Postoperative delirium

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Summary

Delirium in the perioperative period is a wide-reaching problem that directly affects important clinical outcomes. It is essential that anesthesiologists understand how to define and diagnose delirium, identify patients at high risk for developing delirium, recognize precipitating factors to appropriately adjust care plans, and manage patients who develop delirium in the acute postoperative period. Importantly, delirium remains underdiagnosed in the perioperative setting, but many screening and assessment tools are readily available to aid non-psychiatric trained personnel in identifying delirium. Finally, understanding and implementing strategies to prevent patients from developing delirium is of utmost importance, as evidence-based pharmacological treatments for delirium are minimal and have significant limitations.

Introduction

Delirium is a state of acute cerebral dysfunction that manifests as fluctuations in mental status. It is a common problem among all patients admitted to the hospital and has the potential to significantly alter patients’ clinical outcomes. There are many risk factors that predispose patients to delirium including age, frailty, and preexisting comorbid conditions, as well as risk factors unique to the perioperative period, such as severity of concurrent illness, type of operation, and ICU admission after surgery [1]. Perioperative delirium should be of paramount importance to providers, as multiple studies in perioperative patients have found significant associations between development of delirium within the first few days of surgery and increased length of stay, higher cost of care, increased hospital readmission rates, higher likelihood of discharge to institution, prolonged cognitive impairment and dementia, and increased mortality [2–5]. Postoperative delirium occurs commonly, is underdiagnosed, and is associated with worse patient outcomes. Understanding the disease process, risk factors, and management is critical to improving the care provided to patients by anesthesiologists.

Definition

Identifying postoperative delirium requires an understanding of the definition of delirium: a disorder hallmarked by an acute disturbance in attention and cognition that is not explained by a preexisting neurocognitive disorder or severe reduction in arousability. Common characteristics of
altered attention include inability to direct, focus, sustain, or shift attention, and cognitive disturbances include impaired memory, disorientation, or perceptual disturbances [2,3,6-8]. Unlike the gradual onset of dementia, alterations in attention and cognition must be acute and fluctuate throughout the day. Importantly, delirium may be further classified into three subtypes based on psychomotor behavior: hyperactive, hypoactive, or mixed. Hyperactive delirium presents with agitation, restlessness, and hypervigilance. Patients with hypoactive delirium are lethargic with slowed mentation and decreased movement. Importantly, care providers are much more likely to miss a diagnosis of delirium in patients with hypoactive features [9].

Perioperative delirium may be further classified based on the time point at which delirium is diagnosed in relation to the surgical intervention. Emergence delirium refers to psychomotor agitation that occurs as the patient emerges from a general anesthetic. Post-anesthesia care unit (PACU) delirium refers to fluctuations in mental status occurring after emergence but prior to meeting criteria for discharge from a PACU. Once the patient is discharged from the PACU to the hospital ward or ICU, mental status changes that meet delirium diagnosis criteria are referred to as postoperative delirium.

**Diagnosis**

Diagnosing delirium in the perioperative setting is very important, but sedating and analgesic medications administered during perioperative care and the natural course of emergence from general anesthesia add complexity in reaching a diagnosis. The gold standard for diagnosis of delirium is a formal evaluation performed by a psychiatrist using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria [9]. As time, feasibility, and available resources often preclude a formal evaluation in most hospital settings, a number of validated instruments have been developed to aid in rapid and reliable bedside diagnosis. No instruments have been specifically validated in the PACU setting; however, key features of existing instruments are applicable and useful in establishing a delirium diagnosis throughout the perioperative period. The critical first step in assessing a postoperative patient for delirium is to assess the patient’s level of arousal, as the patient must be responsive to voice in order to complete assessment for delirium. Widely used arousal/sedation tools include the Richmond Agitation Sedation Scale (RASS) [10] and the Sedation Agitation Scale (SAS) [11]. Once an appropriate level of arousal is established and the patient is responsive to verbal stimuli, validated assessment tools available include: the Confusion Assessment Method (CAM), [12] the 4AT, [13] the Nursing Delirium Symptom Checklist (NuDESC), [14] the Confusion Assessment Method for Intensive Care Unit (CAM-ICU), [15] and the Intensive Care Delirium Screening Checklist (ICDSC) [16]. Regular use of a validated screening tool is critical in ensuring that delirium is not left undiagnosed. The previously listed screening tools are primarily validated for use in ward or ICU patients. In looking at early postoperative applications, studies have predominantly examined the NuDESC and CAM-ICU in the PACU. Specificity for delirium diagnosis was > 90% for both tools; however, neither tool was sensitive for PACU delirium [17]. Therefore, a positive result on one of these assessment tools is likely to be delirium, but existing tools are not adequate to identify all cases of delirium, especially those that are mild. Examination of delirium severity is an ongoing topic of research. Modifications to existing assessment tools have been made to establish delirium severity scales. Adapted from the CAM and CAM-ICU assessments where features were scored as present or not present, the CAM-S and CAM-ICU-7 tools determine severity by assigning a numbered scale (0-2) to each feature (fluctuation of mental status, inattention, altered level of consciousness, and disorganized thinking). The CAM-S tool has been validated as a measure of delirium severity and correlates to patient outcomes both in-hospital and post-discharge [18]. In the critically ill patient population, the CAM-ICU-7 severity scale has been validated, and severe delirium scores correlate with increased mortality [19]. Validated delirium assessment tools allow for rapid and consistent evaluation of delirium throughout the perioperative period. Further research into validated measures for the immediate postoperative and PACU period, however, are needed.

**Prevalence**

The prevalence of delirium in perioperative patients is highly variable based on the patient population, timing, location within the hospital, delirium subtype, and the selected assessment tool. Card et al. examined a cohort of 400 patients after non-cardiac surgery at various time points to characterize delirium in the immediate postoperative period. On observation of emergence from general anesthesia in the operating room, 19% of patients demonstrated hyperactive agitation [20]. The CAM-ICU tool was utilized in PACU where 37% of patients had delirium upon arrival. Of those determined to have delirium, RASS scores were assessed to determine hypoactive versus hyperactive signs. On arrival to PACU, 47% displayed hypoactive signs and 53% presented with hyperactive signs. During the PACU stay, prior to meeting criteria for discharge from PACU, 16% of patients were found to be positive for delirium with 92% demonstrating hypoactive signs. Once patients met criteria for discharge from PACU as determined by the Aldrete score, 5% were positive for delirium [20]. In a smaller, more selective, study of patients > 70 years old, Neufeld et al. found that 45% of patients had delirium after meeting discharge criteria from PACU, indicating completion of recovery from anesthesia. Of the patients that experienced delirium throughout their hospital stay, 74% were positive for delirium in the PACU [2]. Postoperative delirium rates vary by type of surgery and procedure risk. Otolaryngology and general surgery have a lower risk at 12%
and 13% respectively, whereas delirium prevalence with aortic (up to 29%), major abdominal (up to 50%), and cardiac (up to 51%) surgery is much higher [1]. If patients require postoperative admission to an ICU and mechanical ventilation, the prevalence of delirium has been reported as high as 80%. Of the motoric subtypes of delirium, mixed and hypoactive delirium are by far more common than the more clinically apparent hyperactive delirium, which is reported at around 1.6% [21].

Pathophysiology

The pathophysiology of delirium is multifactorial and continuously evolving with ongoing work exploring the complex physiologic interactions resulting in this condition (figure 1). Many mechanisms of dysfunction have been proposed including inflammation-mediated neuronal injury and altered cerebral perfusion, endothelial dysfunction resulting in increased permeability of the blood-brain barrier, reduced cholinergic activity, altered neurotransmitter balance, and certain clinical pharmacologic interventions [22]. Advancing age with decreased reserve and changes to the physical characteristics of the brain, including cerebral atrophy and changes in white matter, have also been associated with an increased risk of developing delirium [23–25].

Surgical stimulus prompts a release of inflammatory mediators and cytokines including cortisol, CRP, IL-6, and IL-8, all of which have been associated with development of delirium [22,26]. The peripheral mediators induce signaling cascades to produce cytokines and inflammatory mediators within the brain, alter cell proliferation, and stimulate the hypothalamic-pituitary-adrenal axis [27]. Microglial cells serve as a primary mediator of this neuroinflammatory response by upregulating production of pro-inflammatory cytokines. The cytokines are associated with slowing of, and disturbances in, cognitive function. Further, over-activation of microglial cells leads to neuronal apoptosis [22,28]. Thus, microglial cells are thought to play an integral role in the development of delirium during inflammatory states including surgical stress, infection, and pain. The systemic inflammatory response also impacts the endothelial cells of the body. The endothelial cells of the cerebral vasculature comprise the highly selective blood-brain barrier, and damage to these cells allows for increased and dysregulated microvascular permeability. Endothelial dysfunction also promotes activation of coagulation pathways leading to microvascular clotting and alterations in cerebral blood flow [22]. Hughes et al. assessed levels of biomarkers associated with blood-brain barrier permeability and endothelial dysfunction and found that

**Figure 1**

Pathophysiologic mechanisms. Hypothesized mechanisms of delirium include blood-brain barrier (BBB) and endothelial injury, reduced cholinergic inhibition, and neuroinflammation with microglial activation which lead to neurotransmitter imbalances and structural changes.
elevations in S100B, E-selectin, and plasminogen activator-1 were associated with prolonged delirium in critical illness [29]. The earliest association between delirium and neurotransmitter dysfunction came from the observation that toxins and drugs that inhibited cholinergic activity caused a state of delirium [30]. Observations that administration of anti-cholinergic medications to elderly patients leads to delirium further support this cholinergic deficiency hypothesis of delirium. Acetylcholine is an important modulator of the systemic inflammatory response by decreasing the number of inflammatory cytokines released. Critical illness and high stress states may deplete systemic stores and decrease availability of acetylcholine, leading to a loss of the anti-inflammatory regulation. In addition, microglia express acetylcholine surface receptors. States of stress and cholinergic deficiency are thought to contribute to the hyperactivation of microglia associated with the development of delirium [22,31]. Additional neurotransmitter imbalances associated with development of delirium include dopamine, serotonin, and norepinephrine. Elevated levels of dopamine are well established in association with symptoms of delirium, particularly excitability and hyperactive delirium [27]. An excess of serotonin has been associated with impairment in learning, memory, and cognitive measures associated with delirium, and administration of certain selective serotonin reuptake inhibitors has been associated with delirium [22]. Increased norepinephrine levels contribute to agitation, anxiety, impaired attention, and psychosis and are associated with development of hyperactive delirium [30]. Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter of the central nervous system. Dysregulation in GABA levels, both in excess and deficiency, have been associated with delirium. Administration of GABAergic drugs is associated with a higher incidence of delirium [27]. Conversely, elevated systemic levels of IL-6, independently associated with increased delirium, are thought to cause loss of GABAergic interneurons and promote delirium [32]. Though independently associated with delirium, neurotransmitter pathways are highly overlapping and interactive and frequently cause, or amplify, a downstream imbalance in another neurotransmitter.

Neuroimaging in patients with delirium has demonstrated two distinct findings: brain atrophy and disruption of white matter integrity. A cohort of ICU patients with delirium imaged at hospital discharge and 3 months post-discharge demonstrated brain atrophy as measured by an increased ventricle-to-brain ratio. Smaller volumes of certain brain areas at discharge were associated with longer duration of delirium, and persistent brain atrophy at 3 months was associated with cognitive impairment up to 12 months after discharge [24]. Additionally, imaging demonstrated that prolonged duration of delirium was associated with white matter disruption in the corpus callosum and anterior limb of the internal capsule that, if still present at 3 months, was associated with lower cognitive function up to 12 months after discharge [33]. Preoperative and postoperative magnetic resonance imaging was performed in a more recent study of elderly patients undergoing major noncardiac elective surgery [34]. This study found that postoperative delirium was associated with decreased integrity and increased diffusion in periventricular, frontal, and temporal white matter.

Risk factors

Identifying factors that are associated with developing delirium is paramount to recognition and prevention of delirium in the perioperative patient (figure 2). Risk factors can be classified into two categories: predisposing factors that increase a patient’s risk of delirium and factors that precipitate developing delirium. Across a wide variety of surgical specialties, advancing age and baseline cognitive impairment are the most highly cited factors associated with an increased risk of delirium [1,35,36]. Patients with baseline white matter microstructural changes in the cerebellum, hippocampus, and thalamus are also at increased risk of postoperative delirium [37]. Additionally, increasing comorbid medical conditions (including sleep apnea, heart failure, and diabetes) [38] and frailty [39] increase a patient’s risk of developing delirium. Patients with a higher physical and cognitive reserve appear to be more protected from developing delirium and, conversely, those with lower reserve may have a decreased ability to maintain normal brain function after an acute stress insult (e.g., surgery), placing them in a higher risk category for developing delirium [40,41]. Similarly, increasing severity of surgical insult and illness (indicated by an ASA score ≥ 3) and need for postoperative mechanical ventilation all increase the risk of postoperative delirium as compared to lower risk operations [1]. Perioperative neurologic insults, including new cerebral ischemic lesions and deep subcortical white matter hyperintensity changes, have also been associated with postoperative delirium [42].

While recognizing the predisposing factors aids the clinician in early identification of patients at risk for delirium, understanding the precipitating risk factors allows for the development of strategies targeted at minimizing the occurrence of delirium. Two significant and potentially modifiable factors are particularly important for the anesthesiologist to consider in managing patients at risk for perioperative delirium: pain management and exposure to sedative and/or analgesic medications. Inadequately controlled pain in the postoperative period is theorized to heighten the stress response and alter neurotransmission [43]. Supporting this theory, increasing pain scores have consistently been shown to increase perioperative delirium rates [44]. However, optimal strategies for pain management are still being explored and data regarding opioid administration is often conflicting. Opioids have been directly associated with delirium in some postoperative and ICU settings [45]. Conversely, some studies have shown certain opioids to be neutral or protective from developing delirium when used appropriately to manage pain [20,46,47]. Certain sedative/analgesic medications that
Delirium prevention

Many risk factors for delirium are unable to be modified by perioperative providers, but several preventative strategies have been demonstrated to reduce the incidence of delirium. Anesthesia providers should prioritize the prevention of delirium highly, as there are minimal evidence-based therapeutic interventions once a patient develops delirium.

Anesthetic techniques

Most evidence remains inconclusive regarding the effects of general vs. regional anesthesia and choice of anesthetic agent, anesthesia on developing perioperative delirium. When a total intravenous propofol anesthetic has been compared to desflurane, no difference in delirium rates was found [53,54]. Analogously, no difference in the incidence of postoperative delirium was found when comparing propofol-based anesthesia to sevoflurane [55]. Choice of inhalation agent does not appear to affect postoperative delirium either, for no difference in postoperative delirium was found between sevoflurane and desflurane anesthetics [56,57]. Importantly, while the choice of anesthetic agent does not significantly impact postoperative delirium, the depth of anesthesia does. Utilization of intraoperative processed electroencephalography was associated with fewer episodes of deep anesthesia and, subsequently, with less postoperative delirium [58]. Much research has also been conducted to compare outcomes in primary regional versus general anesthesia. In one Cochrane review, regional anesthesia for patients requiring surgery for hip fracture did not demonstrate any difference in postoperative confusion in comparison to general anesthesia [59]. A large prospective trial of elderly patients presenting for hip surgery also concluded that there was no difference in postoperative delirium with regional anesthesia vs. general anesthesia [60] and this was further supported in a meta-analysis [61]. When using sedation with neuraxial anesthesia for hip surgery in elderly patients, lighter sedation has been associated with a decrease the incidence of postoperative delirium [62]. Of note, these studies focused primarily on the use of neuraxial anesthesia as the primary anesthetic for lower extremity orthopedic procedures and do not address the utility of regional anesthesia for postoperative
analgesia. Current clinical guidelines [63] for the prevention of postoperative delirium in older adults state that pre- or postoperative regional analgesia can be used to improve pain control and prevent delirium, as studies have correlated inadequate pain control to higher rates of delirium. A study that randomized patients to patient controlled analgesia (PCA) alone or PCA plus femoral nerve block after total knee replacement found a lower incidence of postoperative delirium in patients with nerve blockade [64]. Recent growing emphasis on a multimodal approach to perioperative pain control with non-opioid adjuncts has been associated with lower rates of perioperative delirium. Opioid sparing analgesia is a fundamental component of enhanced recovery after surgery (ERAS) pathways, and lower rates of delirium have been reported in colonic surgery patients when following an ERAS protocol [65]. Additionally, patients enrolled in a fast-track pathway for knee and hip arthroplasty receiving gabapentin, acetaminophen, and celecoxib for primary pain management demonstrated a low incidence of delirium [66]. Leung et al. studied the effects of gabapentin alone as a non-opioid adjunct on perioperative delirium. In the small pilot trial of patients undergoing spine surgery, those randomized to gabapentin had a lower rate of postoperative delirium than those randomized to placebo [67]. However, in a subsequent large randomized control trial including patients receiving spine, knee, and hip surgery, there was no significant difference in rates of delirium between the gabapentin and placebo groups [68]. Importantly, gabapentin in this study did not lead to reduced postoperative opioid usage. Thus, regional anesthesia and multi-modal pain regimens to ensure adequate pain control are likely important tools in improving delirium outcomes, in particular when improving pain control while minimizing opioid exposure.

Pharmacologic prophylaxis

Many drugs have been studied as prophylactic therapies for postoperative delirium. A major area of investigation is exploring the effects of prophylactic antipsychotic administration on either the incidence or duration of delirium. Results thus far have been conflicting. In elderly patients undergoing elective orthopedic or gastrointestinal surgery, prophylactic administration of haloperidol for 3 days in the postoperative period resulted in a non-significant increase in the incidence of delirium when compared to placebo, with no difference in severity and duration [69]. However, in a randomized controlled trial of elderly patients presenting for hip surgery and determined to have a baseline intermediate or high risk for delirium, perioperative prophylactic haloperidol administration for up to 6 days (up to 3 days prior to and 3 days after surgery) did not affect the incidence of delirium but did significantly reduce delirium duration and total hospital days when compared to placebo [70]. A larger randomized controlled trial compared low dose haloperidol bolus followed by an infusion to placebo in elderly patients presenting to the ICU after non-cardiac surgery. Postoperative delirium incidence was significantly lower in the intervention group, though in subgroup analysis was only found to be significant in patients with intra-abdominal surgery [71]. Olanzapine prophylaxis administered immediately before and after surgery decreased the incidence of delirium with no effect on duration or severity in elderly patients after elective joint replacement surgery [72]. In ICU patients at high risk for developing delirium, a before-after study of prophylactic haloperidol resulted in a significant decrease in incidence and duration of delirium [73]. In a more recent randomized controlled trial, ICU patients given intravenous haloperidol prophylaxis showed no difference in delirium duration when compared to placebo. Patients receiving haloperidol were found to have less agitated delirium but experienced more oversedation [74]. Despite conflicting evidence, antipsychotics remain an area of interest in the prevention of postoperative delirium and may be useful in certain subgroups of the surgical population.

Dexmedetomidine infusions are increasingly being used for sedation but recently have been studied for prophylaxis for postoperative delirium. One study examined the effects of intraoperative administration of dexmedetomidine in elderly patients requiring joint replacement surgery determined preoperatively to have either normal cognitive function or mild cognitive impairment. After randomization to dexmedetomidine or normal saline infusion during the operation, both normal and cognitively impaired patients were found to have a lower incidence of postoperative delirium after dexmedetomidine infusion [75]. More recently, a study compared dexmedetomidine infusion to placebo during surgery in elderly patients undergoing major noncardiac surgery [76]. The study found no difference in PACU or postoperative delirium, as well as no difference in cognitive performance at 3 or 6 months. A large double-blind, placebo-controlled trial studied prophylactic dexmedetomidine infusions in elderly patients admitted to the ICU after noncardiac surgery [77]. Patients in the intervention group received a sub-sedative, low dose dexmedetomidine infusion from the time of arrival to the ICU until 8:00AM the next morning. Mechanically ventilated patients were sedated with propofol or midazolam prior to initiating the study drug. The intervention group demonstrated a significant decrease in the incidence of postoperative delirium over the first 7 days of their hospitalization [77]. Further, patients receiving the dexmedetomidine infusion reported lower pain scores, and the reduction in delirium remained significant after stratifying patients by mechanical ventilation requirement.

Though cholinergic depletion is associated with delirium development, centrally-acting acetylcholinesterase inhibitors have not demonstrated efficacy in treating or preventing delirium. Perioperative administration of rivastigmine did not impact delirium development [78]. Similarly, donepezil did not show any efficacy in the prevention or treatment of delirium [79,80].
As inflammation is thought to have a role in the development of delirium, medications with anti-inflammatory effects (e.g., ketamine, statins, steroids) have been studied, but with conflicting results. Intraoperative administration of a ketamine bolus at induction of anesthesia in patients having major cardiac and noncardiac surgery did not decrease the incidence, time to onset, duration, or severity of delirium compared to placebo [81]. Patients receiving ketamine had increased hallucination and nightmares and had no difference in pain scores or opioid consumption. In one study of cardiac surgery patients after cardiopulmonary bypass, preoperative statin use was associated with a reduced risk of postoperative delirium [82], while another larger study found no difference in delirium incidence in patients prescribed preoperative statin therapy [83]. A study of elderly patients presenting for elective surgery found that preoperative statin use increased the risk of developing postoperative delirium [84]. In the critically ill population, statin administration in the ICU is associated with decreased rates of delirium, [85,86], though statin use prior to admission did not affect delirium development [85]. However, in a randomized controlled trial of patients with acute lung injury, initiation of rosuvastatin therapy was not associated with a reduction in days with delirium over placebo [87]. Importantly, discontinuing preadmission statin therapy in chronic statin users may promote a rebound pro-inflammatory state and has been associated with increased odds of developing delirium [85].

Cardiac surgery

Multiple studies have focused specifically on strategies for preventing delirium after cardiac surgery. The profound inflammatory response to cardiopulmonary bypass and surgery is thought to uniquely contribute to delirium in this patient population. Ketamine and dexamethasone administration have been studied as a means of reducing the inflammatory response and associated delirium. In one small randomized controlled trial, administration of ketamine at induction of anesthesia was associated with a lower incidence of delirium when compared to placebo [88]. However, this finding was not replicated in the subsequent larger trial that was previously discussed [81]. In a large randomized controlled trial where cardiac surgery patients were randomized to high dose intraoperative dexamethasone or placebo, there was no statistical difference in the incidence or duration of delirium within the first four postoperative days [89]. Another proposed mechanism for delirium prevention targets cholinergic pathways in the brain, as decreased acetylcholine activity and medications with anticholinergic activity appear to increase delirium. A randomized controlled trial testing the effects of prophylactic rivastigmine administered the night before cardiac surgery through the perioperative period found no difference in the incidence of postoperative delirium as compared to placebo [78]. Atypical antipsychotics are often used for treatment of delirium, but one study in cardiac surgery patients compared administration of a single prophylactic dose of sublingual risperidone administered after the patient had regained consciousness in the ICU to placebo. This study found a decreased incidence of postoperative delirium with prophylactic risperidone [90]. Another study focused on patients with subsyndromal delirium, a state associated with some signs of delirium but not enough for a positive assessment. Patients with subsyndromal delirium after cardiac surgery who were given repeated doses of risperidone were less likely to develop delirium than those randomized to placebo [91]. Although prophylactic risperidone appears to be a promising intervention, positive effects demonstrated in larger cohorts are needed before routine administration can be recommended. Finally, postoperative sedation after cardiac surgery with dexmedetomidine has shown improvement in delirium outcomes in comparison to morphine- or propofol-based sedation [92-94].

Intensive care unit management

Many successful delirium prevention techniques have been established in the ICU setting. Adjusting sedation paradigms away from deeper levels of sedation and over-sedating medications to regimens that promote lighter levels of sedation and targeted arousal have positively affected the rates of delirium [43]. One key intervention in this paradigm shift has been transitioning to dexmedetomidine infusion for sedation during mechanical ventilation, which has improved delirium outcomes in randomized controlled trials when compared to lorazepam, midazolam, propofol, and morphine [93-96]. One hallmark of the ICU is frequent monitoring and medication administration resulting in the unintended consequence of severe sleep fragmentation for patients, which has been associated with an increased rate of delirium. Thus, sleep hygiene has become an important prevention strategy for perioperative delirium [43]. Efforts to minimize overnight sleep disruptions and promote normal circadian rhythms have been associated with a lower odds of developing delirium [97]. Interestingly, there was no association between a patient's perception of their daily sleep quality and transition to delirium [98]. Exposure to light is an important signal to maintain inherent circadian rhythms; however, dynamic light application alone has not been shown to effectively reduce delirium in ICU patients [99]. The role of sleep disturbances and circadian rhythm disruption in the development of delirium has led to studies investigating melatonin as an agent for delirium prevention. Results have been inconsistent and inadequate to offer formal recommendations [100]. Melatonin administration in the postoperative period did not alter incidence of delirium when compared to placebo in a double-blind randomized controlled trial of patients with hip fracture [101]. A systematic review of sleep interventions in the ICU found promising effects of melatonin administration on delirium but noted that non-pharmacologic methods should be prioritized to maximize the benefit of pharmacologic intervention. Further, while...
sleep interventions appear to be a promising means by which to improve delirium, current research is limited by varied methodologies and significant bias [102]. Early patient mobilization with physical and occupational therapy has been shown to reduce ICU and in-hospital delirium. Therapy interventions range from passive to active range of motion, exercises in bed, sitting, standing, and walking based on the patient’s physical ability and level of sedation. A trial of early mobilization in the medical ICU randomized hemodynamically stable patients to daily sedation interruptions with physical and occupational therapy or usual care as ordered by the team. A remarkable 2 day reduction in ICU and hospital delirium duration was demonstrated in the intervention group [103]. In a more recent randomized controlled trial of surgical ICU patients, early goal-directed mobilization reduced the incidence of ICU delirium and increased the number of ICU delirium-free days when compared to usual care [104].

**Multicomponent intervention**

Another highly effective technique to reduce rates of delirium is the implementation of multicomponent bundles comprised of evidence-based delirium prevention techniques (Table I). Interventions found in multicomponent prevention protocols include reorientation, continuity of caregivers, decreased use of restraints, removal of catheters, reducing hearing and vision deficits through hearing aids and eye glasses, and geriatrics consultation. Implementation of these protocols has been highly successful as demonstrated by reduced incidence and total number of days of delirium in multiple studies of surgical and medical non-ICU patients [100,105–107]. One such bundle presented by Morandi et al. advocated coordinating daily awakening and spontaneous breathing trials, targeting light sedation while avoiding benzodiazepine use, monitoring daily for delirium and providing appropriate intervention if identified, and early patient mobility. Application of this evidence-based bundle, known as the ABCDE bundle, has been associated with improved delirium outcomes [108,109]. In a before-after trial, implementation of the ABCDE bundle resulted in significantly less delirium after implementation [109]. Since the initial presentation, the ABCDE bundle has been expanded to include family engagement, making it the ABCDEF bundle. The ABCDEF bundle was examined in a large-scale implementation study across seven community hospitals, where increasing compliance with the bundle was found to be significantly associated with improved survival and an increased number of days alive without delirium or coma [110].

**Delirium treatment**

Currently, there are no evidence-based guidelines regarding specific pharmacological agents for the treatment of delirium, as large clinical trial data are lacking. Pharmacologic therapy should be reserved for patients who are not responding to non-pharmacologic prevention strategies and are a risk to self or others. The current first-choice pharmacologic agents are antipsychotic medications including haloperidol, olanzapine, and quetiapine. It is critical to note that neither antipsychotics nor dexmedetomidine are FDA-approved for the treatment of delirium. One pilot study of ICU delirium randomized patients to haloperidol, ziprasidone, or placebo. No difference in delirium-free days was found between the three groups [111]. Another study comparing haloperidol to olanzapine for delirium treatment found no difference in length of delirium [112]. In a small trial of patients receiving haloperidol for delirium treatment, subjects were randomized to quetiapine or placebo. Quetiapine

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<td>Minimize postoperative sedation depth</td>
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was increased if patients continued to require haloperidol, and those in the treatment arm were found to have a shorter duration of the first episode of delirium [113]. Much debate remains about the overall efficacy of antipsychotics and choice of typical versus atypical antipsychotics. Larger clinical trials are needed to clarify outcomes of specific agents. A study of rivastigmine as an adjunct to haloperidol in critically ill patients was terminated early, as the rivastigmine group demonstrated a higher mortality [114].

In addition to its increasing use for sedation and delirium prophylaxis, dexmedetomidine is also being used as a primary therapy for delirium. A trial studied the utility of dexmedetomidine in mechanically ventilated patients whose critical illness had otherwise resolved but were unable to be weaned from mechanical ventilation because they were experiencing hyperactive delirium [115]. Patients randomized to receive dexmedetomidine had a significant increase in ventilator-free hours, shorter time to extubation, and faster resolution of their delirium symptoms. In a non-randomized trial of non-intubated medical and surgical critically ill patients, dexmedetomidine was studied as a rescue therapy for hyperactive delirium [116]. Patients were categorized as haloperidol responders or non-responders. Those whose agitated delirium responded to haloperidol were initiated on a haloperidol infusion. Patients whose agitated delirium did not improve after haloperidol were initiated on a dexmedetomidine infusion. Patients receiving dexmedetomidine infusion had a higher percentage of time at target sedation, experienced less over-sedation, and demonstrated shorter time to ICU discharge. There was no difference in hemodynamic side effects between the two groups. Further, the study demonstrated an overall failure rate of haloperidol of 43%, highlighting the limited efficacy of antipsychotic agents as a therapeutic intervention for delirium [116]. Delirium prevention with non-pharmacologic interventions remains a critical strategy as treatment options for delirium are limited and lack evidence to support the efficacy of a single pharmacologic approach. Additionally, the primary agents used to prevent or treat delirium affect the sensorium and may cause significant side effects. Side effects of antipsychotic agents include sedation, respiratory depression, prolonged QT intervals, and neuroleptic malignant syndrome; patients must be closely monitored while receiving this therapy. Dexmedetomidine is commonly administered by infusion, which in many institutions, mandates ICU admission. Dexmedetomidine has been associated with profound bradycardia. Additional studies are needed to examine the effectiveness of dexmedetomidine as a first-line therapy for the treatment of delirium. Alternative alpha₂-agonists that may be administered orally or by intermittent intravenous bolus, including guanfacine and clonidine, have not yet been rigorously studied with regard to delirium, but may also provide another option for the prevention and treatment of delirium.

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