EJAIC

Eur J Anaesthesiol Intensive Care Med 2023; **2:**3(e0022)

OPEN

REVIEW ARTICLE

Postoperative delirium: identifying the patient at risk and altering the course

A narrative review

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Postoperative delirium (POD) is a common neurocognitive syndrome seen in older patients after major surgery. POD is linked to longer stays in hospital and intensive care, a greater incidence of postoperative complications, worse functional outcome, and higher mortality. Researchers have not yet fully elucidated the exact pathophysiology of POD. Several risk factors that contribute to the development of POD have been identified, such as advanced age, cardiac or hip surgery, preoperative cognitive decline or delirium, disturbances in brain levels of neurotransmitters and information processing, oxidative stress and neuro-inflammation.

Identifying patients at risk for POD enables a more precise and efficient allocation of medical resources and facilitates POD prevention and management.

The present review addresses how to identify patients at risk of POD and summarizes the currently available evidence and best-practice recommendations for peri-operative management and prevention of POD.

Published online 26 April 2023

KEY POINTS

- Postoperative delirium (POD) is a common and serious complication in older surgical patients and is associated with excess morbidity and mortality and high costs.
- Assessment of preoperative frailty can guide risk stratification for POD
- Nonpharmacological prevention of POD is more effective than pharmacological treatment.
- Management and prevention of POD requires a multidisciplinary approach and multicomponent bundle of interventions such as identifying and treating precipitating risk factors and metabolic derangements, systematic pre and postoperative cognitive screening, medication review and implementing standard protocols addressing patients' immobility, pain, hypoxia, infection, sleep deprivation, dehydration, anxiety, disorientation and environmental issues.
- Functional and cognitive prehabilitation is a promising strategy that might further reduce the risk of POD in older patients.

Introduction

Postoperative delirium (POD) is a temporary neurocognitive syndrome frequently observed after surgery with an incidence in older surgical patients that varies from 7% to 53%.[1,2] According to the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-V), the hallmarks of delirium are summarized by an acute onset and fluctuating course of disorientation, inattention, memory deficit, and impaired psychomotor activity.[3] Moreover, POD can present in different motor subtypes varying from an agitated state (hyperactive delirium) to an apathetic-like idle state (hypoactive delirium). A combination of both conditions is also possible (mixed delirium).[4,5] Of note, hypoactive delirium is quite

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DOI:10.1097/EA9.0000000000000022

difficult to diagnose and is associated with poor postoperative prognosis.[5,6]

The impact of POD, especially in older surgical patients, remains a serious problem. It prolongs the duration of postoperative mechanical ventilation, intensive care and hospital length of stays and leads to high costs.[7,8] POD has a detrimental impact on the patient's functional outcome and survival.[8]

The preoperative identification of high-risk patients who are more susceptible to POD after surgery enables a more precise and efficient allocation of medical resources.[9] Early detection and multicomponent non-pharmacological management of POD have been shown to improve outcomes.[9–11] Many POD assessment tools are available with differences in purpose, sensitivity, specificity and/or clinical applicability, such as the 4 'A's test (4AT) (Arousal, Attention, Abbreviated Mental Test–4, Acute change), Confusion Assessment Method and Delirium Observation Screening scale.[12] Unfortunately, daily screening for POD is still not routinely performed in each surgical patient, probably due to the misconception of it being difficult to perform and time-consuming.[13]

The cause of POD is believed to be multifactorial and to some degree caused by a breakdown in neuronal network connectivity.[14,15] Several predisposing (specific to the patient's preoperative status) and precipitating (or noxious) risk factors have been identified (Table 1).[16,17] Because of the complex interplay of these risk factors and the different pathophysiological mechanisms involved such as neuro-inflammation, oxidative stress, imbalance of neurotransmitters, systems integration failure, changes in gamma-aminobutyric acid (GABA) activity, and other mechanisms, no magic bullet is available for the prevention of POD.[14,18,19]

Table 1 **Predisposing and precipitating risk factors for postoperative delirium.**[9,16,60,158]

Predisposing	Precipitating
Advanced age (>70 years)	Emergency surgery
Cognitive impairment	Major peri-operative complication
Low level of education	Intensive care unit admission
Antipsychotics	High-risk surgical procedure
History of stroke	Neurological diseases
(Recent) delirium	Pharmacotherapy*
Comorbidity	Postoperative sedation*
Frailty*	Pain*
Polypharmacy*	Infection*
Alcohol/sedative abuse*	Hypoxia*
Malnutrition*	Malnutrition*
Anaemia*	Metabolic derangements*
Dehydration*	Sensory deprivation*
Depression*	Physical restraints*
Sensory impairment*	Prolonged use of catheters*
	Sleep-wake cycle disturbance*

*These risk factors are considered modifiable.

In the current review, we discuss how to identify the patient at risk for POD and summarize the current evidence and best-practice recommendations for peri-operative management and prevention of POD.

Preoperative risk evaluation

Previous research has identified both predisposing and precipitating factors for POD, some of which can be modified preoperatively (Table 1).[17,20] In a vulnerable or high-risk patient with one or more of these predisposing factors an additional trigger could initiate a delirious episode.[17,21] Hence, the American Geriatrics Society and the European Society of Anaesthesiology and Intensive Care advocate preoperative assessment of both cognition and risk factors for POD.[9,22] This can be used in predictive models to estimate the probability of POD,[23] giving carers the ability to stratify patients based on their risk of POD and direct targeted therapies peri-operatively to reduce the risk.[21,24]

Frailty and postoperative delirium

Frailty, a state of vulnerability to stressful events, is common in older surgical patients.[25] It can be evaluated by performing a comprehensive geriatric assessment (CGA) and using one of the several available validated instruments, such as the FRAIL Scale, the Frailty Groupe Iso-Ressource Evaluation (FRAGIRE), Tilburg Frailty Index or the Edmonton Frail Scale.[26] Similar to POD, frailty is associated with poorer postoperative outcomes.[25] A recent meta-analysis provided evidence for the association between frailty and POD.[25] Considering the potential for preoperative and postoperative patient optimisation, frailty assessment should become a standard component in the preoperative evaluation of older patients. As such, effective nonpharmacological interventions for the prevention of delirium such as re-orientation, cognitive stimulation, mobilization, sleep hygiene, nutrition and hydration, oxygenation, medication review, assessment of mood, and bowel and bladder care can be better targeted towards these frail patients.[27]

Modifiable risk factors of postoperative delirium

Improved preoperative physical fitness is positively associated with surgical outcomes.[28] It seems, therefore, reasonable to use the preoperative window in elective surgery for structured prehabilitation of the patients. Enhancing functional and cognitive capacity should improve the patient's ability to better withstand stressful surgery and encouraging results were published a decade ago.[29] A recent meta-analysis demonstrated that inspiratory muscle training, immunonutrition and multimodal interventions, including smoking cessation, moderate intensity aerobic and resistance exercise, and psychological intervention, reduced hospital length of stay (LOS), infections and pulmonary complications.[30] A recent randomized controlled trial (RCT) indicated that cognitive prehabilitation reduced the incidence of POD among

older adults.[31] Unfortunately, prehabilitation regimens cannot be conducted in all high-risk patients for numerous reasons, such as time limits (in case of emergency or urgent surgery), financial issues, hospital facilities, and staff shortages. Nevertheless, a systematic review of RCTs in older patients undergoing hip surgery demonstrated that a peri-operative CGA could reduce the incidence of POD after hip fracture surgery.[32] Accordingly, CGA must be performed when possible and is considered a helpful management strategy in frail older adults at high risk of developing POD. The impact of preoperative anxiety on the development of POD remains controversial.[33,34] More large, well designed randomized controlled trials are needed to investigate the efficacy of multicomponent prehabilitation programs, including, in particular, interventions to reduce preoperative anxiety.[29–31,33]

Several laboratory findings correlate independently with an increased risk for POD,[35] including preoperative anaemia,[35–37] decreased albumin levels and electrolyte disturbances.[35] Ample evidence shows that oral/i.v. iron is the preferred treatment for the timely correction of preoperative iron deficiency anaemia and can reduce red blood cell transfusion.[38] Theoretically, in an elective setting, correcting these abnormalities should reduce the incidence of POD and improve outcomes. To date, no convincing evidence is available to prove this hypothesis.

Polypharmacotherapy has been shown to increase the incidence of POD. Specifically, patients treated with anticholinergic, antihistaminic, anxiolytic, and/or antipsychotic drugs appear to have an increased risk for POD.[39] Impairment of central cholinergic transmission is considered a common denominator in POD.[40] Therefore, prior to prescribing a drug, its potential for anticholinergic effects and causing delirium should be considered.[40]

Disturbances in day-night or circadian rhythm are frequently observed during POD.[14] Other studies' findings confirmed a positive association between sleep disturbances and neurocognitive impairment.[41–44] Moreover, Altman *et al.* demonstrated in a long-term observational follow-up study that the total duration of ICU delirium was significantly related to increased sleep disturbance.[45] The peri-operative use of melatonin or ramelteon, a selective melatonin receptor agonist, has been advocated to target this disruption of circadian rhythm and reduce the incidence of POD.[46] However, a recent RCT in orthopaedic surgery did not support this theory.[47]

Intra-operative risk factors for postoperative delirium

Surgery-related factors

Some operations and interventions in older patients are associated with a higher incidence of POD, such as hip surgery or cardiac surgery with cardiopulmonary bypass (CPB).[48,49] The mechanism of CPB-related neurocognitive complications is complex. It can be attributed to many factors such as cerebral hypoperfusion, ischaemia-reperfusion injury, systemic inflammation and activation of the coagulation cascade and the complement system.[50–53] The risk of POD after cardiac surgery increases with the duration and complexity of the cardiac surgery.[54] Also, micro or macro-emboli arising from manipulation of the aorta have been claimed to play a role in POD after cardiac surgery.[55,56] In addition, comorbidities, peri-operative haemodynamic instability, anaemia and episodes of low cardiac output have been associated with an increased incidence of POD after cardiac surgery.[57]

Older patients undergoing hip surgery also have a high risk of developing POD with incidences varying from 13% to 56%.[58] A recent systematic review with meta-analysis demonstrated that advanced age, male sex, lower body mass index, visual decline, preoperative dementia or delirium, blood transfusion, American Society of Anesthesiologists physical status classification system (ASA) score $\geq$ III, regional anaesthesia and functional dependency are independent risk factors for POD after hip surgery.[59]

The stress response to surgery seems to play an essential role in the initiation of blood-brain barrier dysfunction and POD.[60] Therefore, strategies that aim to diminish tissue damage or restrict its impact on the brain may be valuable. Minimal access or minimally invasive surgical techniques have been associated with a lower incidence of POD.[36,61]

Anaesthesia-related factors

Both volatile and i.v. hypnotics may possess neurotoxic properties, as shown in laboratory and animal studies.[62,63] These studies provide evidence that volatile (VA) in contrast to i.v. anaesthetics, can trigger pathophysiological changes associated with Alzheimer's disease.[62] To date, only a few clinical trials have evaluated the effect of different VA on cognitive outcomes, with inconclusive findings.[64] In 2018, a Cochrane review compared Propofol-based i.v. anaesthesia to VA in noncardiac surgery and found no evidence for a difference in POD incidence and only low-certainty evidence that i.v. anaesthetics reduce the incidence of postoperative cognitive dysfunction.[65] In addition, several recent trials revealed no reduction in POD-rate when using i.v. anaesthetics vs. VA.[66,67]

Neuraxial anaesthesia can be used as an adjunct to general anaesthesia, for example patient-controlled epidural analgesia (PCEA) in major thoracic or abdominal surgery, or as the sole intra-operative anaesthetic technique, for example in hip fracture surgery. The impact of neuraxial anaesthesia on short- and long-term cognitive outcomes seems to be limited.[66,68] An important confounder is (over)sedation, which is frequently co-administered. Recently, the RAGA and REGAIN trials were published in which patients requiring surgery for hip fracture were randomized to either neuraxial anaesthesia

or general anaesthesia.[69,70] No difference was found between these anaesthetic techniques regarding the incidence of POD and short- or long-term outcomes.[69,70]

Sieber *et al.*[71] examined the effect of deep sedation on POD during regional anaesthesia in older patients undergoing hip fracture repair. They found that light sedation decreased the incidence of POD by 50% compared to deep sedation.[71] In contrast, the double-blind randomized STRIDE Trial demonstrated no significant difference in the incidence of POD between the deep and light sedation technique during hip fracture repair,[72] but in subgroup analysis, as stratified by the Charlson comorbidity index, deep sedation doubled the risk of POD compared to light sedation.[72]

Ketamine has been shown to possess potent anti-inflammatory effects in animal and clinical trials and may also decrease the incidence of POD.[73] Therefore, several trials have investigated its role in the prevention of POD[74] but with inconsistent findings. A recent multicentre RCT on POD prevention found no benefit for peri-operative ketamine, haloperidol or a combination, compared to placebo, to prevent POD after elective or emergency surgery.[74] The same results were obtained when ketamine was compared to propofol for ICU sedation.[75] In contrast, ketamine reduced POD rate in patients undergoing cardiac surgery with CPB.[76] In conclusion, there is insufficient quality of evidence to recommend the standard intra-operative use of ketamine for the prevention of POD.

Dexmedetomidine is a potent selective alfa 2 adrenergic receptor agonist.[77] It possesses anxiolytic, sympatholytic, sedative and even analgesic properties.[78] The effects of intra-operative administration of dexmedetomidine to reduce POD are still controversial. Of note, dexmedetomidine administration may be associated with several adverse reactions, such as hypotension, hypertension, bradycardia, and worsening respiratory responses to hypoxia and hypercapnia.[79] Healthcaregivers using dexmedetomidine should be aware of these adverse effects, which might be more pronounced in frail older patients.[79–81] Deiner *et al.* have shown in an RCT performed in older, noncardiac surgery patients that the intra-operative use of dexmedetomidine did not reduce the POD rate compared to the placebo group.[82] This finding has also been confirmed in cardiac surgical patients.[83] In contrast, several trials have shown that an intra-operative loading dose of dexmedetomidine followed by a continuous infusion until the end of surgery results in a significant reduction in POD rates and/or duration in older patients after noncardiac surgery.[84–86] Likewise, Duan *et al.* have shown in their meta-analysis that dexmedetomidine can reduce the incidence of POD in adult patients undergoing cardiac or noncardiac surgery.[87] Though, another review in cardiac surgical patients did not find any benefit of peri-operative dexmedetomidine in reducing the incidence of POD.[88] Further rigorous RCTs are warranted concerning timing, doses and duration of peri-operative dexmedetomidine used to prevent POD, specifically for older patients undergoing cardiac surgery.

Xenon is an inert gas with anaesthetic properties.[89,90] Several animal studies demonstrated that (sub)anaesthetic concentrations of xenon have organ protective properties, including neuro- and cardio-protection.[91–94] Of note, several researchers have suggested that low cardiac output and intra-operative blood pressure may trigger POD, but xenon does not decrease either cardiac contractility nor peripheral vascular resistance and is, therefore, virtually lacking in unfavourable haemodynamic effects.[95–99] Finally, xenon does not interact with the gamma aminobutyric acid adrenergic transmitter system.[100] Theoretically, these properties render xenon a good candidate for use in patients with high risk of POD, and in patients undergoing off-pump coronary artery bypass grafting, xenon, compared to sevoflurane, reduced the incidence of POD.[96] In contrast, in a larger RCT with POD as primary outcome, xenon could not reduce the incidence of POD in older patients undergoing on-pump cardiac surgery.[101] Likewise, in a multicentre trial, xenon anaesthesia did not reduce the incidence of POD in patients undergoing hip fracture surgery when compared to sevoflurane anaesthesia.[102] Therefore, evidence supporting the use of xenon for POD prevention is scarce.

A potential link between intra-operative burst-suppression (indicative of excessive anaesthetic) in the electroencephalogram (EEG) and POD has been repeatedly investigated.[103] Several studies have evaluated the use of depth of anaesthesia monitoring on neurocognitive outcomes.[104–107] These trials reported that the use of processed EEG monitoring and avoidance of too profound levels of anaesthesia in older patients under general anaesthesia probably reduces POD.[106,107] In contrast, the most recent ENGAGES trial (comparing EEG-guided vs. usual anaesthetic care) could not confirm these findings.[108] However, in this trial, both groups had excessive anaesthetic exposure with prolonged bispectral index (BIS) values <40 and burst suppression.[108] Notably, the EEG-guided group had significantly lower mortality than the usual care group. Therefore, the question remains unanswered whether the prevention of low BIS values or burst-suppression EEG can reduce POD.[103] Due to the controversial evidence, the consensus statement of the Peri-operative Quality Initiative-6 no longer recommends processed EEG monitoring in older high-risk patients.[109] However, because of the shortcomings of the ENGAGES trial, this consensus was not unanimous, and 6 out of 21 members voted against it.[108,109]

Haemodynamic factors

Blood pressure (BP) is an essential determinant of organ perfusion. Therefore, optimal and strict peri-operative

BP management could prevent postoperative organ injury.[110] There is still no universally accepted definition for adequate intra-operative BP or intra-operative hypotension (IOH).[111] However, IOH is frequently observed during (non)cardiac surgery.[112,113] Studies reveal an association between IOH, defined as mean arterial pressure (MAP) <55 mmHg or time-weighted average MAP <65mmHg in critically ill patients, and the incidence of POD following major noncardiac surgery.[113–115] In cardiac surgery, maintaining MAP above the lower limit of cerebral autoregulation during CPB, compared to standard practice (>60 mmHg), reduced the incidence of POD.[116] A RCT in major abdominal surgery targeted an individualized systolic BP within 10% of the reference value compared to standard care, which resulted in better postoperative cognitive function.[117] Another trial reported that high blood pressure, exceeding the upper limit of autoregulation, increased the risk for POD.[118] In hip fracture surgery, IOH was associated with POD.[119] In addition, blood pressure fluctuation or variability was found to be an additional risk factor for POD.[119,120] However, in several other studies, mainly in cardiac surgery, no association was found between IOH and cognitive outcomes.[110] Also, when comparing high-target (70 to 80mmHg) to low-target (45–50 mmHg) MAP in an RCT during CPB, no difference was detected in the incidence of POD, but POD was not the primary outcome in this trial.[121] Hence, the impact of IOH on POD is controversial. Most of the evidence is derived from observational and/or retrospective trials. While the association between IOH and postoperative adverse effects is undisputable, it is still unknown whether avoiding IOH improves postoperative outcomes.

Laboratory factors

Anaemia is considered a precipitating factor in the aetiology of POD and is often treated with blood transfusion.[122,123] Transfusion, however, is itself thought to be a precipitating factor for POD,[124] triggering an inflammatory response and cytokine release that, according to the neuro-inflammatory hypothesis, could cause POD.[40,122] In a secondary analysis of patients with hip fracture surgery, the association of anaemia with POD and the impact of blood transfusion on POD was investigated.[125] In this patient group, a haemoglobin level <9.3 g dl^{-1} was associated with an increased POD incidence, while blood transfusion was found to decrease it.[125] In contrast, in major noncardiac surgery, blood transfusion of >1000 ml was found to be an independent risk factor for POD.[126] This agrees with a large retrospective cohort study suggesting an independent association between red blood cell transfusion and POD.[127] A recent systematic review attempted to explain this dilemma.[122] Obviously, many studies do not account for several confounding precipitating factors such as the amount of blood loss, haemodynamic profile, the complexity of the surgery and/or postoperative pain.[122,127] Current evidence on the association between anaemia or blood transfusion with POD is inconclusive and requires further investigations.[122]

Postoperative risk factors

Postoperative pain and analgesia

One of the essential roles of every anaesthesiologist is to effectively manage postoperative pain, which is associated with several adverse postoperative effects including POD.[9] Preoperative pain also is an independent risk factor for POD.[20,128] Opioids are frequently used for pain management but are, unfortunately, considered a risk factor for POD.[9] Intra-operative use of long-acting opioids doubles the odds for POD.[129] Following hip fracture surgery, postoperative morphine use triples the odds for POD.[130] As a result, it is reasonable to think that opioid-free anaesthesia (OFA) would be beneficial. A recent multicentre trial compared balanced OFA with dexmedetomidine to balanced anaesthesia with remifentanil.[80] This study was stopped prematurely because of serious adverse events in the OFA group.[80] Current evidence suggests that a balanced multimodal analgesia concept, with emphasis on minimizing opioids, should be used.[131,132] Within this concept, targeted regional analgesia techniques can be useful to achieve this goal. In patients undergoing hip-fracture surgery, adding repeated fascia iliaca blocks (from admission until discharge) reduced the incidence of delirium.[133] Following abdominal or thoracic surgery, the use of epidural analgesia or para-neuraxial blocks can treat postoperative pain. Considering the conflicting evidence of postoperative regional analgesia on the impact of POD, further research into this topic is required.[134,135]

Sedation

There is increasing evidence to suggest that dexmedetomidine for postoperative ICU sedation in older patients (age ≥65 years) is safe and reduces the incidence of POD when compared to conventional sedatives.[136–139] In contrast, the use of benzodiazepine in the peri-operative setting is associated with a higher incidence of POD.[19,138,140,141]

Management and prevention

According to different reports, delirium, specifically the hypoactive subtype, is considerably under-reported in older hospitalized patients.[142] Therefore, routine daily screening with validated assessment tools, particularly in the older high-risk patient, is essential.[143] Although psychiatric evaluation is considered the gold standard for diagnosing POD, this is not feasible in all patients because of limited resources. Fortunately, several validated assessment tools are available that can be performed by a trained person, such as the 4AT, the Confusion Assessment Method (CAM), Delirium Observation Screening (DOS) scale or the Intensive Care Delirium Screening Checklist (ICDSC).[144,145] Nurses' and physicians'

Table 2 **Summary of interventions to help reduc postoperative delirium with their advantages and limitations.**

	Interventions	Advantages	Limitations
Preoperative			
Elective surgery	Comprehensive geriatric assessment using FRAIL Scale, FRAGIRE, EFS or TFI.	Allows allocation of resources and prehabilitation	More randomised controlled trials are needed to show benefits on outcome
	Preoperative work-up in patients with ≥1 risk factors for POD*)	Prehabilitation	Personnel resources
	(i.e., correction of anaemia using oral or i.v. iron treatment)	Correction of nutritional deficiencies (reduced red blood cell transfusion)	
		Review of medication	
Urgent surgery (required within 48 h)	Multidisciplinary geriatric consultation in patients with ≥1 risk factors for POD*)	Direct involvement of geriatric expert	Personnel resources
		Early correction of derangements	Time constraints
		Reducing polypharmacy	
Intra-operative			
Surgery	Reduce duration of surgery	Reduction of exposure time to noxious stimuli	Surgical expertise
	Reduce procedural invasiveness	Potentially maintain blood-brain barrier function due to a reduction in inflammatory response	Increased surgical expertise required
			Comparative research of different levels of invasiveness for the same condition is limited
Anaesthetic management	Multimodal anaesthesia	Allows a reduction in dosage of single agents and consequently side-effects of these agents.	Potentially increases drug errors
	Anaesthetic depth monitoring	In the older high-risk patient, EEG-guided anaesthesia potentially improves the outcome	Research required into the impact of reducing burst-suppression on POD
		Avoidance of deep sedation	
	Strict peri-operative blood pressure management	Avoidance of intra-operative hypotension	Results based on retrospective association studies
		Minimises blood pressure fluctuations	Strategies to determine patient- specific hypotensive cut-off values
	Attempt to reduce bleeding, anaemia and/or red blood cell transfusion	Reduction in inflammatory response and cost	Untangle the impact of anaemia or transfusion on outcome
Postoperative			
	Multimodal analgesia with emphasis on minimising opioid use	Reduction in dosage of single agents (i.e., morphine), which can reduce the risk for side effects.	Investigation into objective assessment methods of analgesia is required
	Dexmedetomidine for postoperative sedation in the ICU	In older postsurgical ICU patients, this can reduce POD.	Differences between medical and surgical patients
			Bradycardia is considered an important side-effect
Management and prevention			
	Routine daily screening: - 4AT, 3D-CAM, CAM, DOS scale or ICDSC (multiple assessments)	Early detection of POD aids in identifying patients with a hypo-active subtype.	Training of personnel
	Multicomponent nonpharmacological interventions: - Return of hearing aids and eyeglasses - Reorientation - Minimise the use of restraints - Early mobilisation - Pain management protocol - Sleep enhancement - Nutritional support - Geriatric co-management	Variations of combinations have shown: - Reduction in POD incidence and severity - Reduced hospital length of stay - Reduction in hospital cost - Prevention of institutionalisation Part of enhanced recovery programs	System-wide implementation required Verification in well designed studies required Additional personnel resources required for geriatric co-management
	Clinical work-up	Timely detection of derangements and early correction.	Increased resources required

3D-CAM, three-minute diagnostic confusion assessment method; 4AT, 4 'A's test (Arousal, Attention, Abbreviated Mental Test–4, Acute change); CAM, confusion assessment method; DOS scale, Delirium Observation Screening scale; EEG, electroencephalogram; EFS, Edmond Frailty Scale; FRAGIRE, TFI, Tilburg Frailty Index; Frailty Groupe Iso-Ressource Evaluation; ICDSC, Intensive Care Delirium Screening Checklist; ICU, intensive care unit; POD, postoperative delirium. *Based on risk-factors described in Table 1.

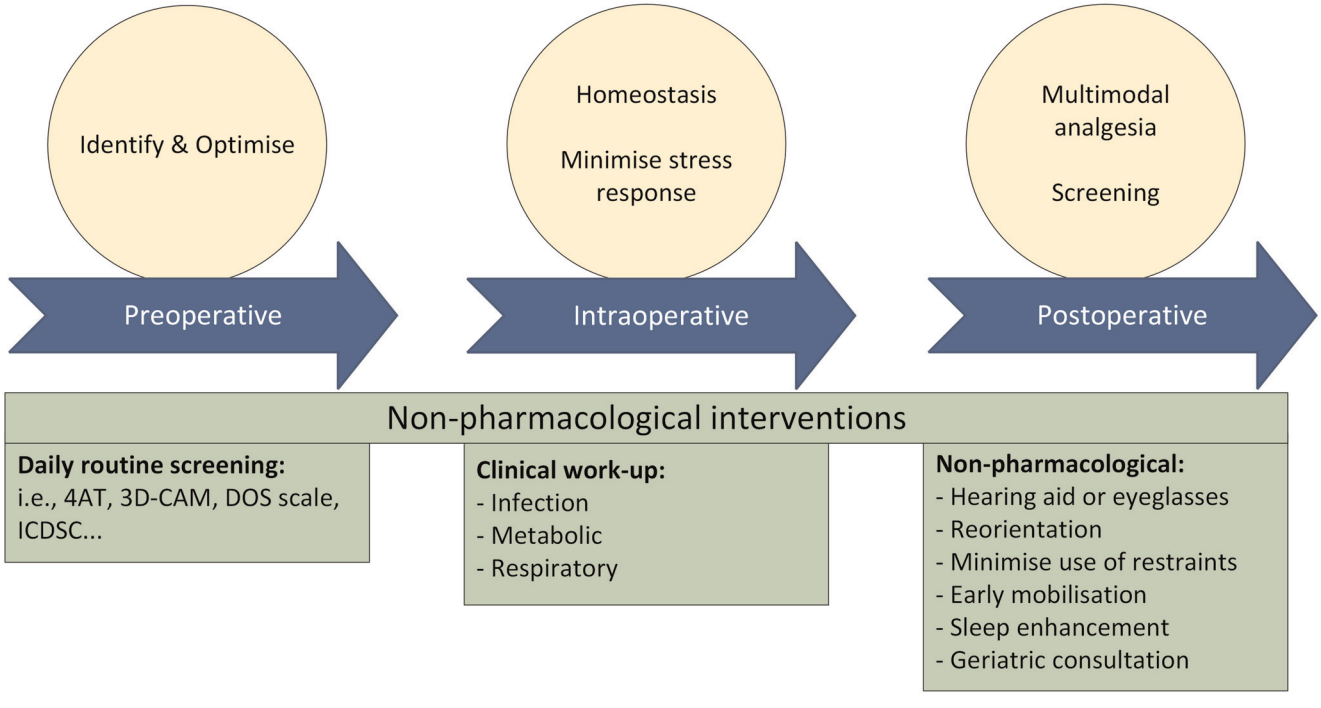
training is essential for good awareness and familiarity with the correct use of these tools. Other screening instruments intended to rule out POD quickly and recognize patients who may necessitate further assessments are available such as the three-minute diagnostic confusion assessment method (3D-CAM) or the ultra-brief two-item bedside test.[146,147] These tests are less challenging in the peri-operative setting and can be carried out by healthcare givers with limited additional training. Moreover, researchers have made several attempts to identify potential biomarkers for POD prediction, monitoring and prognosis,[148–150] but because of a lack of validation studies and for other logistic and practical issues such as test availability, cost, and time to get the result, neuro-biomarkers are not routinely used for POD diagnosis.

Evidence-based multicomponent, nonpharmacologic interventions have been shown to reduce the incidence of POD with no evidence of harm.[151] While these interventions vary according to institutions, the following items are usually considered: return of hearing aids and eyeglasses, re-orientation and minimizing the use of restraints, early mobilization, pain management, sleep enhancement, and nutritional support.[17,152,153] In addition, implementation of a multidisciplinary geriatric consultation or co-management is advocated in older and frail patients.[153,154] These interventions have been implemented in various combinations and consistently show a reduction in the incidence and severity of POD, hospital length of stay, hospital cost and they prevent institutionalisation.[24,151,155] Furthermore, adherence to enhanced recovery after surgery protocols, including admittance on the day of surgery, early return to home and/or ambulatory surgery may be effective for POD prevention.[151,156] This needs to be verified in well designed studies.

Given that POD can be triggered by any derangement of the homeostasis, an adequate workup should be performed.[17] Currently, there is no evidence that administration of prophylactic medications affects the incidence of POD.[151]

If a patient develops POD, first-line treatment consists of assessing and managing underlying triggers, including pain, infection, dehydration, metabolic derangements, urinary retention, constipation, medication, or sleep deprivation (Table 1, Table 2). The pharmacological treatment of POD with antipsychotics has been shown to reduce survival and should, therefore, be used with caution.[157] Finally, nonpharmacological interventions (Fig. 1, Table 2) remain the cornerstone of POD management.

Fig. 1 Peri-operative managements' strategies that need to be considered in preventing postoperative delirium. Detailed description of these strategies are provided in Table 2.



3D-CAM, three-minute diagnostic confusion assessment method; 4AT, 4 'A's test (Arousal, Attention, Abbreviated Mental Test–4, Acute change); DOS scale, delirium Observation Screening scale; ICDSC, Intensive Care Delirium Screening Checklist.

Conclusion

Postoperative delirium is a collection of symptoms that could be induced by numerous triggers, and no single pharmacological or nonpharmacological intervention can reduce or prevent it. Moreover, it develops more commonly in older frail patients undergoing major surgery. It has an unfavourable effect on outcomes and consumes healthcare resources. It is complex, with a pathophysiology that is not fully understood and has many potential risk factors, making prevention and management challenging. Our review outlines which patients are at increased risk of developing POD and points out several modifiable risk factors for POD. Caregivers need to evaluate patients, in particular older patients, for the risk of delirium preoperatively and identify and remove the underlying potential causes of it when possible. Many intra-operative precipitating factors, related to either the type of surgery or anaesthesia, are associated with POD and could be altered. After surgery adequate daily POD screening is essential, combined with a bundle of mainly nonpharmacological interventions to prevent or reduce POD and its impact on patient outcomes. Additional research is required to explore the efficacy and cost-effectiveness of multiple interventions in POD prevention (Table 2).

Acknowledgements relating to this article

Assistance with the article: none.

Funding and disclosures: none.

Conflict of interest: none.

Presentation: none.

This manuscript was handled by Anne-Claire Lukaszewicz.

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