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Review Article

Evidence-based strategies to reduce the incidence of postoperative delirium: a narrative review

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Summary

Delirium is one of the most commonly occurring postoperative complications in older adults. It occurs due to the vulnerability of cerebral functioning to pathophysiological stressors. Identification of those at increased risk of developing delirium early in the surgical pathway provides an opportunity for modification of predisposing and precipitating risk factors and effective shared decision-making. No single delirium prediction tool is used widely in surgical settings. Multi-component interventions to prevent delirium involve structured risk factor modification supported by geriatrician input; these are clinically efficacious and cost effective. Barriers to the widespread implementation of such complex interventions exist, resulting in an 'implementation gap'. There is a lack of evidence for pharmacological prophylaxis for the prevention of delirium. Current evidence suggests that avoidance of peri-operative benzodiazepines, careful titration of anaesthetic depth guided by processed electroencephalogram monitoring and treatment of pain are the most effective strategies to minimise the risk of delirium. Addressing postoperative delirium requires a collaborative, whole pathway approach, beginning with the early identification of those patients who are at risk. The research agenda should continue to examine the potential for pharmacological prophylaxis to prevent delirium while also addressing how successful models of delirium prevention can be translated from one setting to another, underpinned by implementation science methodology.

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Introduction

Delirium is one of the most common postoperative complications in older adults. Defined as a state of acute confusion that is commonly reversible and preventable in approximately 40% of cases [1, 2], delirium is characterised by: fluctuating levels of attention and awareness; disorientation; memory impairment; disturbances of perception; and disorganised thinking [3]. It occurs due to a vulnerability of cerebral functioning to pathophysiological stressors or triggers [4]. The prevalence of postoperative delirium varies significantly between surgical populations. In high-risk surgery, such as trauma and cardiac surgery, 36–40% of adult patients develop postoperative delirium, whereas in low-risk surgery, such as elective arthroplasty, the prevalence of delirium is 5–10% [5, 6].

Delirium is often distressing for patients and their families, resulting in symptoms of post-traumatic stress disorder, depression and anxiety [7]. There is also a negative psychological impact on healthcare staff caring for patients with delirium [8]. Other significant consequences of delirium include: increased duration of hospital stay [5, 9]; greater healthcare costs [1, 5, 10]; increased incidence of complications (including falls, pressure sores, functional decline and incontinence) [4]; increased re-admission rates; lower probability of discharge to original address [11]; worsening of cognitive trajectory [4]; and increased in-hospital mortality [9].

Given the negative sequelae of delirium, research has focused on interventions to reduce its occurrence and severity. Despite this evidence, such interventions are not embedded into routine clinical care pathways for older surgical patients. This article will summarise current thinking regarding the pathophysiology of delirium, the supporting evidence for strategies to reduce postoperative delirium and consider why an 'implementation gap' exists. A summary of strategies for reducing the incidence of postoperative delirium is illustrated in Fig. 1

Pathophysiology of delirium

The aetiology of delirium is diverse and complex, broadly consisting of direct central nervous system insults and aberrant stress responses. Direct brain insults causing delirium include: energy deprivation (hypoxia, hypoglycaemia); metabolic derangement (hyponatraemia, hypercalcaemia); neoplasm; and drug toxicity.

The provocation of delirium by aberrant stress responses can be more difficult to appreciate. Systemic inflammation due to hypothalamic–pituitary–adrenal mediators (e.g. corticotrophin-releasing hormone, adrenocorticotrophic hormone, cortisol, vasopressin), sympathetic nervous system mediators (e.g. acetylcholine, noradrenaline, adrenaline) and inflammatory mediators (e.g. tumour necrosis factor α, prostaglandin E2, interferon and interleukins) result in protective sickness behaviour. Dysfunction of this system occurs in delirium, with an exaggerated tissue stress response or by elevated stress signalling including inappropriately high cortisol and cytokine release. Attention, cognition, perception and mood are negatively affected as a result [12].

These two mechanisms can affect patients of any age but have most phenotypic impact in those with pre-existing neurodegeneration, commonly associated with older age.

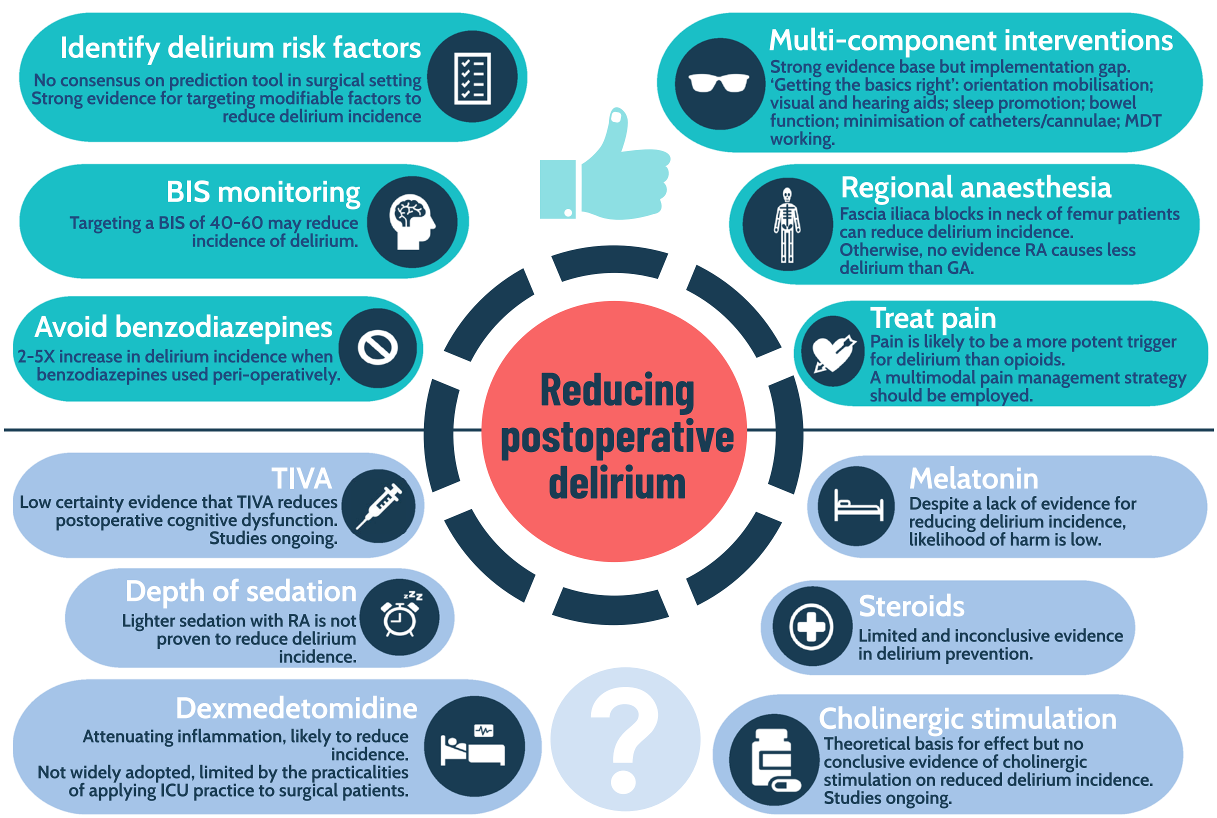

Figure 1 Strategies for reducing postoperative delirium incidence: evidence-based recommendations and areas of ongoing research. BIS, bispectral index; TIVA, total intravenous anaesthesia; RA, regional anaesthesia; MDT, multidisciplinary team; GA, general anaesthesia.

The ageing brain is subject to neuronal loss, reduced cerebral blood flow, declining dopamine and serotonin levels, and an impaired blood–brain barrier. Additionally, patients with dementia display pre-existing neuro-inflammation with a structurally and functionally impaired blood–brain barrier, increasing the influence of systematic stress mediators and resulting in a greater incidence of delirium [13].

Consequently, the focus of delirium prevention is to minimise direct brain insults and physiological stress. Given that surgery under anaesthesia represents controlled trauma with a resultant systemic stress response, the challenges of minimising postoperative delirium are evident.

Risk prediction and modification

The risk factors for development of postoperative delirium reflect the interplay between underlying cerebral vulnerability and exogenous neurocognitive stressors and are considered as predisposing and precipitating factors (Table 1). These can be used to stratify patients according to the risk of postoperative delirium, allowing interventions to be targeted appropriately [1, 14]. Despite this division, overlap between predisposing and precipitating factors exists. For example, the predisposing factors of frailty, dementia and low socio-economic status may delay timely presentation at an early stage when pathology is amenable to elective surgical management. This can result in a patient without cognitive issues presenting with symptoms of stable claudication and being treated electively with risk factor management, exercise and planned revascularisation for peripheral arterial disease. Conversely, a patient who has dementia and is socially isolated may fail to seek help with similar symptoms. This can result in an acute presentation with critical limb-threatening ischaemia and sepsis from wet gangrene already causing a systemic stress response and delirium. This commonly necessitates emergency surgery without opportunity for peri-operative optimisation.

Table 1 Predisposing and precipitating risk factors for delirium (not exhaustive) [4, 11, 15].

Predisposing	Precipitating
Increased age	Hospital admission
Male sex	Surgical procedure
Lower body mass index	Sleep deprivation
Hearing loss	Bladder catheter
Sight loss	Polypharmacy (≥ 3 medications added)
Social isolation	Medications
Multimorbidity	Severe illness (e.g. infection, fracture, stroke)
Prior cognitive impairment	Hyper- or hypothermia
Malnutrition	Dehydration
Low serum albumin	Increasing duration of surgery
Frailty	Urgency of surgery
Cancer	

Several delirium risk prediction tools are based around these predisposing and precipitating factors. Inouye et al. developed a risk score to predict delirium in older medical patients which considered cognitive function, physical health and vision [15]. This score was validated subsequently in patients suffering hip fracture [16]. Another delirium risk scoring system created by Kim et al. uses nine items including: age; low physical activity; hearing impairment; heavy alcohol intake; history of prior delirium; critical care admission; emergency surgery; open surgery; and elevated pre-operative C-reactive protein. This prediction tool has been validated in general surgical patients at a single centre [17].

However, there is no universally accepted delirium risk prediction tool that has been validated in all elective and emergency surgical specialities. Furthermore, across older adult hospital inpatients, existing models show variable and inadequate predictive capabilities [18]. The ideal postoperative delirium risk prediction tool would incorporate relevant and easily measurable predisposing and precipitating risk factors, be brief and clinically feasible, have robust validation data across different surgical specialities and balance sensitivity and specificity. Developing such a tool would require a sizeable and comprehensive dataset of older surgical patients and their outcomes, but could improve targeting of delirium prevention interventions, inform shared decision-making and enhance healthcare resource allocation.

Prevention of delirium: non-pharmacological methods

Most of the published evidence supports the use of non-pharmacological approaches to prevent delirium. A number of different approaches have been studied including: multi-component intervention; comprehensive geriatric assessment; delirium units; and educational initiatives.

Multi-component intervention

The first studies demonstrating the benefit of multi-component interventions in the prevention of delirium in medical and surgical patient populations were published

> 20 years ago [1, 19]. These complex, multi-component interventions target predisposing and precipitating risk factors for delirium and have been shown to reduce the incidence of delirium from 15% to 10% in medical inpatients (odds ratio (OR) 0.6 (95% CI 0.39–0.92)) [1] and from 50% to 32% in patients following hip fracture surgery [1, 19].

The Hospital Elder Life Program (HELP) is an example of a multi-component intervention to prevent delirium [10]. The evaluation of the HELP model to prevent postoperative delirium in patients aged ≥ 70 y undergoing elective surgery showed a number needed to treat of 5.9 (95% CI 4.2–11.1) [2] with the observation that certain patient groups were more likely to benefit, for example, patients without pre-existing cognitive impairment or dependence for activities of daily living [19]. Systematic reviews and meta-analyses of HELP-type models of delirium prevention have shown the benefits of such an intervention on reducing the incidence of delirium and falls with non-significant trends towards a reduction in duration of stay and institutionalisation in a cost-effective manner [10]. Despite these research findings, standardised multi-component delirium prevention systems are not employed consistently in the UK National Health Service [20]. An example of a multi-component intervention to prevent delirium is shown in Table 2.

Comprehensive geriatric assessment

Comprehensive geriatric assessment and optimisation offers a methodology to underpin systematic structured pre-operative assessment, including identifying risk factors and clinically optimising physical, psychological, functional and social issues in older patients with the aim of minimising postoperative complications including delirium. The process incorporates many components from the delirium reduction strategies described above and results in an individualised care plan that encompasses investigation, treatment, rehabilitation and long-term follow-up [21]. It is therefore unsurprising that evidence examining comprehensive geriatric assessment as a pre-operative intervention shows a reduction in the incidence of postoperative delirium in a number of different elective surgical groups: orthopaedic (5.6% vs. 18.5%; p = 0.036); vascular (11% vs. 24%; p = 0.018); and colorectal (11% vs. 29%; p < 0.001) [21–23].

Table 2 Example of a multi-component intervention programme (adapted from existing multi-component intervention programmes [4, 10]).

Interventions	Description
Daily visitor/orientation	Orientation board with names of care team members and daily schedule, orientating communication
Therapeutic activities	Cognitive stimulation activates three times a day (e.g. discussion of current events, structured reminiscence or word games)
Early mobilisation and physiotherapy	Ambulation of active range of motion exercises three times daily, minimise the use of immobilising equipment (e.g. urinary catheters, restraints)
Sensory protocol	Visual and hearing aids and equipment provided. Special communication techniques and earwax disimpaction as required.
Nutrition and hydration	Feeding and fluid assistance and encouragement during meals
Sleep enhancement	Non-pharmacologic sleep protocol: warm drink; relaxation tapes/music; noise reduction; schedule adjustment to allow sleep.
Analgesia	Effective pain management using multimodal analgesia
Bowel function	Regulation of bowel motion with appropriate hydration and laxatives
‘Normalisation’ where possible	Remove unnecessary cannulae, catheters and other equipments.
Geriatric nursing assessment and intervention	Nursing assessment and intervention for cognitive and functional impairment, dehydration, nutrition, psychoactive medication use and discharge planning.
Interdisciplinary rounds	Twice weekly rounds to discuss care, set goals and review issues with interdisciplinary input. Recording and tracking of interventions. Identification and treatment of underlying causes of postoperative complications.
Provider education programme	Teaching sessions, one-on-one interactions and resources to educate nursing and physician staff about the programme.
Community linkages and telephone follow-up	Referrals and communication with community agencies to optimise transition to home. Telephone follow-up within 7 days for all patients.
Geriatrician consultation	Targeted consultation on geriatric issues, referred by nursing staff or other physicians.
Interdisciplinary consultation	Provide as needed consultation and input about the programme on referral.

Delirium units and joint care wards

Delirium units offer a novel model of joint geriatric medicine and psychiatric co-management in a safe physical environment for patients with delirium. These units aim to avoid unnecessary intra-hospital transfers and provide homely, yet secure, environments conducive to rehabilitation. They are staffed by a dedicated multidisciplinary team with strong links to community services. Such an approach to care is in keeping with National Institute for Health and Care Excellence (NICE) recommendations that "*people at risk of delirium are cared for by a team of healthcare professionals who are familiar to the person at risk*" and to "*avoid moving people within and between wards or rooms unless absolutely necessary*" [14].

Despite the intuitive benefits of such units, they have not been proven to reduce mortality, duration of hospital stay or improve discharge destination [24–26]. However, delirium units may have positive benefits in terms of patient experience and carer satisfaction [25, 26]. In addition, the practicalities of delivering care in delirium units are problematic. Over one-third of acute hospital patients will have delirium at any one time, making cohorting into delirium beds impractical. This is particularly evident in the peri-operative setting where ongoing surgical expertise is required in the postoperative pathway of care.

Education programmes for patients and families

Education programmes which aim to pre-emptively increase knowledge about a particular condition have face validity in reducing anxiety and distress and improving patient experience. Patients at risk of delirium, and their families, may benefit from education about the surgical pathway, outcomes and exposure to the environment they will experience. This educational approach has been examined in 133 surgical patients without pre-existing cognitive impairment who had cardiac surgery using cardiopulmonary bypass. The patients and their families who received an individualised education session, critical care tour and information leaflet had a lower incidence of postoperative delirium compared with those patients receiving standard care (10% vs. 24%; $p = 0.038$) [27]. Similarly, multi-component interventions for the prevention of delirium may include an educational facet [28]. The potential benefit of educational interventions is reflected in the recent expert consensus paper by Peden et al. [29] This endorses offering patients and their families education about the risk of developing delirium, the risk of a delayed return to cognitive baseline and techniques to reduce delirium incidence.

Pharmacological interventions

A review of strategies to prevent postoperative delirium would not be complete without a discussion of pharmacological interventions, despite the lack of conclusive evidence in support of pharmacological prophylaxis to prevent delirium. The pathophysiology of delirium discussed earlier illustrates potential pathways that pharmacological drugs could act on. Examples of these include reducing anticholinergic medication burden, managing direct brain insults such as infection or drug toxicity and tempering the stress response with steroids, dexmedetomidine or melatonin.

Avoidance of certain medications

The strongest evidence for pharmacological delirium prevention involves medication avoidance, specifically benzodiazepines, with a two- to five-fold increased incidence of delirium in patients given peri-operative benzodiazepines [28, 30].

The provision of intra- and postoperative analgesia often centres around the administration of opioids. Opioids can themselves cause delirium while also treating pain, one of the frequent triggers for postoperative delirium [31, 32]. Apart from pethidine, which has anticholinergic effects, and meperidine, which metabolises to the neuro-excitatory normeperidine, no difference is seen in the rates of postoperative delirium according to opiate type [32, 33]. Furthermore, pain is probably a more potent trigger of delirium than opioid administration, as shown in a study of patients undergoing surgery for hip fracture. Participants who received low doses of opioid analgesia (<10 mg of intravenous morphine sulphate equivalents per day) had a greater predicted incidence of delirium than those receiving higher doses (relative risk 5.4 (95% CI 2.4–12.3)) [32]. Multimodal analgesia, which may include the careful titration of opioid medication, is therefore recommended.

Cholinergic stimulation

It would seem plausible that cholinergic stimulation could prevent delirium; however, this intuitive solution is not supported by evidence. A double-blind randomised controlled trial of patients undergoing hepatic surgery compared a physostigmine bolus and subsequent infusion for 24 h with a placebo with no significant difference in the incidence of delirium between the groups [34]. A meta-analysis of a further two studies found a possible association between the administration of cholinesterase inhibitor and reduced postoperative delirium [35], but this requires further research.

Steroids

The role of systemic inflammation in the pathophysiology of delirium has prompted studies to investigate whether prophylactic glucocorticoids may reduce the incidence of delirium. A meta-analysis of two studies in cardiac surgery and a randomised controlled trial of patients undergoing surgery for hip fracture found that peri-operative dexamethasone did not influence the incidence of delirium [36, 37]. This is in contrast to another randomised controlled trial of patients undergoing hip fracture surgery where methylprednisolone was compared with placebo [38]. This study found that prevalence of postoperative delirium was reduced in patients allocated to receive methylprednisolone administration; however, the severity of delirium was unaffected. Further larger studies with greater generalisability including patients with and without pre-existing cognitive impairment are required.

Dexmedetomidine

Recent studies in surgical populations have shown a benefit of dexmedetomidine in reducing delirium incidence (by up to 50%) and duration (by 0.7 days) [30,35]. In a double-blind randomised controlled trial of older patients undergoing laparoscopic, major, non-cardiac surgery, giving an initial bolus (1 $\mu g.kg^{-1}$) followed by a continuous infusion (0.2–0.7 $\mu g.kg^{-1}.h^{-1}$ from induction to the end of surgery) reduced the incidence and severity of delirium, compared with just giving a bolus dose (1 $\mu g.kg^{-1}$ 15 min before the end of surgery) or placebo. This study also showed that interleukin-6 levels were significantly lower in patients who received a dexmedetomidine bolus and infusion; this may indicate an attenuated inflammatory response as the mechanism of action for a reduction in the incidence of delirium [39]. Clinical application of this evidence is limited by generalising ICU practice and findings to the surgical setting. In addition, there is a potential for adverse effects such as bradycardia [40].

Melatonin

Melatonin regulates and synchronises circadian rhythms, accelerating sleep initiation and improving sleep maintenance. It also has anti-excitatory effects on the central nervous system. Ageing results in deranged melatonin secretion, most notably in those patients with dementia, who are known to be at increased risk of delirium [41]. This gives melatonin a theoretical biological basis for delirium prevention. Ramelteon is a melatonin receptor antagonist, which has a high affinity for the melatonin receptor and longer half-life and better absorption than melatonin. The literature surrounding melatonin use in delirium prevention is conflicted [42]. A meta-analysis found that melatonin and ramelteon only significantly reduced delirium incidence in older medical but not surgical patients [43]. A randomised controlled trial of melatonin use in patients having cardiac surgery found that it did not impact the incidence of postoperative delirium [44]. Another meta-analysis showed a variable reduction in the frequency of postoperative delirium with melatonin use from 4–33% in the comparator groups to 0–30% in the melatonin group (OR 0.63 (95%CI 0.46–0.87); $p = 0.006$) [45]. The potential for harm from melatonin is low and the possibility of positive effects on delirium prevention makes it an attractive proposition for further research.

Dopamine antagonists

Antipsychotic drugs including haloperidol and olanzapine also have a theoretical biological basis for delirium management due to their role as dopamine antagonists [46]. Despite some positive trials in surgical and critical care patients, a meta-analysis showed there is no evidence that dopamine antagonists prevent delirium [42], although they remain useful for the treatment of delirium [14].

Intra-operative interventions

A diverse range of anaesthetic techniques and intra-operative medications to prevent delirium have been evaluated, without sufficient evidence to make firm recommendations about their implementation into routine clinical use.

Depth of sedation

Sedation and analgesia have been identified as iatrogenic risk factors for delirium in ICU [47]. Sedation administered alongside regional anaesthesia can often vary in depth from light sedation to unintended general anaesthesia. Intuitively, the administration of less sedative and analgesic medications should result in lower rates of postoperative delirium. A double-blind randomised controlled trial evaluated the effects of light and deep propofol sedation for hip fracture repair under regional anaesthesia. The initial results did not demonstrate a significant improvement in delirium rates between the two groups. When the authors conducted a pre-specified subgroup analysis, they found that those with a Charlson comorbidity index of zero (least comorbidity) were 2.3 times more likely to experience postoperative delirium after receiving heavy sedation than light sedation. This may be because multimorbidity is more pertinent in the causation of delirium than the depth of sedation [47]. The careful titration of sedation levels does not appear to reliably reduce postoperative delirium.

Total intravenous anaesthesia

Whether or not administering total intravenous anaesthesia (TIVA) over inhalational maintenance anaesthesia reduces delirium incidence remains uncertain. A recent review by the Cochrane group concluded that there was low certainty that TIVA may reduce postoperative cognitive dysfunction (OR 0.52 (95%CI 0.31–0.87)) [48]. There are ongoing studies investigating this area of interest.

Processed electroencephalogram monitoring

Processed electroencephalogram monitoring to guide the depth of anaesthesia has been used to try and reduce the incidence of postoperative delirium [42, 49, 50]. A randomised clinical trial by Evered et al. studied the incidence of postoperative delirium in patients undergoing major surgery under volatile anaesthesia [51]. Participants were allocated to anaesthesia targeting a bispectral index (BIS) reading of 35 or 50. The incidence of postoperative delirium in the group targeting BIS 35 was 28%, compared with 19% in the group targeting BIS 50 ($p = 0.01$). This equates to an OR of 0.58 (95%CI (0.38–0.88)) and a number needed to treat of 10 (95%CI 6–43). Limitations of this and previous studies include: concerns about BIS as an accurate gauge of depth of anaesthesia; potential for bias; heterogeneity between study sites; and influence from genetic diversity to anaesthetic maintenance and recovery [52].

Regional vs. general anaesthesia

Regional anaesthesia presents the opportunity to effectively manage pain while reducing systemic analgesic and anaesthetic requirements. Studies on this topic have focused on the management of older patients undergoing surgery for a hip fracture. A systematic review found that mode of anaesthesia did not influence the incidence of postoperative delirium or survival [53]. At present, there is insufficient evidence to recommend one anaesthetic technique over another in order to reduce the incidence of postoperative delirium [53].

Another area of interest is the provision of regional anaesthetic techniques for peri-operative analgesia and anaesthesia. The most studied blocks are fascia iliaca compartment blocks for patients with a hip fracture. These blocks are relatively straightforward to teach and administer, and appear to be effective in pain management while being unlikely to cause significant harm. Studies of single-shot and continuous regional fascia iliaca techniques have shown a reduction in the incidence of postoperative delirium and peri-operative pain [54, 55]. Wider investigation into the efficacy of other regional anaesthetic techniques for different surgical procedures in the prevention of delirium would be beneficial.

Challenges in implementing complex multi-component interventions

The studies of multi-component interventions for the prevention of postoperative delirium have demonstrated clinical and cost effectiveness [1, 19, 42]. As a result, NICE guidance recommends the use of multi-component interventions to prevent delirium [14]. Although the proportion of UK hospitals that have implemented a multi-component delirium prevention intervention is not known, the challenges of adopting these models into clinical practice are discussed frequently [20]. This 'implementation gap' from research findings to routine clinical service delivery may be due to the inherent complexity of embedding and evaluating multi-component interventions. This is widely acknowledged and is in part addressed through the Medical Research Council framework for developing and evaluating complex interventions [56].

A complex intervention has several interacting components that must integrate into an already complicated pathway or service. Implementing a multi-component intervention model, therefore, often requires several staff groups to commit to different ways of working within a new organisational structure. Furthermore, an evidence-based complex intervention should be tailored to the local context in order to maximise the chances of sustained success [56]. Studies of nurse-led, protocolised multi-component care pathways have not shown the same benefits in delirium prevention as fuller multi-component interventions involving the wider multidisciplinary team [57, 58]. This suggests that, despite the inherent difficulties in involving and engaging all stakeholders, true multi-component interventions are preferable to simplified models of care.

The practical challenges of implementing multi-component interventions were described by Goldberg et al., who carried out a preliminary study employing a prevention of delirium system in six wards across five UK hospitals. The implemented model required the provision of training and materials, integration of delirium management processes into ward systems and ongoing review by the central team [20]. The system was implemented successfully in four wards [59]. The vital role of leadership at senior level to legitimatise the model, and at ward level to support and encourage staff was recognised [20]. The barriers to implementation were as follows: staffing levels; agency staff use; time for ward-level planning tasks; volunteer recruitment and retainment; and organisational challenges such as ward closures [59]. Despite significant investments of time and money, this study showed that implementation of multi-component intervention models was problematic, even in self-selecting hospitals where 'buy-in' existed. Medical Research Council guidelines and implementation science methods are supporting ongoing efforts to address these challenges [20].

Conclusion

Postoperative delirium is common, with implications including increased postoperative mortality, morbidity, psychological sequelae and healthcare costs. Evidence shows that multi-component interventions are the mainstay of preventing delirium, although medication management is an important part of this. The implementation gap between research findings supporting multi-component interventions to prevent delirium and delivering these through clinical services remains, although attempts to address the gap are ongoing using implementation science methodology.

Addressing postoperative delirium requires a collaborative, whole pathway approach, beginning with the routine identification of those at risk of delirium early in the pre-operative setting. A delirium prediction tool validated across surgical specialities may enable this, providing opportunities to employ individualised patient-centred management to modify delirium risk in a cost-effective manner. Multi-component interventions to reduce the incidence of delirium should be implemented through involvement of all peri-operative stakeholders including patients and their families. The research agenda should continue to examine potential pharmacological prophylaxis for delirium while also addressing how successful models of delirium prevention can be translated from one setting to another, underpinned by implementation science methodology.

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