hospitalized older people. J Am Geriatr Soc. 2008;56:630-5.
62. McCaffrey R, Locsin R. The effect of music listening on acute confusion and delirium in elders undergoing elective hip and knee surgery. J Clin Nurs. 2004;13:91-6.
63. Hshieh TT, Yue J, Oh E, Puelle M, Dowal S, Travison T, et al. Effectiveness of multicomponent nonpharmacological delirium interventions: a meta-analysis. JAMA Intern Med. 2015;175:512-20. Erratum in: JAMA Intern Med. 2015;175:659.
64. Akunne A, Davis S, Westby M, Young J. The cost-effectiveness of multi-component interventions to prevent delirium in older people

undergoing surgical repair of hip fracture. Eur J Orthop Surg Traumatol. 2014;24:187-95.
65. Akunne A, Murthy L, Young J, Cost-effectiveness of multi-component interventions to prevent delirium in older people admitted to medical wards. Age Ageing .2012; 41:285–91.
66. Lee E, Kim J. Cost-benefit analysis of a delirium prevention strategy in the intensive care unit. Nurs Crit Care. 2016;21:367-73
67. Petersen PB, Jørgensen CC, Kehlet H; Lundbeck Foundation Centre for Fast-track Hip and Knee Replacement Collaborative Group. Delirium after fast-track hip and knee arthroplasty - a cohort study of 6331 elderly patients. Acta Anaesthesiol Scand. 2017;61:767-72.
68. McCusker J, Cole M, Abrahamowicz M, Han L, Podoba JE, Ramman-Haddad L. Environmental risk factors for delirium in hospitalized older people. J Am Geriatr Soc. 2001;49:1327-34.
69. Wesselius HM, van den Ende ES, Alsma J, Ter Maaten JC, Schuit SCE, Stassen PM, et al.; "Onderzoeks Consortium Acute Geneeskunde" Acute Medicine Research Consortium. Quality and Quantity of Sleep and Factors Associated With Sleep Disturbance in Hospitalized Patients. JAMA Intern Med. 2018;178:1201-8.
70. Jia Y, Jin G, Guo S, Gu B, Jin Z, Gao X, et al. Fast-track surgery decreases the incidence of postoperative delirium and other complications in elderly patients with colorectal carcinoma. Langenbecks Arch Surg. 2014;39:77-84.
71. Kalogera E, Dowdy S. Prehabilitation: enhancing the Enhanced Recovery after Surgery pathway. Int J Gynecol Cancer 2019;29:1233-4.
72. Inouye SK, Bogardus ST Jr, Charpentier PA, Leo-Summers L, Acampora D, Holford TR, et al. A Multicomponent Intervention to Prevent Delirium in Hospitalized Older Patients. N Engl J Med 1999; 340:669-76.
73. Boockvar KS, Teresi, JA, Inouye SK. Preliminary Data: An Adapted Hospital Elder Life Program to Prevent Delirium and Reduce Complications of Acute Illness in Long-Term Care Delivered by Certified Nursing Assistants. J Am Geriatr Soc. 2016;64:1108-13.
74. Chen CC, Li HC, Liang JT, Lai IR, Purnomo JDT, Yang YT, et al. Effect of a Modified Hospital Elder Life Program on Delirium and Length of Hospital Stay in Patients Undergoing Abdominal Surgery: A Cluster Randomized Clinical Trial. JAMA Surgery. 2017;152:827-34.
75. Wang YY, Yue JR, Xie DM, Carter P, Li QL, Gartaganis SL, et al. Effect of the Tailored, Family-Involved Hospital Elder Life Program on Postoperative Delirium and Function in Older Adults: A Randomized Clinical Trial. JAMA Intern Med. 2019: 180:e194446.
76. Huson K, Stolee P, Pearce N, Bradfield C, Heckman GA. Examining the Hospital Elder Life Program in a rehabilitation setting: a pilot feasibility study. BMC Geriatr. 2016;16:140
77. Vidán MT, Sánchez E, Alonso M, Montero B, Ortiz J, Serra JA. An intervention integrated into daily clinical practice reduces the incidence of delirium during hospitalization in elderly patients. J Am Geriatr Soc. 2009;57:2029-36.
78. Ochiai K, Fukushima H, Nakata H,Takamatsu N, Honda M, Prevention of Delirium by Introducing Modified HELP (Hospital Elder Life Program) in Acute Medical Wards. An Official Journal of the Japan Primary Care Association. 2020;43:105-11.
79. Gorski S, Piotrowicz K, Rewiuk K, Halicka M, Kalwak W, Rybak P, et al. Nonpharmacological Interventions Targeted at Delirium Risk Factors, Delivered by Trained Volunteers (Medical and Psychology Students), Reduced Need for Antipsychotic Medications and the Length of Hospital Stay in Aged Patients Admitted to an Acute Internal Medicine Ward: Pilot Study. BioMed Res. Int. 2017; Article ID 1297164,8 pages.
80. Zaubler TS, Murphy K, Rizzuto L, Santos R, Skotzko C, Giordano J, et al. Quality improvement and cost savings with multicomponent delirium interventions: replication of the Hospital Elder Life Program in a community hospital. Psychosomatics. 2013;54:219-26.
81. Gustafson Y, Brännström B, Berggren D, Ragnarsson JI, Sigaard J, Bucht G, et al. A geriatric-anesthesiologic program to reduce acute confusional states in elderly patients treated for femoral neck fractures. J Am Geriatr Soc. 1991;39:655-62.
82. Gan TJ, Glass PS, Windsor A, Payne F, Rosow

C, Sebel P, et al.; Bispectral Index Monitoring Allows Faster Emergence and Improved Recovery from Propofol, Alfentanil, and Nitrous Oxide Anesthesia . Anesthesiology 1997; 87:808–15.
83. Recart A, White PF, Wang A, Gasanova I, Byerly S, Jones SB; Effect of Auditory Evoked Potential Index Monitoring on Anesthetic Drug Requirements and Recovery Profile after Laparoscopic Surgery: A Clinical Utility Study. Anesthesiology 2003; 99:813–18.
84. Bocskai T, Kovács M, Szakács Z, Gede N, Hegyi P, Varga G, et al. Is the bispectral index monitoring protective against postoperative cognitive decline? A systematic review with meta-analysis. PLoS ONE. 2020;15:e0229018.
85. Punjasawadwong Y, Chau-in W, Laopaiboon M, Punjasawadwong S, Pin-on P. Processed electroencephalogram and evoked potential techniques for amelioration of postoperative delirium and cognitive dysfunction following non-cardiac and non-neurosurgical procedures in adults. Cochrane Database Syst Rev. 2018;5:CD011283.
86. Shan W, Chen B, Huang L, Zhou Y. The Effects of Bispectral Index-Guided Anesthesia on Postoperative Delirium in Elderly Patients: A Systematic Review and Meta-Analysis. World Neurosurg. 2020;S1878-8750(20)32495-5.
87. Wildes TS, Mickle AM, Ben Abdallah A, Maybrier HR, Oberhaus J, Budelier TP, et al.; ENGAGES Research Group. Effect of Electroencephalography-Guided Anesthetic Administration on Postoperative Delirium Among Older Adults Undergoing Major Surgery: The ENGAGES Randomized Clinical Trial. JAMA. 2019;321:473-83.
88. Hughes CG, Boncyk CS, Culley DJ, Fleisher LA, Leung JM, McDonagh DL, et al.; Perioperative Quality Initiative (POQI) 6 Workgroup. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Postoperative Delirium Prevention. Anesth Analg. 2020;130:1572-90.
89. Sieber FE, Zakriya KJ, Gottschalk A, Blute MR, Lee HB, Rosenberg PB, et al. Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair. Mayo Clin Proc. 2010;85:18-26.
90. Sieber FE, Neufeld KJ, Gottschalk A, Bigelow GE, Oh ES, Rosenberg PB, et al. Effect of Depth of Sedation in Older Patients Undergoing Hip Fracture Repair on Postoperative Delirium: The STRIDE Randomized Clinical Trial. JAMA Surg. 2018 ;153:987-95.
91. Patel V, Champaneria R, Dretzke J, Yeung J. Effect of regional versus general anaesthesia on postoperative delirium in elderly patients undergoing surgery for hip fracture: a systematic review. BMJ Open. 2018;8:e020757.
92. Li T, Yeung J, Li J, Zhang Y, Melody T, Gao Y, et al.; RAGA-Delirium Investigators. Comparison of regional with general anaesthesia on postoperative delirium (RAGA-delirium) in the older patients undergoing hip fracture surgery: study protocol for a multicentre randomised controlled trial. BMJ Open. 2017;7:e016937.
93. Mann C, Pouzeratte Y, Boccara G, Peccoux C, Vergne C, Brunat G, et al. Comparison of Intravenous or Epidural Patient-controlled Analgesia in the Elderly after Major Abdominal Surgery. Anesthesiology 2000; 92:433.
94. Cerejeira J, Nogueira V, Luís P, Vaz-Serra A, Mukaetova-Ladinska EB. The cholinergic system and inflammation: common pathways in delirium pathophysiology. J Am Geriatr Soc. 2012;60:669-75.
95. Cerejeira J, Firmino H, Vaz-Serra A, Mukaetova-Ladinska E B. The neuroinflammatory hypothesis of delirium. Acta Neuropathol. 2010;119:737–54.
96. Li LQ, Wang C, Fang MD, Xu HY, Lu HL, Zhang HZ. Effects of dexamethasone on post-operative cognitive dysfunction and delirium in adults following general anaesthesia: a meta-analysis of randomised controlled trials. BMC Anesthesiol. 2019;19:113.
97. Cui Y, Li G, Cao R, Luan L, Kla KM. The effect of perioperative anesthetics for prevention of postoperative delirium on general anesthesia: A network meta-analysis. J Clin Anesth. 2020;59:89-98.
98. Fan H, Zhao Y, Sun M, Ye JH, Chen GD, Zhu JH. Dexmedetomidine Based Sedation for Post-surgery Critically Ill Adults: A Meta-analysis of Randomized Controlled Trials. Iran J Public

Health. 2017 ;46:1611-22.
99. Pereira JV, Sanjanwala RM, Mohammed MK, Le ML, Arora RC. Dexmedetomidine versus propofol sedation in reducing delirium among older adults in the ICU: A systematic review and meta-analysis. Eur J Anaesthesiol. 2020;37:121-31.
100. Carli F. Prehabilitation for the Anesthesiologist. Anesthesiology 2020; 133:645–52.
101. Valecha1 UK, Vohra VK, Patil R, Kulkarni S, Shastri N, Keloth RE, et al. Enhanced recovery after surgery (ERAS) for the anaesthesiologist. Indian J Clin Anaesth 2020;7:553–62.
102. Su X, Meng ZT, Wu XH, Cui F, Li HL, Wang DX, et al. Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomised, double-blind, placebo-controlled trial. Lancet. 2016;388:1893-902.
103. Sellers D, Djaiani G. Dexmedetomidine: magic bullet or firing blanks? J Thorac Dis. 2016;8:3024-27.
104. Wu M, Liang Y, Dai Z, Wang S. Perioperative dexmedetomidine reduces delirium after cardiac surgery: A meta-analysis of randomized controlled trials. J Clin Anesth. 2018;50:33-42.
105. Kim JA, Ahn HJ, Yang M, Lee SH, Jeong H, Seong BG. Intraoperative use of dexmedetomidine for the prevention of emergence agitation and postoperative delirium in thoracic surgery: a randomized-controlled trial.Can J Anaesth. 2019; 66:371-9.
106. Donovan AL, Whitlock EL. Intraoperative dexmedetomidine to prevent postoperative delirium: in search of the magic bullet. Can J Anaesth. 2019;66:365-70.
107. Hovaguimian F, Tschopp C, Beck-Schimmer B, Puhan M. Intraoperative ketamine administration to prevent delirium or postoperative cognitive dysfunction: A systematic review and meta-analysis. Acta Anaesthesiol Scand. 2018;62:1182-93.
108. Avidan MS, Maybrier HR, Abdallah AB, Jacobsohn E, Vlisides PE, Pryor KO, et al.; PODCAST Research Group. Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: an international, multicentre, double-blind, randomised clinical trial. Lancet. 2017;15;390:267-75.
109. Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM. Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis. J Am Geriatr Soc. 2016;64: 705-14.
110. van den Boogaard M, Slooter AJC, Brüggemann RJM, Schoonhoven L, Beishuizen A, Vermeijden JW,et al.; REDUCE Study Investigators, van der Woude MCE, Besselink A, Hofstra LS, Spronk PE, van den Bergh W, Donker DW, Fuchs M, Karakus A, Koeman M, van Duijnhoven M, Hannink G. Effect of Haloperidol on Survival Among Critically Ill Adults With a High Risk of Delirium: The REDUCE Randomized Clinical Trial. JAMA. 2018;319:680-90.
111. Igwe EO, Nealon J, Mohammed M, Hickey B, Chou KR, Chen KH, et al. Multi-disciplinary and pharmacological interventions to reduce post-operative delirium in elderly patients: A systematic review and meta-analysis. J Clin Anesth. 2020;67:110004.
112. Rosenberg PB, Mielke MM, Han D, Leoutsakos JS, Lyketsos CG, Rabins PV, et al. The association of psychotropic medication use with the cognitive, functional, and neuropsychiatric trajectory of Alzheimer's disease. Int J Geriatr Psychiatry. 2012;27:1248-57.
113. Milisen K, Foreman MD, Abraham IL et al. A nurse-led interdisciplinary intervention program for delirium in elderly hip-fracture patients. J Am Geriatr Soc 2001;49:523–32.
114. Inouye SK, Marcantonio ER, Metzger ED. Doing Damage in Delirium: The Hazards of Antipsychotic Treatment in Elderly Persons. Lancet Psychiatry. 2014;1:312-5.
115. Nguyen PV-Q, Malachane A, Minh TTV. Antipsychotic prescription patterns in the management of delirium symptoms in hospitalized elderly patients. Proc. Singapore Healthc. 2017;26:230 –4.
116. van Velthuijsen EL, Zwakhalen SMG, Mulder WJ, Verhey FRJ, Kempen GIJM. Detection and management of hyperactive and hypoactive delirium in older patients during hospitalization: a retrospective cohort study evaluating daily

practice. Int J Geriatr Psychiatry. 2018;33:1521-9.
117. Jasiak KD, Middleton EA, Camamo JM, Erstad BL, Snyder LS, Huckleberry YC. Evaluation of Discontinuation of Atypical Antipsychotics Prescribed for ICU Delirium. J Pharm Pract. 2013;26:253-6.
118. Davis D, MacLullich A. Understanding barriers to delirium care: a multicentre survey of knowledge and attitudes amongst UK junior doctors. Age Ageing. 2009;38:559–63.
119. Limpawattana P, Paopongpaiboon P, Worawittayakit k, Chotmongkol V, Manjavong M, Sawanyawisuth k, et al. Understanding Beliefs and Knowledge Gaps Regarding Delirium Among Trainee physicians in Thailand. J Med Assoc Thai. 2018;101(Suppl.7):S9-S14.
120. National Clinical Guideline Centre. DELIRIUM: diagnosis, prevention and management. Clinical Guideline 103 July 2010. Available at; https://www.nice.org.uk/guidance/cg103/evidence/full-guideline-pdf-134653069. Accessed January22, 2021.
121. Aldecoa C, Bettelli G, Bilotta F, Sanders RD, Audisio R, Borozdina A, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. Eur. J. Anaesthesiol. 2017;34:192-214.
122. Hughes CG, Boncyk CS, Culley DJ, Fleisher LA, Leung JM, McDonagh DL, et al.; Perioperative Quality Initiative (POQI) 6 Workgroup. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Postoperative Delirium Prevention. Anesth Analg. 2020;130:1572-90.