

EVALUATING THE EFFECTS OF A NURSE-LED INTERVENTION
FOR DELIRIUM AND PAIN MANAGEMENT AMONG OLDER ADULTS
IN THE SURGICAL INTENSIVE CARE UNIT

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Kara J. Pavone

DEDICATION

*It is the hands that turn nursing tasks and skills into acts of nursing and human caring...
guided not only by their new knowledge and skills but also by their spirits and their
hearts.*

May your hands provide fervent and skillful nursing care.

May your spirit of compassion and gentleness guide your hands.

May your hands bring comfort and promote healing to all who come into your care.

*Go in peace with the knowledge of the human and spiritual caring that your hands will
convey.*

Excerpt from "Dedication of Hands to Nursing: A Ceremony of Caring"
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ABSTRACT

EVALUATING THE EFFECTS OF A NURSE-LED INTERVENTION FOR DELIRIUM AND PAIN MANAGEMENT AMONG OLDER ADULTS IN THE SURGICAL INTENSIVE CARE UNIT

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Delirium, a prevalent disorder in older adults, is an acute brain dysfunction characterized by disturbances in attention, awareness and cognition not explained by a pre-existing neurocognitive disorder. The *ICU Liberation Executing the ABCDEF Bundle Daily* (iLEAD) is a nurse-driven intervention aimed at reducing the consequences of delirium in the intensive care unit (ICU). It was posited that when nurses routinely assess non-modifiable risk factors and manage modifiable risk factors for delirium, including those related to pain and pain management, patient outcomes will improve. This dissertation research: 1) systematically reviewed the use of the pharmacotherapy dexmedetomidine to treat or prevent delirium (**Chapter 2**); 2) compared patient outcomes in older adults with delirium in the surgical ICU (SICU) before and after implementation of the iLEAD intervention (**Chapter 3**); and 3) assessed the relationship among pain, its treatment with opioids, and the onset of delirium in the post-implementation cohort (**Chapter 4**). The pre- and post-iLEAD intervention cohorts consisted of 93 patients who developed delirium while admitted to the SICU at the Hospital of the University of Pennsylvania. The analysis evaluated the effects of implementing the iLEAD protocol on the number of days of delirium, SICU and hospital length of stay, 30-day readmission and 30-day mortality. In addition, this research examined the role of pain, pain management with

opioids, and delirium onset. Results from this study have meaningfully contributed to better informed care of older adult patients with delirium in critical care environments.

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Chapter 1

Introduction

Delirium is the most common complication affecting hospitalized older adults (age ≥ 65 years) admitted to the intensive care unit (ICU),¹ totaling more than 2.6 million older adults in the United States (U.S.) each year.² Delirium is defined as an acute change in cognition and attention not explained by a pre-existing condition or established or evolving dementia.³ Spending the majority of their time at the bedside, nurses are at the forefront of delivering care in the ICU. As the U.S. population continues to age, nurses will be continually challenged with identifying, managing and treating delirium. Not surprisingly, the economic burden of delirium is significant with total costs attributable to the condition estimated at \$164 billion (2011 U.S. dollars) per year.⁴ Moreover, delirium contributes to distress in both patients and caregivers, and is associated with long-term cognitive deficits,⁵⁻¹⁰ a greater likelihood for needing residential care post-hospitalization,⁵⁻¹⁰ and increased mortality.¹¹⁻¹³ **Delirium can be a life-threatening condition, yet with early identification and management it may be preventable.**¹

Nurses are uniquely prepared to drive solutions to address this clinically significant problem by recognizing risk factors and initiating evidence-based nursing interventions.

To date, no single cause or mechanism for delirium has been identified. Postulated mechanisms contributing to delirium include; inflammation, neurotransmitter disruptions, physiological stressors, metabolic derangements and genetic factors.² Commonly recognized risk factors for delirium in surgical intensive care unit (SICU) patients are pain, and its treatment with opioids.^{2,14,15} Pain is defined as an unpleasant physical and/or emotional experience related to potential or actual tissue damage,¹⁶ and the physiological stress associated with unrelieved pain is believed to contribute to delirium.^{15,17} The cognitive effects of the primary class of medications used to manage

acute pain, opioids, have also been implicated in the development of delirium.^{14,15,17} A systematic review of 14 studies found that that risk of developing delirium was 2.5 times greater in patients receiving opioids.¹⁸ Studying the relative roles of pain and pain management on the onset of delirium is vital to improve patient outcomes.

The 2013 Society for Critical Care Medicine Clinical Practice Guidelines for Management of Pain, Agitation, and Delirium (PAD)¹⁹ recommends routine monitoring of pain, sedation and delirium for all patients in the ICU. To encourage dissemination of these guidelines, the Society for Critical Care Medicine created *ICU Liberation* which utilizes the so-called “ABCDEF bundle” to help guide care (**Figure 1.1**). The individual and collective elements of the ABCDEF bundle aim to ameliorate delirium, improve pain management, and reduce levels of deep sedation, leading to improved outcomes for adult patients in the ICU. Utilizing the principles of health systems science, which encompass improving quality, outcomes, and costs of health care delivery for patients and populations within systems of medical care,²⁰ in 2018 the Hospital of the University of Pennsylvania (HUP) implemented the *ICU Liberation Executing the ABCDEF Bundle Daily* (iLEAD) protocol (see **APPENDIX A**). The goal of iLEAD is to empower nurses to improve delirium-related outcomes by employing evidence-based nursing interventions.

The **overall objectives** of this research were to: 1) determine if implementation of the iLEAD intervention resulted in fewer days of delirium, decreased length of stay in the SICU and hospital, and improved 30-day patient outcomes among patients in the SICU; and 2) evaluate the relationships among pain severity, opioid analgesic administration and the onset of delirium. The **central hypothesis** of this dissertation research is that implementation of the nurse-led iLEAD intervention will reduce the consequences of delirium in hospitalized older adults.

Specifically, a retrospective pre- and post-implementation cohort study was performed to assess the impact of the iLEAD intervention on delirium and patient outcomes in critically ill patients in the SICU aged 65 years and older. A convenience sample of patients were examined from March to August 2017 for the pre-implementation cohort and from March to August 2018 for the post-implementation cohort; the intervention was implemented in January 2018. Primary outcome measures were days of delirium, SICU length of stay, hospital length of stay, 30-day readmission rates and 30-day mortality. Secondly, in the post-implementation cohort, a cross-sectional study examined the relationships among pain severity, pain management with opioids, and the onset of delirium. The specific aims were to:

Specific Aim 1: Complete an integrative review of publications in peer-reviewed journals evaluating the use of a novel pharmacotherapy, dexmedetomidine, for the prevention and/or treatment of delirium. This review served as the foundation for the dissertation research aims and hypotheses by providing an increased understanding of the most current treatment strategies, delirium research methods, and the issues associated with identifying and managing delirium (**Chapter 2**).

Specific Aim 2: Compare outcomes (days of delirium, SICU length of stay, hospital length of stay, 30-day readmission and 30-day mortality rates) between older adults in the pre- and post-iLEAD intervention cohorts (**Chapter 3**).

Hypothesis 1: Patients' delirium, pain and healthcare utilization outcomes (SICU length of stay, hospital length of stay, 30-day readmission and 30-day mortality rates) will improve when nurses routinely assess and manage modifiable risk factors for delirium (*i.e.*, implementing the iLEAD intervention).

Specific Aim 3: Evaluate the relationships among pain severity, opioid analgesic administration, and the onset of delirium in older adults in the SICU in the post-intervention cohort (**Chapter 4**).

Hypothesis 1: Pain severity scores will be positively correlated with the onset of delirium.

Hypothesis 2: Exposure to opioid analgesics will be positively correlated with the onset of delirium.

With respect to **outcomes**, this work provides findings to 1) determine if early identification and prevention strategies associated with the iLEAD intervention result in fewer days of delirium and better delirium-related clinical outcomes; and 2) examine the relative roles of pain and opioid pain management on the onset of delirium.

Background

Delirium is an acute change in awareness and attention developed over a short course, with likely disruption to cognitive processing, that is not better described by a pre-existing, established or evolving condition.³ Patients with delirium can experience altered perceptions of reality that are intense, and induce feelings of panic, uncertainty or distress.²¹ They may have trouble communicating their distress and feel misunderstood by family members and health care providers.

The clinical presentation of delirium is classified into three subtypes; hyperactive, hypoactive, or mixed.¹⁰ With hyperactive delirium, patients may be hyperalert and exhibit restlessness and agitation. In contrast, those with hypoactive delirium generally present as lethargic or sedated and respond slowly to questions or show little purposeful movement. Patients with mixed delirium demonstrate the features of both hyper- and hypoactive delirium. Notably, older adults are more likely to express hypoactive delirium,

and too often, these patients go unnoticed or are mistakenly identified as having dementia or depression.¹

A 2003 study by Poole and Mott reported that when caring for patients with hyperactive delirium, nurses' often felt frustrated and irritated, admitting that these patients were difficult to work with and took up too much of their time, citing "nothing else gets done" (p. 309).²² With respect to hypoactive delirium, recent literature found that nurses failed to detect delirium in up to three out of four cases.^{23,24} Further, even when identified, interventions aimed at its management were not consistently implemented. Investigators showed that some clinicians view delirium as an inevitable part of a hospital stay for older adult patients, while others see it as a transient condition from which patients can recover without long-term consequences and clinical implications.⁴ Failure to recognize and manage delirium, stemming from its lack of pathognomonic features, can be a life-threatening issue for older adult patients with delirium.²⁵ **Taken together, these concerns represent a critical gap in clinical practice that results in nurses and other healthcare professionals poorly identifying patients with delirium and initiating new approaches to minimize its consequences.**

Delirium in Older Adults in the Intensive Care Unit

Delirium is believed to occur in approximately 50% of all older hospitalized adults¹ and 70-87% of older adults admitted to the ICU following surgery.¹⁰ Following a systemic challenge, such as surgery, older adults are increasingly vulnerable to developing delirium secondary to hypothesized inflammatory processes, neurotransmitter disruptions, physiological stressors, and metabolic derangements.^{2,5,26-28} In addition, aging itself has been described as a risk factor for developing delirium.^{5,26-28} A substantial proportion of patients who survive delirium are likely to experience long-term

cognitive impairment similar to mild Alzheimer's disease^{5-10,29} for up to one year post-discharge.¹⁹ A recent study placed the odds of requiring of institutional care following hospitalization at rates 2.4 times higher in patients who suffer from delirium than those who did not.³⁰

In addition to being a serious health threat, delirium is a costly condition.^{5,10,24,29,31} An investigation of one-year health care costs associated with delirium in older adult patients showed that patients with delirium are 2.5 times more costly than patients without delirium.³² Supplementary costs per hospitalization attributable to delirium range from \$16,303 to \$64,421 per patient.⁴ While causal relationships have not been established specifically in SICU patients, there is evidence linking increased length of stay and higher mortality rates in older adult patients with delirium in general ICU settings.¹¹

Effects of Delirium on Patient and Healthcare Outcomes

The impact of delirium on patients and health care systems is substantial. A report by the American Association of Retired Persons identifies delirium as one of six leading causes of injuries associated with hospitalization in patients over 65 years of age.³³ Key patient and health care outcomes associated with delirium include days of delirium, SICU and hospital length of stay, 30-day readmissions and 30-day mortality.

Days of Delirium and Length of Stay. Delirium is associated with longer ICU and overall hospital lengths of stays.³⁴ Of patients who develop delirium in the medical ICU, the typical length of stay ranges from four to five days, with an average of two to three days of delirium.^{11,34,35} Ely and colleagues showed that the number of days spent in a delirious state predicted length of stay.³⁴ Among a cohort of non-ventilated critically ill patients, delirium was associated with a one-day longer ICU stay and a two-day longer overall hospital stay.³⁶ A recent systematic review estimated that the average length of stay in

patients with delirium in the ICU was 1 day and 9 hours longer than patients without delirium.³⁷ Compared to patients who never develop delirium, patients undergoing a delirious episode may spend a median of 10 days longer in the hospital. At any given time over the course of their hospitalization, patients with delirium had an adjusted risk of staying in the hospital that was two times higher than those who never developed delirium.¹¹ Reducing the number of days with delirium, and ICU and hospital stays would lessen the health and economic burdens to patients and healthcare systems.

30-day Readmissions. Medicare and Medicaid reimbursements are reduced to hospitals with excessive 30-day readmissions,³⁸ and some of the delirium-related costs cited above are attributed to readmissions of patients with delirium. In addition to costs, hospital readmissions are associated with unfavorable patient outcomes.³⁹ Hospitals are now connecting with entities across the healthcare industry to implement best practices in reducing readmission rates, including the prevention, early diagnosis and treatment of delirium.³⁹ In a study of older adult patients undergoing cardiac surgery, of those readmitted within 30 days for any reason, 80% had delirium during their initial inpatient stay.⁴⁰ However, little evidence is available describing the impact of days of delirium on hospital readmissions, a key driver of healthcare costs.^{4,32,39,40}

30-day Mortality. Delirium has also been identified as an independent marker for increased mortality in older medical inpatients during the 12 months following hospitalization.⁴¹ ICU delirium is associated with a 2- to 4-fold increased risk of overall mortality¹ with the duration of ICU delirium linked with one-year all-cause mortality.³⁵ Investigators demonstrated that 50% of patients who were delirious during their ICU stay died within one year post-hospitalization.³⁵ A hallmark study by Ely and colleagues documented that in patients receiving mechanical ventilation, ICU delirium was an independent predictor of mortality, such that during a six-month follow-up, 34% of the

patients in the delirium group died versus 15% of the patients without delirium.¹¹ This corresponded with a greater than three times higher risk of dying within 6-months of hospital discharge.¹¹

Nurse-Led Interventions for Delirium

Devising innovative strategies to assess, prevent and manage delirium is well within the scope of nursing practice. Nurses are at the forefront of care and many evidence-based delirium interventions do not require a physician's order.^{42,43} Nurse-led models of care have been used in a variety of settings, including promoting optimal aging of older adults,⁴⁴ managing diabetes⁴⁵ and cardiovascular risk,⁴⁵ improving medication adherence,⁴⁶ expanding palliative care,⁴⁷ and reducing pre-surgical anxiety.⁴⁸ This study capitalized on the clinical acumen of nurses who routinely care for older adults in the SICU by expanding previous nurse-driven protocols^{49,50} and routine clinical assessments to include interventions to help prevent and/or manage delirium.

Current strategies aimed at reducing the severity of delirium involve the recognition of non-modifiable risk factors and amelioration of modifiable risk factors (**Figure 1.2**). Many of these risk factors are routinely evaluated as part of a critical care nursing assessment. Non-modifiable risk factors for delirium outlined in the iLEAD protocol include: advancing age (≥ 65 years); history of dementia or cognitive impairment; prior history of delirium, stroke, neurological disease, falls or gait disorder; visual or hearing impairments and two or more chronic health conditions.⁵¹ Modifiable risk factors include: pain; sensory impairment (hearing or vision); immobilization (catheters or restraints); medications that have the potential for psychoactive effects on the central nervous system (sedatives, hypnotics, opioids, anticholinergic drugs, corticosteroids, polypharmacy); surgery; environment (for example, admission to an ICU); emotional distress; and sustained sleep deprivation.⁵¹

Reliance on nurse-led interventions is especially critical in view of the lack of effective pharmacologic interventions to treat delirium. To date, no single pharmacological intervention has been demonstrated to be effective in its treatment.⁵ A number of pharmacological strategies to both prevent and treat delirium have been, and continue to be actively tested, including antipsychotic medications,⁵² acetylcholinesterase inhibitors,⁵³ melatonin,⁵⁴ benzodiazepines,^{55,56} intravenous acetaminophen⁵⁷ and gabapentin.⁵³ In addition, numerous studies suggest that use of the alpha-2 agonist, dexmedetomidine, may reduce the incidence or duration of delirium (**Chapter 2**) by addressing its underlying cause, ameliorating pain or preserving sleep architecture.^{5,26,28,51,58,59} However, thus far, no single pharmacologic strategy has amassed enough evidence to support its role in delirium prevention or treatment. Hence, it is critical that nurses have a firm understanding of the risk factors for delirium and the non-pharmacological interventions available to help reduce the incidence and duration of delirium. Understanding these risk factors and treatment strategies will aid nurses in providing optimal care and advocating for patients' needs.

The development of the ABCDEF bundle (**A**wake and pain free; spontaneous **B**reathing trials; **C**onsideration of Analgesia and Sedation; **D**elirium; **E**xercise; **F**amily engagement) has been well-described in the literature and published in numerous peer-reviewed high-impact journals.⁶⁰⁻⁶³ While many studies have reviewed the effectiveness of the individual elements of the ABCDEF bundle, few have evaluated the effect of implementing the bundle as a whole.⁶⁴⁻⁶⁸ In January 2019, the first large scale evaluation of the ABCDEF bundle was published. This multicenter, prospective cohort study led by the Society of Critical Care Medicine *ICU Liberation Collaborative* included over 15,000 adult patients (18+ years of age) from 68 ICUs (including mixed medical/surgical, medical, surgical/trauma, neurological, cardiac/surgical and surgical). The primary

objective of this analysis was to evaluate the relationship between ABCDEF bundle performance on patient and healthcare systems outcomes.⁶⁸ Complete performance of the ABCDEF bundle (*i.e.*, a patient day in which every eligible element of the bundle was performed) was associated with a lower likelihood of next-day mechanical ventilation, delirium, ICU readmission and 7-day mortality. The impressive results of this large-scale trial show that implementation of the ABCDEF bundle can improve patient and health system-level outcomes.

Similarly, the iLEAD intervention evaluated in this study is based on the implementation of the ABCDEF bundle, with its goal being to enable nurses to monitor sedation, manage pain more effectively, and ameliorate delirium utilizing independent nursing interventions (**APPENDIX A**). The iLEAD intervention includes three key standardized assessments; the Richmond Agitation-Sedation Scale (RASS) to measure level of sedation, the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) to screen for delirium, and the numeric rating scale to measure pain severity. Based on their assessment findings, nurses are guided to manage delirium, analgesia and sedation while also utilizing the interventions of early mobility and family engagement interventions.

Specifically, upon admission to the SICU, a patient's level of sedation was assessed with the RASS tool, which is the first step in completing the CAM-ICU to screen for the presence of delirium. RASS evaluates a patient's level of sedation on a -5 (unarousable) to +4 (combative) scale, with 0 corresponding to calm and alert. Patients with a RASS of -4 or -5 are unable to be assessed by the CAM-ICU. Patients with a positive CAM-ICU score are evaluated for new infections, or cardiac or neurological events that may explain the change in their mental status. Inpatient and home medications are also reviewed to evaluate high-risk medications, such as opioids and benzodiazepines.

Nurses are then encouraged to employ at least two independent non-pharmacological interventions from a menu of interventions (**Table 1.1**) to help manage the delirium. Additional collaboration with the interdisciplinary team is then required to determine the potential cause of delirium and appropriate treatment approaches. Delirium is continually reassessed using the CAM-ICU every 12 hours to monitor responses to the interventions.

A limited number of studies have examined the effectiveness of these independent nursing interventions, although the use of such supportive measures has nevertheless become standard practice on the basis on clinical experience and lack of adverse effects.¹⁰ A systematic review of 39 trials in non-ICU patients concluded that multicomponent interventions (interventions included an educational component, individualized care, reorientation, and early mobilization) concurrently targeting several risk factors are effective in prevention of delirium (reduction in incident of delirium by approximately one-third).⁶⁹ The review cites moderately strong evidence to support the use of these interventions in delirium prevention, but provide less robust evidence to support decreasing severity or duration of delirium.⁶⁹ Reducing known risk factors and precipitants of delirium may decrease the factors contributing to, and possibly prolonging, an episode of delirium.⁷⁰ Ultimately, more research is needed to understand the benefits of individual nursing interventions on reducing the number of days of a delirious episode and other delirium-related patient outcomes.

Pain

Pain is a potent and common stressor present in approximately 80% of critically ill patients admitted in the SICU.⁷¹ Related to the surgical incision, and/or tissue manipulation and removal during surgical procedure, moderate to severe pain is present in up to three out of four postsurgical patients.⁷² In addition, the majority of patients

regard some degree of pain following surgery as “necessary” (p. 1093).⁷² Due to its subjective nature, pain can only be reported by the individual who is experiencing it.⁷³ Verbal rating scales, numerical rating scales and visual analogue scales provide simple, effective, and minimally invasive measures of pain intensity; however, many patients admitted to the ICU are unable to report their pain because of mechanical ventilation, neuromuscular blockade, or deep sedation.⁷⁴ When pain is not routinely assessed and managed, patients may be inappropriately be given sedative medications rather than analgesic medications.⁷⁵ Payen and colleagues⁷⁶ found that when routinely assessed for pain, mechanically ventilated patients were more likely to receive analgesic medications (non-opioids or opioids) and less likely to receive sedatives (in particular, deliriogenic benzodiazepines) than patients who never had a pain assessment.⁷⁶

Older adults may be stoic or reticent about reporting pain for fear of complaining.⁷⁷ A review by Schofield estimates that 50% to 60% of patients aged over 75 years suffer pain or discomfort, yet are consistently less likely than younger patients to receive appropriate pain management.⁷⁷ In addition, both the peripheral and central nociceptive nervous systems are affected by the aging process, including reductions in the concentration of serotonin receptors and GABA synthesis, which are important modulators of pain, resulting in slowing of endogenous inhibitory pain process and increased sensitivity to pain in older adults.⁷⁸ Finally, older adults are more likely to have age-related changes in pharmacokinetics and pharmacodynamics related to analgesic medication administration. Taken together, these changes in pain processing, physiologic pain response and medication metabolism in older adults have important implications in the management of their pain.

In critical care patients, suboptimal pain management has been associated with an array of negative consequences, including increased cost of care, decreased quality of

life, prolonged opioid use during and after hospitalization, and increased morbidity.^{77,79-81}

Uncontrolled pain is a stressor and can have harmful effects on several different body systems including, cardiovascular, respiratory, musculoskeletal and, most notably, cognitive function.¹⁷ Furthermore, unrelieved moderate to severe pain may lead to persistent or chronic pain.⁷⁹ The prevalence of persistent pain following major surgeries remains between 10% and 30%.⁸² More aggressive analgesic measures are needed to reduce the incidence and intensity of acute pain, and to prevent the evolution from acute to chronic pain.⁷⁹ In addition to chronic post-surgical pain, the consequences of insufficient pain management also include sleep deprivation, fatigue, anxiety, and delirium.⁸²

Delirium and Pain

In the literature, untreated pain is frequently identified as a precipitating factor for the development of delirium.^{19,80,81} In fact, in the iLEAD intervention, pain is identified as a primary modifiable risk factor for delirium. However, there is surprisingly limited evidence to support a causal relationship between pain and the development of delirium. Because the relationship between pain and delirium has not been well-elucidated, there is no evidence-based strategy to both pharmacologically manage pain and prevent delirium in critically ill patients. Few studies have examined the SICU population and how the presence of pain contributes to the occurrence of delirium,⁸¹ and conflicting data exist regarding this relationship. Vaurio and colleagues in their investigation with older adults scheduled for non-cardiac surgery concluded that pain was independently associated with the development of delirium.⁸¹ In that any patient reports of pain are typically and aggressively addressed with opioid administration in the inpatient setting, newer evidence has not sufficiently drawn definitive conclusions about the relationship of pain and delirium.

Delirium and Opioid Analgesia

To date, pain management in the ICU has relied almost exclusively on opioid administration.^{14,15} The mu-opioid receptors are involved in the regulation of sensory and affective components of the pain experience. The most common opioids analgesics used include; morphine, oxycodone, hydromorphone, hydrocodone, and fentanyl. For acute pain, opioids are generally administered by intravenous and oral routes. Literature suggests that pain management with opioids may be a precipitating factor for the development of delirium.¹⁵ The method or mode of administration (oral, patient-controlled analgesia, neuraxial, intravenous) of opioid administration appears to play a more important role in the development of delirium than absolute dose, likely due to onset of action.¹⁵ For example, the use of oral opioid analgesic as the primary means of pain control is less likely to induce delirium compared to intravenous patient-controlled analgesia.⁸¹ As previously noted, when prescribing pain management for older adults, it is important to consider age-related changes in pharmacokinetics and pharmacodynamics of opioid medications. Due to slowed drug metabolism, older adults are more susceptible to the central nervous system depressant effects of these medications.

Opioid use has been implicated in development of delirium in patients admitted to the ICU⁸³ and across various hospital settings.¹⁸ These medications have psychoactive and depressant effects on cortical function, including cognitive performance, which may contribute to the decline in cognitive function hallmark of delirium.^{14,84} Opioids inhibit calcium channel opening by binding to regulatory G-protein-coupled mu-opioid receptors, and thereby block presynaptic terminal depolarization in cholinergic pathways.⁸⁵ This deficit in cholinergic activity is thought to contribute to delirium.¹⁴ In a study of 216 patients in a medical/surgical ICU, 40 patients developed delirium (19%),

and use of opioid analgesics (morphine and epidural) was strongly correlated to the development of delirium.⁸³ A systematic review of 9 studies reported opioid use in both medical, surgical and medical/surgical ICU settings, and concluded that opioids are a risk factor for the development of delirium.¹⁸ However, these studies have limited generalizability and were noted to be of low to moderate quality evidence.^{18,83} Therefore, the role of opioid analgesics in the development and duration of delirium requires additional clarification.

Summary

Delirium is a significant and costly problem for older adults in the ICU. It is commonly under-recognized and undertreated, and the consequences are not only evident in length of SICU and hospital stay, but in the more worrisome outcomes of 30-day readmissions and mortality. Empirical evidence for independent nurse-led interventions to mitigate the development and duration of delirium is accumulating, and this evaluation of the iLEAD intervention at HUP contributes to this body of knowledge. Interestingly, both pain and opioid administration are identified as independent risk factors for the development of delirium,¹⁵ suggesting that by attempting to ameliorate one risk factor (pain), nurses may in fact be contributing to another (delirium). Examination of the relative roles of pain and opioid administration on the onset of delirium experienced by this population provides the foundation for evidence-based guidelines on pain management approaches which minimize negative outcomes related to delirium.

Significance

The dissertation research is significant in two principal ways. First, this work focuses on **a uniquely nurse-led intervention**. While iLEAD is described as an interdisciplinary intervention, nurses are the key stakeholders driving this intervention forward. Their clinical expertise and front-line responsibilities make nurses uniquely qualified to

champion this effort and facilitate the prevention and management of delirium with the interdisciplinary care team. Although nurse-led interventions have been demonstrated to improve patient outcomes in multiple health problems (diabetes,⁴⁵ cardiovascular disease,⁴⁵ medication adherence,⁴⁶ palliative care,⁴⁷ pre-surgical anxiety⁴⁴), this is one of the first evaluations to determine the impact of iLEAD bundled independent nursing interventions to treat the significant and costly problem of ICU delirium.

Second, pain is commonly cited as a primary risk factor for the development of delirium.⁸⁶ However, close examination of the **literature reveals that there is little empirical evidence to support this oft-cited causal relationship**. Further, the role of pain management with opioids in the development of delirium requires explication. If, in fact, untreated pain results in delirium, analgesia should improve delirium outcomes, however the depressant cognitive effects of the analgesics most commonly used to treat pain, opioids, may worsen delirium. This raises the question as to whether opioids administered to counter pain-induced delirium contribute to its development. This study is among the few to characterize the relative roles of pain and opioid administration on the onset of delirium.

In summary, the overall contribution of this study is to describe the effectiveness of the nurse-led iLEAD intervention to reduce the burden of delirium and its associated adverse outcomes and to examine two modifiable risk factors associated with delirium (*i.e.* pain, opioid administration). The variables examined in this study are described in **APPENDIX B**. This dissertation research: 1) evaluates a nurse-led identification, treatment and management strategy for delirium; 2) expands knowledge of delirium-related patient outcomes (days of delirium, length of stay, readmissions, mortality); and 3) facilitates continued investigation into the link between pain, opioid pain management and the onset of delirium. Overall, this dissertation research has important implications in

moving forward nurse-driven approaches to the clinical care of aging adults in critical care environments at risk for experiencing delirium.

Chapter Aims and Rationale

The major goals of this dissertation research were to: 1) conduct an integrative review of the literature to examine the use of dexmedetomidine to prevent and/or treat delirium (**Chapter 2**); 2) determine if identification and prevention strategies associated with the nurse-led iLEAD intervention result in fewer days of delirium and better delirium-related clinical outcomes (**Chapter 3**); and 3) explicate the relative roles of pain and opioid pain management on the onset of delirium (**Chapter 4**).

Chapter 2

Aim: To date, no single pharmacological intervention has been shown to be effective in treating or preventing delirium. Studies suggest the novel alpha-2 agonist, dexmedetomidine, may reduce or prevent delirium due to its unique actions on sleep preservation and pain control. An integrative review of the literature to determine if use of dexmedetomidine was associated with a lower incidence and/or duration of delirium as compared to other non-dexmedetomidine pharmacologic strategies was conducted. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines directed this integrative review. A table of evidence reviews 16 high-quality studies using dexmedetomidine for the prevention or treatment of delirium in three patient populations: mechanically ventilated, those undergoing cardiac surgery and those undergoing non-cardiac surgery. This work informed the aims addressed in the data-based papers to follow, and presented a unique integrative review evaluating the effects of dexmedetomidine for the prevention or treatment of delirium. This work has been published in *Heart & Lung: The Journal of Acute and Critical Care* (2018 impact factor 1.73).

Rationale: The results of this review found that postoperative administration of dexmedetomidine may reduce delirium in patients, particularly following cardiac surgery. Further research is needed to determine the benefits of dexmedetomidine in patients on mechanical ventilation and optimal timing and duration of administration. The themes identified in this review informed the basis for this dissertation research and future lines of inquiry. Specifically, the limitations of pharmacotherapy in treating delirium became evident, and sorely missing from the studies reviewed was any discussion of the use or effect of nurse-led interventions on reported outcomes. Further, the suggestion that dexmedetomidine efficacy could be attributed to its analgesic effects, and therefore opioid-sparing approaches, provided the foundation for research questions about the relationships between pain, opioid pain management and delirium.

Chapter 3

Aim: Although protocolized nurse-led interventions have been evaluated for several health conditions or diseases, the success of these in the management of SICU delirium in older adult patients has not been empirically examined. Outcomes in older adult patients in the SICU before and after the implementation of the iLEAD intervention, a nurse-driven delirium assessment, treatment and management protocol, were compared. **Chapter 3** has been formatted for possible publication in *The Joint Commission Journal on Quality and Patient Safety* (2018 acceptance rate 26.4%) describing delirium outcomes before and after implementation of iLEAD in the SICU at HUP.

Rationale: By 2060, it is estimated that older adults will comprise nearly 25% of the population. Consequently, nurses in acute care settings will be challenged to care for higher numbers of older adults experiencing delirium in future decades. Literature that specifically addresses the effectiveness of delirium management interventions for older

adults admitted to the SICU is limited, and primarily focuses on comparing various pharmacologic approaches. This data-based paper compares the number of days of delirium and patient-centered delirium outcomes following implementation of the nurse-led iLEAD intervention. This paper highlights the contributions of nurses in integrating iLEAD into routine clinical care and explicates the impact of independent nurse-initiated interventions on patient outcomes.

Chapter 4

Aim: Literature suggests that pain and opioid administration may each independently be precipitating factors in the development of delirium. However, there is diverse and limited evidence to support these relationships, particularly among older adults in the SICU. As such, the relative roles of pain, opioid analgesic administration and the onset of delirium were examined. The findings for this cross-sectional analysis are reported in **Chapter 4** and formatted for publication in the *American Journal of Critical Care* (2018 impact factor 2.055) exploring the relative roles of acute pain and opioid administration on the onset of delirium experienced by patients in the SICU at HUP.

Rationale: Limited evidence suggests that pain and use of opioids for pain management are precipitating factors in the development of delirium. However, empirical evidence to support the association between pain and delirium is sparse. In addition, literature that specifically addresses the effects of pain and pain management on delirium for older adults admitted specifically to the SICU is limited. This cross-sectional analysis evaluated the relationships among pain, its management with opioids, and the onset of delirium. This data-based paper is among the first to specifically evaluate the relationships among the onset of delirium, pain and pain management following implementation of the iLEAD intervention.

Figures and Tables

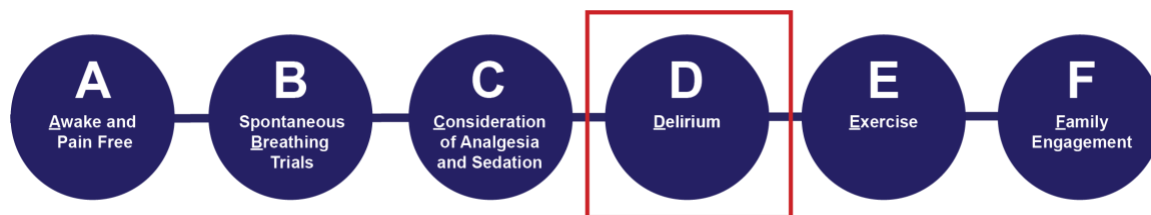


Figure 1.1 ABCDEF Bundle

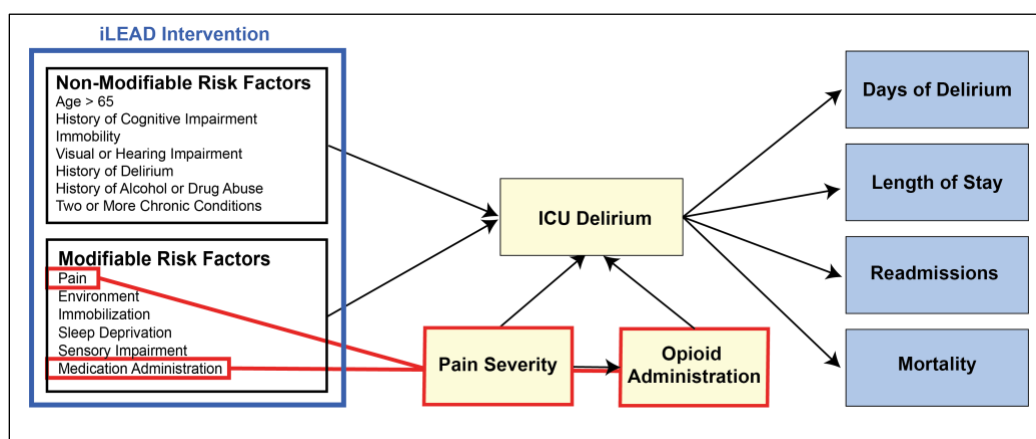


Figure 1.2 Conceptual Model of the iLEAD Intervention, Delirium and its Consequences

Table 1.1 Independent Non-Pharmacologic Nursing Interventions for Management of Delirium

Manage pain (repositioning, massage, etc.)	Provide music therapy
Use communications tools	Adjust room temperature
Ensure adequate nutrition, assist with feeding	Manage bowel and bladder
Constantly provide reorientation	Provide cognitively stimulating activities
Expose to sunlight	Manage thirst sensation
Provide physical activity	Manage stimuli from tubes, lines and drains
Encourage family engagement	Avoid physical restraints
Have eye glasses or hearing aids available at the bedside	Provide sleep hygiene with 2-4-hour blocks of minimal interruptions and noise minimization

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Chapter 2

Evaluating the use of dexmedetomidine for the reduction of delirium:

An integrative review¹

Abstract

Delirium, an acute change in cognition and attention not secondary to a pre-existing condition or dementia, affects nearly 40,000 hospitalized older adults in the United States every day. Delirium is associated with increased healthcare costs of \$16,303 to \$64,421 per patient. To date, no single pharmacological intervention is effective in preventing or treating delirium in critically ill patients. Evidence suggests the alpha-2 agonist, dexmedetomidine, may reduce or prevent delirium. An integrative review examined whether dexmedetomidine was associated with a lower incidence of delirium compared to other analgesic and sedation strategies. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guided this review and 16 publications met quality criteria for inclusion. These studies support that postoperative administration of dexmedetomidine may reduce delirium in patients, particularly following cardiac surgery. Further research is needed to determine the benefits of dexmedetomidine in patients on mechanical ventilation and optimal timing and duration of administration.

¹ This chapter is the author's original work. A final version of this manuscript is published as Pavone, K. J., Cacchione, P. Z., Polomano, R. C., Winner, L. & Compton, P. Evaluating the use of dexmedetomidine for the reduction of delirium: An integrative review. *Heart Lung* **47**, 591-601, doi:10.1016/j.hrtlng.2018.08.007 (2018). © 2018 Elsevier Inc. No modifications are permitted without the permission of the copyright holder.

Introduction

Delirium, a common problem for hospitalized older adults particularly after surgery or with acute illness, is defined as an acute change in cognition and attention not described by a pre-existing condition, established or evolving dementia.¹ Delirium contributes to distress in patients, caregivers and families, and more seriously is associated with increased mortality,²⁻⁴ long-term cognitive deficits, and a greater likelihood for requiring post-hospitalization residential care.⁵⁻¹⁰ Older adult patients (ages ≥ 65) are more vulnerable to developing delirium as a result of surgery and acute illness than younger patients, and aging itself is a risk factor for developing delirium. By 2060, it is estimated that the number of older adults in the United States will rise to 98.2 million, nearly 25% of the population. Consequently, healthcare providers in acute care settings will be expected to care for higher numbers of older adults with delirium in future decades. To date, no single pharmacological intervention has been shown to be effective in treating delirium.⁵ Multiple variables contribute to the development of delirium, including underlying health conditions, but the pathophysiology of delirium remains poorly understood. Current interventions for the prevention of delirium involve the recognition and amelioration of modifiable risk factors. These risk factors include pain, immobility, sleep disturbances, and exposure to medications that have the potential for psychoactive effects on the central nervous system such as opioids and benzodiazepines.¹¹ A number of pharmacological strategies to both prevent and treat delirium have been, and continue to be, highly tested including, antipsychotic medications,¹² acetylcholinesterase inhibitors,¹³ melatonin,¹⁴ benzodiazepines,^{15,16} corticosteroids, statins and gabapentin.¹³ Thus far, no single strategy has amassed enough evidence to support its role in delirium prevention or treatment.

Studies purport that dexmedetomidine (Precedex©) may reduce or prevent delirium.^{5,17-}

²⁴ Dexmedetomidine, approved by the FDA in 1999 for short-term sedation (not to exceed 24 hours), is the most specific alpha-2 receptor agonist currently used in clinical care.²⁵ Dexmedetomidine, like clonidine, exerts its anti-nociceptive effects in two ways. Primarily, it acts at alpha-2 receptors in the descending inhibitory nociceptive pathway in the spinal cord.^{26,27} Dexmedetomidine helps down-regulate nociceptive information transmission by disinhibiting inhibitory interneurons, which in turn block early nociceptive information transmission into the spinal cord by dorsal root ganglion neurons.²⁶ Dexmedetomidine also exerts a key anti-nociceptive effect by decreasing arousal.

Traditionally, dexmedetomidine is administered as an anesthetic adjunct in non-intubated patients prior to and/or during surgical and other procedures. Additionally, it is indicated for sedation of intubated and mechanically ventilated patients in critical care settings. Patients who are sedated with dexmedetomidine are arousable and responsive in a manner that is similar to that seen in people who are sleeping.^{28,29} The neurophysiological and behavioral characteristics of the sedative state induced by dexmedetomidine closely resemble non-rapid eye movement sleep.^{28,30,31}

It is hypothesized that dexmedetomidine may reduce delirium by addressing its underlying cause or ameliorating pain.^{5,17-21} Maldonado and colleagues⁵ attribute an intrinsic “delirium-saving” property of all alpha-2 adrenoceptor agonists, which typically have minimal effects on cognitive impairment. They postulate that dexmedetomidine may lessen the occurrence and severity of delirium because it decreases the need for gamma-Aminobutyric acid (GABA)ergic agents, benzodiazepines and opioids typically required for sedation and analgesia.^{11,32} In addition, dexmedetomidine has limited effects on the cholinergic system, which is involved in cognitive function and in the subsequent development of delirium.³³ It has also been proposed that dexmedetomidine may reduce

delirium by ameliorating pain, an independent risk factor for the development of delirium.³⁴⁻³⁷ As such, an integrative review to examine whether use of dexmedetomidine was associated with a reduction in delirium as compared to other analgesic and sedation strategies was conducted.

Methods

Our literature search, article selection, and evaluation were guided by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) for quality of reporting for systematic and meta-analyses.³⁸ A literature search was conducted with National Library of Medicine Medical Subject Headings (MeSH) terms dexmedetomidine and delirium. The search was further refined by keywords (elderly, intensive care, critical care and clinical trial) entered into the electronic search. Studies published between 1986 and 2017 were reviewed by using three electronic databases: PubMed, Scopus and Embase. Inclusion criteria included: 1) articles written in English; 2) search terms found in the title or as keywords; 3) study sample defined as adult population; and 4) delirium as a primary or secondary outcome. Exclusion criteria included: 1) articles related to the pediatric critical care setting; 2) mixed adult/pediatric studies; 3) case studies, commentaries, expert consensus, editorials and grey literature; and 4) chronic or cancer pain populations. The search strategy conducted with a health science librarian yielded 309 articles, 53 titles and keywords that met inclusion criteria and were screened for relevancy. Upon further review, 20 articles were retained and evaluated for scientific rigor of study design, methods and analysis. After reading the full text, four additional articles were excluded not meeting the inclusion and exclusion criteria, leaving a total of 16 articles chosen for analysis and review (**Figure 2.1**). Using the Johns Hopkins Nursing Evidence-Based Practice Research Appraisal Guidelines,³⁹ the design

and quality of evidence of the articles were assigned an evidence level of I, II, III, IV or V and graded A (high quality) B (good quality) or C (low quality or major flaws) (**Table 2.1**).

Study Characteristics

The 16 articles selected for review included: seven randomized, double-blind, controlled studies; four randomized, open label, controlled studies; and five retrospective cohort analysis studies (**Table 2.2**). All articles were published in peer-reviewed journals between 2007 and 2017. For nine studies, delirium was the primary outcome measure. Delirium was a secondary outcome for seven of the studies. The primary outcome measurements of these studies were: 1) percentage of time within target Richmond Agitation-Sedation Scale (RASS) range⁴⁰; 2) mortality and postoperative major adverse cardio-cerebral events⁴¹; 3) time to randomization and proportion of RASS assessments in the first 48 hours in the light to deep sedation range⁴²; 4) time on mechanical ventilation⁴³; 5) incidence of agitation in the post anesthesia care unit (PACU)⁴⁴; 6) in-hospital, operative and 1-year mortality⁴⁵; and 7) mortality and ventilator free days.⁴⁶ Of the studies reporting the mean age for the dexmedetomidine group, the sample population ranged from 55 to 74 years of age.

Identification of Delirium

The Confusion Assessment Method (CAM) and the CAM for the Intensive Care Unit (CAM-ICU) were most commonly used to identify delirium. These tools screen for delirium based on four features: 1) acute onset of mental status changes or a fluctuating course; 2) inattention; 3) disorganized thinking; and; 4) altered level of consciousness. For delirium to be present, a patient must display features 1 and 2, with either 3 or 4.^{47,48} Both the CAM and CAM-ICU have been derived and validated against diagnostic criteria established by the Diagnostic and Statistical Manual of Mental Disorders (DSM-V),¹ the

“gold standard” for diagnosing delirium. The CAM and CAM-ICU are the most widely used tools to identify delirium.⁴⁸

Results

Across studies, there was relative consistency in how delirium was identified. Twelve of the studies relied on the CAM-ICU for evaluation of delirium; one study utilized a trained neuropsychiatrist,¹⁹ and three studies defined the development of delirium as “the presence of illusions, confusion, cerebral excitement having a comparatively short course.”^{41,45,49} The studies retained for this review were delineated into three patient subgroups; those: 1) on mechanical ventilation; 2) having had cardiac surgery; and 3) having had non-cardiac surgery.

Mechanical Ventilation

Shehabi and colleagues (2013)⁴² evaluated early goal-directed sedation with dexmedetomidine compared to standard sedation with midazolam and/or propofol. The results showed dexmedetomidine resulted in an equal portion of patients who experienced delirium during the study period (38%; $p = 0.97$).⁴² The MENDS (Maximizing Efficacy of Targeted Sedation and Reducing Neurocognitive Dysfunction)¹⁵ study compared dexmedetomidine and lorazepam. Authors concluded that patients who received dexmedetomidine had more days alive without delirium and coma compared to those who received lorazepam (median 7 verses 3 days; $p = 0.01$). A subgroup analysis of these data showed no significant difference in the development of delirium between septic and non-septic patients.¹⁶ Following this line of investigation, the DESIRE (Dexmedetomidine for Sepsis in Intensive Care Unit Randomized Evaluation) trial prospectively evaluated patients with and without sepsis,⁴⁶ and again reported the incidence of delirium to be not statistically significantly different between groups.⁴⁶ Riker and colleagues⁴⁰ compared midazolam to dexmedetomidine. The prevalence of delirium

in patients treated with dexmedetomidine was 54.0% compared to 76.6% in patients treated with midazolam (22.6% difference, 95% CI: 14% to 33%; $p < 0.001$).

Cardiac Surgery

Maldonado and colleagues¹⁹ compared dexmedetomidine to propofol and midazolam. The incidence of delirium for the entire study population was 34%, with those receiving dexmedetomidine just 3%, compared to 50% for propofol, and 50% for midazolam ($p < 0.001$).¹⁹ Wanat and colleagues⁴³ also compared the use of dexmedetomidine and propofol, however the incidence of delirium (any vs. none) was similar (9.09% vs. 7.52%, $p = 0.747$) across both groups. Djaiani and colleagues also reported no statistically significant difference between patients in receiving dexmedetomidine (16 of 91, 17.5%) versus propofol (29 of 92, 31.5%) (Odds ratio, 0.46; 95% CI, 0.23 to 0.92; $p = 0.028$).⁵⁰

Li and colleagues studied dexmedetomidine in a placebo-controlled trial, and the authors found no significant difference between the two groups in the incidence of delirium, 4.9% (7/142) in the dexmedetomidine group vs 7.7% (11/143) in the control group (OR; 0.62, 95% CI, 0.23-1.65; $p = 0.341$). Lastly, Shehabi and colleagues⁴⁰ compared dexmedetomidine to morphine-based treatment regimens in the DEXCOM study (DEXmedetomidine COmpared to Morphine). Of note, this is the only study retained in this review that evaluates dexmedetomidine against an opioid comparator. The overall incidence of delirium within five (5) days was 11.7% (35 out of 299 patients) with 8.6% occurring in the dexmedetomidine group compared to 15% in the morphine group (RR, 0.571, 95% CI 0.256 to 1.099, $p = 0.088$).⁴⁰ Several retrospective studies by Fuhai and colleagues^{41,45,49} have also examined the effect of dexmedetomidine on the development of delirium in different groups of cardiac surgery patients. All three investigations found a statistically significant reduction in the incidence of delirium between dexmedetomidine and non-dexmedetomidine groups.

Non-Cardiac Surgery

The effect of dexmedetomidine has also been assessed in studies of patients undergoing non-cardiac surgical procedures. These studies include heterogeneous surgical patient populations, and they are distinct from the mechanical ventilation subgroup in that they include a defined surgical period. Yang and colleagues (2015)⁴⁴ examined whether dexmedetomidine sedation could decrease agitation and delirium after free flap maxillofacial surgery. These authors detected that the incidence of delirium was similar between the dexmedetomidine (5.1%; 2 of 39 patients) and control (saline) groups (12.5%; 5 of 40 patients; $p = 0.432$).⁴⁴ Next, Su and colleagues (2016)⁵¹ investigated a prophylactic low-dose dexmedetomidine versus placebo in patients undergoing abdominal, thoracic, spinal and transurethral surgeries. Postoperative delirium was observed in just 32 (9%) patients receiving dexmedetomidine compared to 79 (23%) patients receiving placebo (OR, 0.35, 95% CI 0.22 – 0.54; $p < 0.0001$). Deiner and colleagues⁵² also studied dexmedetomidine versus placebo in spine, thoracic, orthopedic, and/or general surgery patients, however they found no statistically significant difference in post-operative delirium between the dexmedetomidine and placebo groups.

Discussion

Overview of findings

Across studies, there was significant variability in the timing of administration of dexmedetomidine including preoperative, intraoperative and postoperative, and sample populations (e.g., mechanically ventilated patients not following a surgical procedure, cardiac surgery patients, or other surgical patients). Within the cardiac surgery sample, there was evidence favoring the use of dexmedetomidine to reduce the incidence of

delirium, while the mechanically ventilated and non-cardiac surgery samples helped generate hypotheses to explain the unsuccessful outcomes with administration.

Pre-operative Administration

Pre-operative administration of dexmedetomidine was observed in cardiac surgery patients as demonstrated by Li and colleagues⁵³ and a non-cardiac surgery population as demonstrated by Deiner and colleagues.⁵² Neither instance resulted in a reduction of delirium following administration of dexmedetomidine. In both studies, dexmedetomidine was started upon entering the operating room and continued for either two hours postoperatively (Deiner et al; infusion rate $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) or until extubation (Li et al; infusion rate $0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$). Both studies specifically targeted older adult patients (aged greater than 68 and 60 years respectively) and were placebo controlled (normal saline). As such, propofol and or midazolam were allowed for sedation in the treatment (dexmedetomidine) group. This older adult population presented with additional vulnerability to the development of delirium associated with the aging process. The presence of intraoperative general anesthetics, in combination with postoperative sedation with propofol and or midazolam, may result in blocking the intrinsic properties of dexmedetomidine thought to prevent delirium. A second consideration for the lack of efficacy may be due to the short time course of drug administration in the study by Deiner and colleagues (only two hours postoperatively), and the low infusion rate ($0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) in the study by Li and colleagues. Preoperative administration with concomitant propofol or midazolam appears to reduce the efficacy of dexmedetomidine in the reduction of postoperative delirium. Large scale clinical trials should be conducted with higher infusion rates and longer durations of drug administration to see if preoperative use of dexmedetomidine may be effective in prevention of postoperative delirium.

Intraoperative Administration

Intra-operative administration of dexmedetomidine was observed in three cardiac surgery studies (Maldonado et al.¹⁹; Fuhai et al. 2013⁴¹; and Fuhai et al. 2014⁴⁹); and one non-cardiac surgery study (Yang et al.⁴⁴). All three of the cardiac surgery studies in this group report a decrease in the incidence of delirium (Maldonado et al.¹⁹ Fuhai et al. 2013⁴¹ and Fuhai et al. 2014⁴⁹), while the one non-cardiac study reported no statistically significant reduction of delirium (Yang et al.⁴⁴) after use of dexmedetomidine in the intra-operative period. Dosing across all four studies was similar ($0.2 - 0.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$) and drug administration occurred in all instances 60 minutes prior to the end of surgery and continued for no more than 24 hours. The total length of surgical time reported by Yang and colleagues was 399.1 ± 94.6 minutes in the dexmedetomidine group and 402.7 ± 92.6 minutes in the control group. This total surgical time is significantly longer than reported in the cardiac surgery study by Maldonado and colleagues (dexmedetomidine group: 302 ± 106 minutes; control group 306 ± 97 minutes). As in the preoperative studies, the extended length of time under general anesthesia may have influenced the efficacy of intraoperative dexmedetomidine in the study by Yang and colleagues. To test this hypothesis, additional studies would need to evaluate the duration of surgical time in relation to dexmedetomidine dosing. However, these results do show promise that dexmedetomidine is effective in reducing the incidence of postoperative delirium in cardiac surgery patients. An important limitation of this group however, is two of the cardiac surgery studies are retrospective analyses. Therefore, prospective studies are still needed to validate this mechanism.

Postoperative Administration

Postoperative administration of dexmedetomidine was observed in four cardiac surgery studies (Shehabi et al.⁴⁰; Wanat at al.⁴³; Cheng et al.⁴⁵ and Djaiani et al.⁵⁰) and one non-

cardiac surgery study (Su et al.⁵¹). The incidence of delirium was reduced in four out of five studies (three cardiac surgery and one non-cardiac surgery). Patients undergoing cardiac surgery are at an increased risk of developing delirium due of the complexity of the surgical procedure and the high risk of postoperative complications.^{19,41,45,53} First line therapy for sedation in patients admitted to the cardiac ICU is typically propofol and/or midazolam. This result is highly suggestive that dexmedetomidine given postoperatively may be able to overcome the neurochemical milieu of general anesthesia. All studies in this group used active comparators (morphine, propofol and/or midazolam) which reduced the administration of these agents in the dexmedetomidine group possibly contributing to the efficacy of treatment with dexmedetomidine. Sedation in patients admitted to the cardiac ICU is typically managed with propofol and/or midazolam which have both been shown to increase rates of delirium. The reduction of these agents may explain the increased efficacy of dexmedetomidine as the sole sedative agent. Study drug dosing across studies was similar ranging from $0.1 - 0.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, titrated to the desired clinical effect. In the four studies which showed effectiveness of dexmedetomidine, the time on medication was up to 24 hours. The duration of study drug infusion was unspecified in the one study in which dexmedetomidine was not effective in preventing delirium. This study by Wanat and colleagues⁴³ was a retrospective investigation which limits the generalizability of its results. The five studies reported in this cohort represent three randomized clinical trials and two retrospective investigations. All three of the randomized clinical trials showed superiority of dexmedetomidine when compared to morphine and propofol in reducing the incidence of postoperative delirium.

Mechanical Ventilation

Standard management of sedation in the general ICU typically relies heavily on GABA receptor agonists such as propofol and benzodiazepines, such as midazolam and/or lorazepam.^{2,54,55} Mechanically ventilated patients not following a surgical procedure were evaluated in five studies (Pandharipande et al. 2009¹⁵; Riker et al.⁴⁰; Pandharipande et al. 2010¹⁶; Shehabi et al.⁴²; and Kawazoe et al.⁴⁶). Delirium and coma-free days were decreased in three out of the five studies. In the two studies where the incidence of delirium was not reduced (Shehabi and Kawazoe), delirium was a secondary endpoint, thus these studies may not have been adequately powered to detect changes in the prevalence of delirium. The three studies in which dexmedetomidine was effective in reducing delirium consisted of two randomized clinical trials, and one retrospective cohort study. Therefore, additional research is needed to support the use of dexmedetomidine for sedation not following a surgical procedure.

Aging

Lastly, among the 16 studies, five studies specifically targeted adults aged 70 years and older (Shehabi et al.⁴⁰; Djaiani et al.⁵⁰; Cheng et al.⁴⁵; Deiner et al.⁵²; and Su et al.⁵¹). The occurrence of delirium was reduced following usage of dexmedetomidine in four out of five studies. These studies included four randomized controlled trials with reduction of delirium as the primary outcome measure^{40,50-52} and one retrospective cohort analysis with delirium as a secondary outcome measure.⁴⁵ This cohort also characterizes three cardiac surgical studies and two non-cardiac surgical studies. In each of the four studies in which delirium was reduced following administration of dexmedetomidine, it was administered in the postoperative setting. In the study by Deiner and colleagues,⁵² which did not report a statistically significant reduction in delirium, the drug was administered in the preoperative setting (these concerns have been discussed above). Taken together,

these outcomes support that the administration of dexmedetomidine is safe in older adults, often with the advantageous consequence of decreasing and/or preventing the development of delirium. Specifically, in older adults undergoing cardiac surgical procedures, there is compelling evidence to support postoperative sedation with dexmedetomidine may reduce the incidence of delirium.

Gaps in the Research and Future Directions

Patients included in the cardiac surgery subgroup were admitted to the cardiac ICU following some type of cardiac surgical procedure, whereas patients in the mechanically ventilated subgroup may not have undergone a surgical procedure (*i.e.* admitting diagnosis sepsis, pneumonia, shock, etc.). The cardiac surgery subgroup, therefore, reflects a more homogenous patient population as the procedures during and following cardiac surgery tend to be more routine. However, it also presents greater variability in study drug administration and is possibly confounded due to exposure to general anesthesia during surgery. Additionally, some studies used dexmedetomidine for sedation or prevention of delirium over a short time period. When given later on in the ICU course or for longer durations dexmedetomidine may not have the same effects.

None of the studies included reports of non-pharmacological interventions as part of their reduction strategies. Recent evidence supports the promotion of sleep, aiming to provide at least 4 hours of sleep per night, for the reduction of delirium.⁵⁶ Only one study included in this review evaluated patient's quality of sleep. Pain management is another unaddressed concern in this evidence-based review. Only two of the 16 studies reported pain scores. The short-term consequences of undermanaged pain include higher energy expenditure and immunomodulation, both of which can contribute to the incidence of delirium. Sensory stimulation and early mobilization are other facets of the delirium prevention bundle that were not addressed in the articles included in this review.⁵⁶

Unreported inclusion of some, or all, of these factors may have aided in reduction of delirium in the presented studies. The lack of this information makes it difficult to assess if these non-pharmacologic strategies, incorporated in many ICUs, played a role in the development of the results.

An additional limitation of this work is the lack of studies using age as a control variable. As noted, the older adult population (≥ 65 years) is at the greatest risk for developing delirium. Also, there is no consensus on the duration and timing of drug administration. Additional studies are needed comparing the duration of infusion. In accordance with the hypothesis that dexmedetomidine may mimic natural sleep architecture, studies should also be completed to evaluate day-time versus nighttime drug administration. If sleep is a potential curative or preventative measure for reducing the incidence of delirium, nighttime administration of dexmedetomidine may be advantageous in aligning patients with their natural circadian rhythms to facilitate more restful and restorative sleep. This mechanism should be evaluated more thoroughly in randomized clinical studies.

Conclusions

At present, dexmedetomidine administration does not reduce the incidence and/or duration of delirium uniformly across all patient populations included in this review. However, there is good evidence to support the administration of dexmedetomidine during and following cardiac surgical procedures. This finding is in good agreement with the results of three recent meta-analysis in ICU patients.⁵⁷⁻⁵⁹ In future work, non-pharmacologic interventions, pain management, and quality of sleep need to be included in these validation studies. Each of these capacities (pain management, sleep, drug administration) are areas in which bedside care providers are important stakeholders and should help drive this research forward. As the population continues to age and the

incidence of comorbid illnesses grows, addressing the prevention and reduction of delirium is a timely and imperative objective.

Figures and Tables

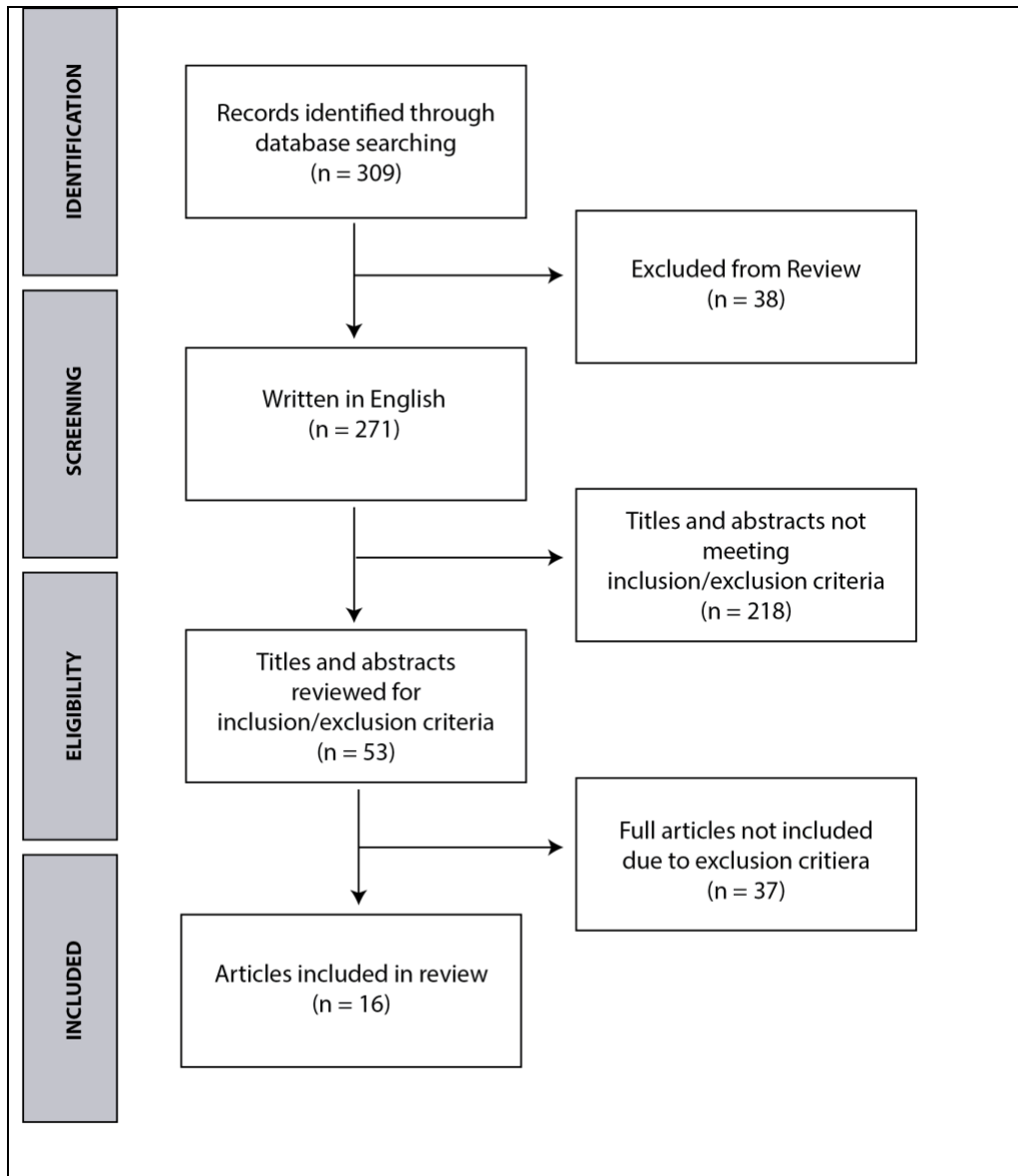


Figure 2.1 PRISMA Diagram

Table 2.1 Johns Hopkins Evidence Level and Quality Guide

Evidence Levels	Quality Guides
Level I Experimental study, randomized controlled trial (RCT) Systematic review of RCTs, with or without meta-analysis	A <u>High quality:</u> Consistent, generalizable results; sufficient sample size for the study design; adequate control; definitive conclusions; consistent recommendations based on comprehensive literature review that includes thorough reference to scientific evidence B <u>Good quality:</u> Reasonably consistent results; sufficient sample size for the study design; some control, fairly definitive conclusions; reasonably consistent recommendations based on fairly comprehensive literature review that includes some reference to scientific evidence C <u>Low quality or major flaws:</u> Little evidence with inconsistent results; insufficient sample size for the study design; conclusions cannot be drawn
Level II Quasi-experimental study Systematic review of a combination of RCTs and quasi-experimental, or quasi-experimental studies only, with or without meta-analysis	
Level III Non-experimental study Systematic review of a combination of RCTs, quasi-experimental and non-experimental studies, or non-experimental studies only, with or without meta-analysis Qualitative study or systematic review with or without a meta-synthesis	
Level IV Opinion of respected authorities and/or nationally recognized expert committees/consensus panels based on scientific evidence Includes: <ul style="list-style-type: none"> • Clinical practice guidelines • Consensus panels 	
Level V Based on experiential and non-research evidence Includes: <ul style="list-style-type: none"> • Literature reviews • Quality improvement, program or financial evaluation • Case reports • Opinion of nationally recognized experts(s) based on experiential evidence 	

Table 2.2 Table of Evidence

Authors/Year/ Country	Study Aim	Methodology, Study Design	Sample Characteristics	Major Findings/Outcomes	Evidence Level and Grade
Mechanical Ventilation					
Pandharipande et al. ¹ 2007, United States	Evaluate if dexmedetomidine reduces the duration of delirium and coma in mechanically ventilated ICU patients while providing adequate sedation as compared with lorazepam.	<p>Randomized, double-blind, controlled trial</p> <p>Patients were randomized upon arrival to the ICU. The study drug was infused as needed until extubation or for the maximum time allowed (120 hours).</p> <p>Dexmedetomidine: $0.15 - 1.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$</p> <p>OR</p> <p>Lorazepam: $1 - 10 \text{ mg} \cdot \text{h}^{-1}$</p> <p>Delirium assessed using the CAM-ICU.</p>	<p>Mechanically ventilated medical and surgical ICU patients at 2 tertiary care centers between August 2004 and April 2006.</p> <p>Sample size: 106</p> <p>Age, Median (Interquartile Range) Dexmedetomidine 60 (49 - 65) Lorazepam 59 (45 - 67)</p>	Dexmedetomidine patients had more days alive without delirium or coma (median, 7 vs. 3; $p = 0.01$)	Level I Grade A
Riker et al. ² , 2009, United States	To compare the efficacy and safety of prolonged sedation with dexmedetomidine vs midazolam for mechanically ventilated patients.	<p>Prospective, randomized, double-blind, controlled trial</p> <p>Patients were randomized with in 96 hours of being intubated. The study drug was infused as needed until extubation, after a maximum of 30 days, or at the discretion of the investigator.</p> <p>Optional loading dose: Dexmedetomidine: up to $1.0 \mu\text{g} \cdot \text{kg}^{-1}$</p> <p>OR</p> <p>Midazolam $0.05 \text{ mg} \cdot \text{kg}^{-1}$</p> <p>Maintenance Infusion Rate Midpoint: Dexmedetomidine: $0.8 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$</p> <p>OR</p> <p>Midazolam $0.06 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$</p> <p>Delirium assessed using the CAM-ICU.</p>	<p>Medical/surgical ICU patients with expected mechanical ventilation for more than 24 hours. Conducted in 68 centers in 5 countries between March 2005 and August 2007.</p> <p>Sample size: 375</p> <p>Age, mean (SD) Dexmedetomidine 61.5 (14.8) Midazolam 62.9 (16.8)</p>	<p>Using a generalized estimating equation analysis, the effect of dexmedetomidine treatment on delirium was 24.9% reduction (95% CI; 16% - 34%, $p < 0.001$).</p> <p>The prevalence of delirium was 54% (132/244) in dexmedetomidine treated patients vs. 76.6% (93/122) in midazolam patients. (22.6% difference, 95% CI; 14% to 33%, $p > 0.001$)</p>	Level I Grade A

Pandharipande et al. ³ , 2010, United States	Evaluate if dexmedetomidine compared to lorazepam would provide greater improvements in clinical outcomes among septic patients than among non-septic patients.	<p>Subgroup analysis of Pandharipande et al.¹ in patients with and without sepsis identified within 48 hours of enrollment.</p> <p>Patients were randomized upon arrival to the ICU. The study drug was infused as needed until extubation or for the maximum time allowed (120 hours).</p> <p>Dexmedetomidine: $0.15 - 1.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$</p> <p>Delirium assessed using the CAM-ICU.</p>	<p>Adult medical/surgical mechanically ventilated patients.</p> <p>Sample size: 103</p> <p>Age, Median (Interquartile Range)</p> <p>With Sepsis Dexmedetomidine 60 (46 - 65) Lorazepam 58 (44 -66)</p> <p>Without Sepsis Dexmedetomidine 61 (50 - 68) Lorazepam 60 (52-67)</p>	<p>Septic patients sedated with dexmedetomidine had a mean (95% CI) of 3.2 (1.1 to 4.9) more delirium/coma free days than patients receiving lorazepam.</p> <p>However, no significant difference was seen between patients treated with dexmedetomidine and lorazepam in non-septic patients.</p>	Level III Grade B
Shehabi et al. ⁴ , 2013, Australia and New Zealand	To assess the feasibility and safety of delivering early goal-directed sedation with dexmedetomidine compared with standard sedation with midazolam and/or propofol.	<p>Multicenter, prospective, open label, randomized controlled trial</p> <p>Patients were randomized within 12 hours of arrival to the ICU or intubation. The study drug was infused as needed until sedation was no longer required or up to 28 days.</p> <p>Early Goal-Directed Sedation Dexmedetomidine: $0.1 - 1.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$</p> <p>Delirium assessed using the CAM-ICU.</p>	<p>Critically ill adults mechanically ventilated for greater than 24 hours.</p> <p>Sample size: 37</p> <p>Age, mean (SD) Standard Sedation 61.6 (17)</p> <p>Early Goal-Directed Sedation 65 (15)</p>	An equal portion of patients experienced one or more positive CAM-ICU assessments during the study period (38%; $p = 0.97$).	Level I Grade B
Kawazoe et al. ⁵ , 2017, Japan	To examine whether a sedation strategy with dexmedetomidine can improve clinical outcomes in patients with sepsis undergoing ventilation.	<p>Open-label, multicenter randomized clinical trial</p> <p>Study drug administration occurred upon ICU admission. The study drug was infused as needed until sedation was no longer required.</p> <p>Dexmedetomidine: $0.1 - 0.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$</p> <p>Delirium assessed using the CAM-ICU.</p>	<p>Patients with sepsis requiring mechanical ventilation for at least 24 hours.</p> <p>Sample size: 201</p> <p>Age, mean (SD) Dexmedetomidine 68 (14.9) Control Group 69 (13.6)</p>	The rate of delirium free days was not significantly different between groups ($p = 0.17$).	Level I Grade A

Cardiac Surgery					
Maldonado et al. ⁶ , 2009, United States	Investigated the effects of postoperative sedation on the development of delirium in patients undergoing cardiac-valve procedures.	<p>Randomized, open-label, controlled trial</p> <p>After successful weaning from CPB, patients were started on one of three randomly assigned, postoperative sedation regimens. Patients were extubated while still on the medication and were kept on the maintenance infusion as deemed clinically necessary for a maximum of 24 hours.</p> <p>Loading dose: Dexmedetomidine: $0.4 \mu\text{g} \cdot \text{kg}^{-1}$</p> <p>Infusion Rate: Dexmedetomidine: $0.2 - 0.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$</p> <p>OR</p> <p>Propofol: $25 - 50 \text{ g} \cdot \text{kg}^{-1} \cdot \text{m}^{-1}$</p> <p>OR</p> <p>Midazolam: $0.5 - 2.0 \text{ mg} \cdot \text{h}^{-1}$ Delirium assessed by a trained neuropsychiatrist.</p>	<p>Patients schedule for elective cardiac valve operations.</p> <p>Sample size: 118</p> <p>Age, mean (SD) Dexmedetomidine 55 (16) Propofol 58 (18) Midazolam 60 (16)</p>	Using a per-protocol analysis, the incidence of delirium for patients receiving dexmedetomidine was 3% (1/30); propofol 50% (15/30); and midazolam 50% (15/30).	Level I Grade A
Shehabi et al. ⁷ , 2009, Australia and New Zealand	To assess the neurobehavioral, hemodynamic, and sedative characteristics of dexmedetomidine compared with morphine-based regimen after cardiac surgery at equivalent levels of sedation and analgesia.	<p>Randomized, double-blind, controlled trial</p> <p>Study drug infusions were started in the ICU. The infusion was continued until the removal of chest drains, when patient was ready to discharge from ICU, or for up to 48 hours of mechanical ventilation.</p> <p>Dexmedetomidine: $0.1 - 0.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$</p> <p>OR</p> <p>Morphine: $10-70 \text{ g} \cdot \text{kg}^{-1} \cdot \text{ml}^{-1}$</p> <p>Delirium assessed using the CAM-ICU.</p>	<p>Cardiac surgery patients 60 years of age or older. Conducted in two tertiary university affiliated hospitals between 2004 and 2007.</p> <p>Sample size: 306</p> <p>Age, Median (Interquartile Range) Dexmedetomidine 71.5 (66 – 76) Morphine 71 (65 – 75)</p>	The overall incidence of delirium within 5 days was 11.7% (35 of 299) with 8.6% occurring in the dexmedetomidine group and 15% occurring in the morphine group (RR 0.571, 95% CI 0.256-1.099, $p = 0.088$).	Level I Grade A

Fuhai et al. ⁸ , 2013, United States	To determine whether the perioperative use of dexmedetomidine could reduce the incidence of complications and mortality after cardiac surgery	<p>Retrospective cohort study</p> <p>Perioperative dexmedetomidine was administered after CPB and continued for less than 24 hours postoperatively in the ICU.</p> <p>Dexmedetomidine: $0.24 - 0.6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$</p> <p>Delirium was assessed by the presence of illusions, confusion, cerebral excitement having a comparatively short course.</p>	<p>Patients who underwent coronary artery bypass surgery and coronary artery bypass or other cardiac procedures were included.</p> <p>Sample size: 1134</p> <p>Age, mean (SD) Dexmedetomidine 63 (12) Non-dexmedetomidine 63.5 (11)</p>	The multivariate model assessing delirium (5.46% versus 7.42%; adjusted odds ratio, 0.53; 95% confidence interval, 0.37–0.75; $p = 0.0030$) was statistically significant between the dexmedetomidine and non-dexmedetomidine groups.	Level III Grade B
Fuhai et al. ⁹ , 2014, United States	This study retrospectively investigated the effect of dexmedetomidine on outcomes of patients undergoing coronary artery bypass graft (CABG) surgery.	<p>Retrospective cohort study</p> <p>Perioperative dexmedetomidine was administered after CPB and continued for less than 24 hours postoperatively in the ICU.</p> <p>Dexmedetomidine: $0.24 - 0.6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$</p> <p>Delirium was assessed by the presence of illusions, confusion, cerebral excitement having a comparatively short course.</p>	<p>Patients undergoing CABG surgery.</p> <p>Sample size: 724</p> <p>Age, mean (SD) Dexmedetomidine 62.9 (11.8) Non-dexmedetomidine 64.1 (11.4)</p>	The adjusted rates of delirium (adjusted OR, 0.431; 95% CI, 0.265 to 0.701, $p = 0.0007$) were statistically significant between the dexmedetomidine and non-dexmedetomidine groups.	Level III Grade B
Wanat et al. ¹⁰ , 2014, United States	Comparison of dexmedetomidine versus propofol for sedation in mechanically ventilated patients after cardiovascular surgery	<p>Retrospective cohort study</p> <p>Sedation orders were based on individual physician ordering upon arrival to the ICU.</p> <p>Average Dose Dexmedetomidine: $0.489 \pm 0.13 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$</p> <p>Delirium assessed using the CAM-ICU.</p>	<p>Patients admitted to the ICU after cardiovascular surgery from January through June 2011.</p> <p>Sample size: 352</p> <p>Age, mean (SD) Dexmedetomidine 63 (14.1) Propofol 68 (11.2)</p>	CAM-ICU scores were reported in 79% of dexmedetomidine patients and 84% of propofol patients ($p = 0.411$). Incidence of delirium (any vs. none) was similar between both groups (9.09% vs. 7.52%, $p = 0.747$).	Level III Grade B

Cheng et al. ¹¹ , 2016, United States	The goal of this retrospective study was to investigate the effects of perioperative use of dexmedetomidine on outcomes for older patients undergoing cardiac surgery.	<p>Retrospective cohort study</p> <p>Drug infusion was initiated after CBP and continued for 24 hours postoperatively in the ICU.</p> <p>Dexmedetomidine: $0.24 - 0.6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$</p> <p>Delirium was assessed by the presence of illusions, confusion, cerebral excitement having a comparatively short course.</p>	<p>Patients underwent coronary artery bypass graft (CABG) or valve surgery.</p> <p>Sample size: 505</p> <p>Age, mean (SD) Dexmedetomidine 73.6 (6.1) Non-dexmedetomidine 73.5 (6.2)</p>	Results of multivariate analysis show that postoperative delirium (adjusted OR, 0.350; 95% CI, 0.212-0.578; $p = 0.007$) was decreased significantly in the dexmedetomidine group.	Level III Grade B
Djaiani et al. ¹² , 2016, Canada	Dexmedetomidine sedation after cardiac surgery would reduce the incidence of postoperative delirium	<p>Single-blind, prospective, randomized controlled trial</p> <p>Upon arrival to ICU sedation was initiated. The infusion was continued for a maximum period of 24 hours.</p> <p>Loading dose: Dexmedetomidine: $0.4 \mu\text{g} \cdot \text{kg}^{-1}$</p> <p>Infusion Rate: Dexmedetomidine: $0.2 - 0.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$</p> <p>OR</p> <p>Propofol: $25 - 50 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{m}^{-1}$</p> <p>Delirium assessed using the CAM-ICU.</p>	<p>Patients undergoing cardiac surgery.</p> <p>Sample size: 185</p> <p>Age, mean (SD) Dexmedetomidine 72.7 (6.4) Propofol 72.4 (6.2)</p>	A total of 11 (12.1%) and 25 (27.1%) in the dexmedetomidine and propofol groups respectively, developed delirium.	Level I Grade B

Li et al. ¹³ , 2017, China	The purpose of this study was to investigate the impact of perioperative dexmedetomidine administration on the incidence of delirium in elderly patients after cardiac surgery.	<p>Randomized, double-blind, placebo-controlled trial</p> <p>In the operating room, study drug infusion was started once the intravenous access was established until the end of surgery. After surgery, study drug infusion was continued until the end of mechanical ventilation.</p> <p>Loading dose: Dexmedetomidine: $0.6 \mu\text{g} \cdot \text{kg}^{-1}$</p> <p>Infusion Rate During Surgery: Dexmedetomidine: $0.4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$</p> <p>Infusion Rate Post-Operatively: Dexmedetomidine: $0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$</p> <p>Delirium assessed using the CAM-ICU.</p>	<p>Patients after cardiac surgery.</p> <p>Sample size: 285</p> <p>Age, mean (SD) Dexmedetomidine 66.4 (5.4) Control Group 67.5 (5.3)</p>	<p>There was no significant difference between the two groups in the development of delirium during the first 5 days following surgery, 4.9% (7/142) in the dexmedetomidine group vs 7.7% (11/143) in the control group (OR; 0.62, 95% CI 0.23-1.65; $p = 0.341$)</p>	Level I Grade A
Non-Cardiac Surgery					
Yang et al. ¹⁴ , 2015, China	To determine whether dexmedetomidine sedation in the post-anesthesia care unit could decrease agitation and delirium after free flap surgery	<p>Prospective, randomized, double-blind, controlled trial</p> <p>Infusion of the blinded study drug was started approximately 60 minutes before the end of surgery until the operation was completed; infusions were continued in the PACU until 6:00 AM the next morning.</p> <p>Infusion Rate During Surgery: Dexmedetomidine: $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$</p> <p>Infusion Rate Post-Operatively: Dexmedetomidine: $0.2 - 0.7 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$</p> <p>OR</p> <p>0.9% Saline</p> <p>Delirium assessed using the CAM-ICU.</p>	<p>Patients scheduled for maxillofacial surgery from June to October 2013.</p> <p>Sample size: 80</p> <p>Age, mean (SD) Dexmedetomidine 50.3 (15) Control group 50.6 (12.3)</p>	<p>The incidence of delirium within 5 days postoperatively was similar between the dexmedetomidine (5.1%; 2 of 39 patients) and control (saline) groups (12.5%; 5 of 40 patients; $p = 0.432$)</p>	Level I Grade A
Su et al. ¹⁵ , 2016, China	To investigate whether prophylactic	Randomized, double-blind, placebo-controlled trial	Patients admitted to intensive care units after non-cardiac surgery.	Post-operative delirium occurred in	Level I Grade A

	low-dose dexmedetomidine could safely decrease the incidence of delirium in elderly patients after non-cardiac surgery.	<p>Infusion was started from study recruitment on the day of surgery (usually within 1 hour after ICU admission) until 0800 h on the first day after surgery.</p> <p>Dexmedetomidine: $0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$</p> <p>OR</p> <p>0.9% Normal Saline</p> <p>Delirium assessed using the CAM-ICU.</p>	<p>Sample size: 700</p> <p>Age, mean (SD)</p> <p>Dexmedetomidine 74.3 (6.7)</p> <p>Control group 74.4 (7.0)</p>	<p>79 (23%) of patients receiving placebo, and in 32 (9%) of patients receiving dexmedetomidine (OR, 0.35, 95% CI 0.22 – 0.54; p = <0.0001)</p>	
Deiner et al. ¹⁶ , 2017, United States	To evaluate whether an intraoperative infusion of dexmedetomidine reduces postoperative delirium.	<p>Multicenter, double-blind, randomized, placebo-controlled trial</p> <p>Infusions were started in patients on entering the operating room and was continued until 2 hours into recovery.</p> <p>Dexmedetomidine: $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$</p> <p>OR</p> <p>0.9 % Saline</p> <p>Delirium assessed using the CAM-ICU.</p>	<p>Patients undergoing major elective non-cardiac surgery.</p> <p>Sample size: 404</p> <p>Age, Median (Interquartile Range)</p> <p>Dexmedetomidine 74 (71-78)</p> <p>Control group 74 (71-78)</p>	<p>In total 12.2% (23 of 189) of patients who received dexmedetomidine and 11.4% (23 of 201) of patients who received placebo experienced delirium.</p>	Level I Grade A

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Chapter 3

Evaluating a nurse-led intervention for delirium among older adults in the surgical intensive care unit

Abstract

Background. Delirium, a prevalent condition in hospitalized older adults (≥ 65 years), is an acute brain dysfunction characterized by disturbances in attention, awareness and cognition not explained by a pre-existing neurocognitive disorder. The *ICU Liberation Executing the ABCDEF Bundle Daily (iLEAD)* is a nurse-driven protocol aimed at reducing the severity of delirium in the surgical intensive care unit (SICU) via the implementation of independent nursing interventions.

Objectives. When nurses routinely assess and manage modifiable risk factors for delirium (pain; sensory impairment; immobilization; medication administration; surgery, environment; emotional distress; and sustained sleep deprivation), the number of days of delirium will decrease and patient outcomes will improve. This retrospective analysis evaluated the impact of the iLEAD intervention on the number of days with delirium, length of stay in the SICU, overall hospital length of stay, 30-day readmission rates and 30-day mortality experienced by older adults.

Methods. Employing an observational cohort design, this study compared delirium outcomes pre- versus post-iLEAD implementation. The sample consisted of 93 patients admitted to the SICU at the Hospital of the University of Pennsylvania. Outcomes were evaluated by medical record review.

Results. Rates of delirium screening more than doubled following iLEAD implementation. Consistent with previous reports, delirium contributed to both SICU and overall hospital length of stay and 30-day mortality. Other than a trend for improvements

in rates of 30-day readmissions, no improvement in delirium outcomes were noted for the patients who received iLEAD delirium-informed care.

Conclusions. This work examined the nurse-management of delirium among older adult patients admitted to the SICU. Improved patient outcomes, while not statistically significant, were achievable in the early stages of the iLEAD intervention and may inform prospective systems-level organizational change. With continued adherence to the iLEAD intervention, it is hypothesized that outcomes will progressively improve.

Introduction

Delirium is an acute brain dysfunction characterized by disturbances in attention, awareness and cognition not explained by a pre-existing neurocognitive disorder.¹

Delirium in the intensive care unit (ICU) is common for hospitalized older adult patients (≥ 65 years) due to the severity of their illnesses, the number of their comorbidities and their advanced age,¹⁻³ and has been reported to occur in approximately 50% of all hospitalized older adults.² The clinical presentation of delirium can be hypoactive, hyperactive or mixed.¹ Notably, the hypoactive form occurs most frequently in older adult patients, and too often, these patients are overlooked or misdiagnosed as having depression or dementia as opposed to delirium.² Aging itself has also been described as a risk factor for developing delirium.⁴⁻⁷

Older adults consume nearly 60% of all ICU days⁸ and are predisposed to higher rates of delirium than adults under the age of 65 years. For these older adults, delirium poses a significant health threat.^{3,5,9,10} Delirium has been associated with longer ICU and hospital stays,^{9,11-13} increased health care costs and poorer outcomes related to readmissions¹⁴⁻¹⁶ and increased mortality.^{9,12,17-19} Delirium has been identified as one of six leading causes of injuries associated with hospitalization in older adults.²⁰

In a study of 304 older adult patients admitted to the medical ICU, the typical length of ICU stay was five days, with an average of three days of delirium.¹² Added costs per hospitalization attributable to delirium range from \$16,303 to \$64,421 per patient.¹⁴ A one-year study of hospitalized adults 70 years or older, reported 109 patients (13.0%) developed delirium while 732 did not.¹⁵ The subsequent health care costs associated with delirium suggested that patients with delirium were more than 2.5 times as costly than patients without delirium.¹⁵ In that Medicare and Medicaid reimbursements are tied to rates of 30-day readmissions,²¹ some delirium-related costs are attributed to

readmitted patients with delirium. Readmissions alone also have also been associated with unfavorable patient outcomes in patients with delirium.¹⁶ Finally, delirium has been reported to be an independent marker for increased mortality in older medical inpatients both 6- and 12-months after hospital admission.^{9,18} Because delirium can be a life-threatening condition for older adults,² limiting its occurrence and severity is imperative to improving patient outcomes. To date, there are few studies that have specifically examined the effect of delirium on outcomes of older adults admitted to the surgical intensive care unit (SICU).

The 2013 revised Society for Critical Care Medicine (SCCM) Clinical Practice Guidelines for Management of Pain, Agitation, and Delirium²² recommend routine monitoring of sedation, pain and delirium for all patients in the ICU. The SCCM's *ICU Liberation Collaborative* initiative offers a broad program to enable the application of these guidelines across hospital systems.²³⁻²⁶ ICU Liberation uses a set of interventions known as the “ABCDEF Bundle” to guide execution of their recommendations. The elements of ABCDEF bundle individually and collectively aim to reduce delirium, pain, agitation and the long-term negative health consequences of delirium in adult ICU patients.^{24,25,27,28} The first large scale evaluation of the ABCDEF bundle included over 15,000 adult patients (18+ years of age) from 68 ICUs (including mixed medical/surgical, medical, surgical/trauma, neurological, cardiac/surgical and surgical). Complete performance of the ABCDEF bundle was associated with a lower likelihood of next-day mechanical ventilation, decreased rates of delirium, reduced ICU readmissions and decreased 7-day mortality rates.²⁶

Utilizing the principles of systems science, which encompass improving quality, outcomes, and costs of health care delivery for patients and populations within systems of medical care,²⁹ The Hospital of the University of Pennsylvania created the *ICU*

Liberation Executing the ABCDEF Bundle Daily (iLEAD), a nurse-driven intervention designed by an interprofessional team to implement the ABCDEF bundle and reduce the consequences of delirium in the ICU within their health system. A study was undertaken to compare (1) days of delirium, (2) SICU and (3) hospital length of stay, (4) 30-day readmission rates and (5) 30-day mortality in cohorts of older adults in the SICU prior to and following implementation of the iLEAD intervention. A conceptual model (**Figure 3.1**) illustrates the relationships of risk factors outlined in the iLEAD protocol for delirium to the clinical outcomes of interest. It is postulated that the assessment of non-modifiable risks for delirium and management of modifiable risks will lead to fewer days of delirium and improved patient outcomes. When nurses routinely assessed and managed modifiable risk factors for delirium (*i.e.*, implement the iLEAD intervention), it was hypothesized that patient outcomes would improve.

Methods

Design

A retrospective observational pre- and post-intervention cohort study was designed to examine delirium-related outcomes in older adult patients in the SICU which might have contaminated the care received prior to formal implementation. All data were extracted from the electronic health record (EHR). The primary patient outcomes of this investigation were: days of delirium; SICU length of stay in days; hospital length of stay in days; rates of 30-day readmissions and rates of 30-day mortality. The study was approved by the University of Pennsylvania Institutional Review Board with exempt status and waiver of informed consent. Study design and reporting conformed with criteria outlined in the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.³⁰

Setting and Sample

Study participants were selected from a 24-bed surgical critical care unit at a 795-bed urban academic medical center. Consecutive patients 65 years or older admitted to the SICU between March 15 and August 15, 2017 were screened for inclusion in the pre-iLEAD implementation cohort. These patients were compared to a similar cohort of patients admitted to the same SICU between March 15 to August 15, 2018, representing the post-iLEAD implementation cohort. The iLEAD intervention was implemented in January 2018. These cohorts were intentionally selected with several factors in mind. First, the two cohorts were sampled during the same 6-month calendar periods, accounting for differences in SICU admission by time of year. Second, March was chosen as the start date to reflect sufficient duration from the start of the iLEAD implementation in January, so compliance rates to the intervention would be sufficiently high. The pre-iLEAD intervention cohort were admitted before any iLEAD planning or education occurred. During the post-implementation cohort study period, the interventions for **A**wake and pain free, spontaneous **B**reathing trials, **C**onsideration of Analgesia and Sedation and **D**elirium were fully implemented, however interventions for **E**xercise and **F**amily engagement were still being introduced to the nursing workflow.

Inclusion criteria were; age ≥ 65 , English speaking, admitted to the SICU for >24 hours, and having screened positive for delirium during the first seven days of ICU stay. Patients were excluded if they had an admitting diagnosis related to neurological or central nervous system injury; for patients readmitted to the SICU, only the index admission was evaluated. Patients not evaluated for delirium using the confusion assessment method for the intensive care unit (CAM-ICU) between day 1 and day 7 during their admission to the SICU were also excluded. As illustrated in **Figure 3.2**, the pre-implementation 2017 sampling pool contained 101 patients, and the post-

implementation 2018 sampling pool, 172 patients. Of the total sample, 37 and 56 patients screened positive for delirium in the 2017 and 2018 cohorts respectively.

Intervention

The iLEAD intervention is a nurse-driven protocol aimed at reducing delirium in the ICU. As described above, it incorporates a set of interventions designed to coordinate care, with a specific focus on delirium, as a component of the overall care patients receive.²⁵ Specifically, upon admission to the SICU, the nursing staff reviewed a patient's medical history for relevant delirium risk factors (age, history of cognitive impairment, immobility, audio or visual impairments, history of alcohol use, history of delirium, etc.). Delirium assessments (CAM-ICU) were conducted twice daily (AM and PM) beginning upon admission. Patients with a positive CAM-ICU assessment were evaluated for new infections, or cardiac or neurological events that may explain the change in their mental status. Inpatient and home medications were also reviewed to assess for medications likely to induce delirium, such as opioids and benzodiazepines. For those patients who screened positive for delirium, nurses initiated at least two independent non-pharmacological interventions selected from a menu of interventions based on the risk factors identified. Additional engagement with the interdisciplinary team was utilized to identify possible causes of delirium and treatment approach. Delirium was continually reassessed with the CAM-ICU every 12 hours to monitor for response to the interventions.

Measures

Delirium. The primary study outcome was the number of days of delirium calculated using the highly reliable and well-validated CAM-ICU assessment tool.³¹⁻³³ Reliability for the CAM-ICU has been established against the DSM-V diagnostic criteria for delirium (interrater reliability kappa = 0.79-0.96).³¹ Compared with a reference standard

(psychiatrist) diagnosis of delirium, the CAM-ICU used by nursing staff had sensitivity estimates of 93-100% and specificity of 89-100%.³¹ The CAM-ICU recognizes delirium based on four features: 1) acute onset of mental status changes or a fluctuating course; 2) inattention; 3) disorganized thinking; and 4) altered level of consciousness.^{32,33} For delirium to be scored as present, a patient must display both a change in mental status and inattention, along with either disorganized thinking or altered level of consciousness.^{32,33} The CAM-ICU was completed and scored by trained nursing staff every 12 hours. Each assessment generated one of four possible results; positive, negative, unable to assess (comatose), or no test performed. One day of “no delirium” was defined as either two negative CAM-ICU assessments, or one negative and one unable to assess evaluation in a 24-hour period. One day of “delirium” was defined as one positive CAM-ICU screening in a 24-hour period. The number of days of at least one positive CAM-ICU screen were calculated beginning at the time of SICU admission through SICU discharge or up to 7 days. Delirium that emerges beyond 7 days may be related to an underlying medical abnormality or complications, and therefore not representative of ICU delirium.^{34,35}

Length of SICU Stay. SICU length of stay was calculated beginning at the time a patient was admitted to the SICU until they left the SICU.

Length of Hospital Stay. Hospital length of stay was measured beginning at hospital admission until discharge.

30-day Readmission Rates. Readmission rates were counted as being readmitted to the hospital for any cause within the 30 days after discharge from a hospitalization. Due to the limitations of the Penn Medicine EHRs, only readmissions to in-system hospitals are captured.

30-day Mortality Rates. Mortality rates were counted as a death occurring within 30 days of hospital admission; deaths could be for any cause and occur in the hospital or after discharge.

We also used the EHR to ascertain clinical and demographic data that were used as covariates. These included age, sex, race, use and duration of mechanical ventilation, Richmond Agitation-Sedation Scale (RASS) scores, and admitting medical diagnosis. Admitting diagnoses were utilized as a proxy measure for severity of illness.

Data Analysis

Descriptive statistics (mean, standard deviation, median, range and percentages) were produced to describe and compare sample characteristics of the pre- and post-implementation cohorts using Student's t-tests for independent groups for continuous variables and chi-square (χ^2) tests for categorical variables. Fisher's exact test was used for assessment of categorical variables where the cell counts were less than 5. Data were closely examined for any systematic patterns of missingness. P-values of 0.05 or less were considered to indicate statistical significance.

Cox Proportional Hazards Regression models were conducted using the PHREG procedure in SAS to assess cohort (study year) as a predictor of SICU and hospital length of stay while accounting for both censored and non-censored data. The PHREG procedure is widely used in analyzing the effect of explanatory variables on time-to-event variables. Patients who died during their SICU stay or had a SICU stay longer than 30 days were classified as censored observations, indicating that they are not assessed as a true SICU discharge event. Similarly, patients who died during their hospital stay or had a hospital stay longer than 60 days were classified as censored observations. Analyses were adjusted for age, sex, race, RASS, use of mechanical ventilation and admitting diagnosis. The four most prevalent admitting diagnosis were included as

covariates (neoplasms, diseases of circulatory system, diseases of digestive system and symptoms, signs & abnormal labs) to control for the effects of medical condition on the efficacy of the intervention. Kaplan-Meier survival curves were produced for graphical presentation of these time-to-event analyses. As a preliminary assessment, Cox Proportional Hazards Regression models were also used to compare SICU and hospital length of stay between patients with and without delirium across both study years.

Chi square tests were used to evaluate the association between cohort (study year) and 30-day readmissions, as well as 30-day mortality. Adjusted logistic regression analyses were then conducted and included age, sex, race, RASS, use of mechanical ventilation and admitting diagnosis as covariates. As a preliminary assessment, chi square tests were used to compare readmission and mortality rates between patients with and without delirium across both study years.

Results

In total, 653 patients were admitted to the SICU between March 15 and August 15, 2017 and 630 patients were admitted between March 15 and August 15, 2018. After screening for inclusion and exclusion criteria, 101 patients in 2017 and 172 patients in 2018 were evaluated; of these, 37 patients in 2017 and 56 patients in 2018 screened positive for delirium, thus comprised the pre- and post-implementation cohorts. Demographically, the cohorts were comparable (**Table 3.1**) with the exception that patients with delirium in the 2018 cohort received more hours of mechanical ventilation during their SICU stay ($p = 0.032$).

Outcomes of Patients with and without Delirium

To validate previously described consequences of delirium, preliminary assessments were performed to compare patients with and without delirium in each cohort. As expected, **Figure 3.3** reflects poorer outcomes for patients with delirium compared those

without delirium. The results were unchanged in the adjusted models. The unadjusted preliminary models are described as follows:

SICU Length of Stay. In both cohorts (**Figure 3.3, A and B**), delirium exhibited a strong association with SICU length of stay (2017 $\chi^2 = 21.1942$, Hazard Ratio (HR): 0.394, $p < 0.0001$; 2018 $\chi^2 = 40.3134$, HR: 0.316, $p < 0.0001$). Three patients in 2017 and eight patients in 2018 were censored due to either death or a SICU stay longer than 30 days.

Hospital Length of Stay. Similarly, delirium exhibited a strong association with overall hospital length of stay (**Figure 3.3, C and D**) in 2017 ($\chi^2 = 4.2657$, HR: 0.649, $p = 0.0389$) and 2018 ($\chi^2 = 26.2117$, HR: 0.436, $p < 0.0001$). Eight patients in 2017 and 15 patients in 2018 were censored due to either death or a hospital stay of longer than 60 days.

Readmissions. No association between delirium and 30-day readmissions in 2017 ($\chi^2 = 0.0004$, $p = 0.9833$) or 2018 ($\chi^2 = 0.0076$, $p = 0.9304$) were noted (**Figure 3.3, E**). Of patients with delirium in 2017, 18.92% were readmitted within 30 days of hospital admission compared to 18.75% of patients without delirium. In 2018, 14.29% of patients with delirium were readmitted within 30 days of hospital admission, compared to 13.79% of patients without delirium.

Mortality. With respect to 30-day mortality (**Figure 3.3, F**), in 2017, 16.22% of patients with delirium died within 30 days of hospital admission, compared to 3.13% of patients without delirium ($\chi^2 = 5.5092$, $p = 0.0189$). In 2018, 16.07% of patients with delirium died within 30 days of hospital admission, compared to just 3.45% of patients without delirium ($\chi^2 = 8.6133$, $p = 0.0033$).

Summary of CAM-ICU Assessments

To illustrate adherence to the iLEAD intervention, the daily results of the CAM-ICU assessments were evaluated (**Table 3.2**). The number of days with a positive CAM-ICU

assessment was similar between the 2017 and 2018 cohorts ($p = 0.7200$). Notably, the number of days of a negative CAM-ICU assessment ($p = 0.0178$) and the number of days where no test was performed ($p < 0.001$) were statistically different between study year, reflecting the nurse's uptake of the iLEAD intervention. The number of days with coma ($p = 0.8873$) remained similar between cohorts.

Days of Delirium

The incidence of delirium (37% vs. 33%, $p = 0.511$) and the average number of days of delirium ($p = 0.1660$) did not vary significantly by study year (**Table 3.1**).

SICU Length of Stay

Pre-iLEAD implementation, the median length of stay in the SICU for patients with delirium was 7 days compared to 8 days for patients following iLEAD implementation ($p = 0.7499$) (**Table 3.1**). Among the 2017 cohort, 51.35% of patients with delirium had been discharged from the SICU by one week, compared to 43.39% among the 2018 cohort. Within the 2017 cohort, 96.29% of patients with delirium had been discharged from the SICU after 30 days, compared to 100% in the 2018 cohort (**Figure 3.4, A**). Study year was not found to be a significant predictor of SICU length of stay ($\chi^2 = 0.3403$, HR: 0.881, $p = 0.5597$). After adjusting for covariates of interest, study year remained a nonsignificant predictor of SICU length of stay ($\chi^2 = 1.6655$, HR: 0.770, $p = 0.1969$).

Hospital Length of Stay

For patients with delirium, the median length of stay in hospital was 15 days in 2017 compared to 17.5 days for patients in 2018 ($p = 0.1909$) (**Table 3.1**). Among the 2017 cohort, 13.51% of patients had been discharged after one week, compared to just 1.77% of patients in the 2018 cohort. After 30 days, 79.76% of the 2017 cohort had been discharged, compared to 59.98% in the 2018 cohort (**Figure 3.4, B**). Study year was not

found to be a significant predictor of hospital length of stay ($\chi^2 = 2.299$, HR: 0.695, $p = 0.1294$). After adjusting for covariates of interest, study year was significant predictor of hospital length of stay ($\chi^2 = 4.4103$, HR: 0.618, $p = 0.0357$) favoring the 2017 cohort.

30-day Readmissions

In the 2017 cohort, 18.92% of patients with delirium were readmitted within 30 days of hospital admission compared to 14.29% in the 2018 cohort. Despite this trend for decreased 30-day readmissions (**Figure 3.4, C**), study year did not exhibit a significant association with hospital readmission ($\chi^2 = 0.3535$, $p = 0.5521$). After adjusting for covariates of interest, study year remained not a significant predictor of readmission rates ($\chi^2 = 0.12$, $p = 0.7336$).

30-day Mortality

Rates of 30-day mortality were essentially unchanged following the iLEAD intervention; in the 2017 cohort, 16.22% of patients with delirium died within 30 days of hospital admission, compared to 16.07% in the 2018 cohort (**Figure 3.4, C**). Study year did not exhibit a significant association with 30-day mortality ($\chi^2 = 0.0003$, $p = 0.9852$). Similarly, after adjusting for covariates of interest, study year was not a significant predictor of readmission rates ($\chi^2 = 0.23$, $p = 0.6289$).

Discussion

Delirium is a significant and costly problem for older adults in the ICU. It is commonly under-recognized and undertreated, and the consequences are not only evident in length of ICU and hospital stay, but in the more worrisome outcomes of 30-day readmissions and mortality. Empirical evidence for independent nurse-led interventions to mitigate the development and duration of delirium is accumulating and this evaluation of the iLEAD intervention contributes to this body of knowledge. In this study, patient-

level outcomes attributable to delirium in older adults admitted to the SICU were examined prior to and following the implementation of the iLEAD intervention.

These data support that delirium contributes to both SICU and overall hospital length of stay, and to 30-day mortality in older patients admitted to the SICU. No differences in 30-day hospital readmission rates were observed in this sample between those with and without delirium. Increased ICU length of stay was previously reported in a prospective cohort study of 261 patients admitted to the medical ICU in which 125 patients (48%) experienced at least one episode of delirium. Patients who experienced delirium had a 29% greater risk of remaining in the ICU (compared to patients who never developed delirium) even after adjusting covariates (HR: 1.29; CI: 0.98-1.69, $p = 0.07$).³⁶ A similar study performed to determine the effects of delirium on length of hospital stay, concluded in-hospital delirium (36 of 359 patients) was an important predictor of longer hospital stay. The median length of stay for patients with delirium was 16.5 days compared to 7.5 days for patients without delirium (difference 9 days).³⁷ With respect to mortality, a cohort study of 275 mechanically ventilated patients concluded that 50% of patients who experienced delirium during their ICU stay died within one-year post-hospitalization,⁹ supporting similar studies that reported increased mortality following an episode of delirium.^{12,18} The SCCM *ICU Liberation Collaborative* also reported that implementation of the ABCDEF bundle was associated with a decreased rates of delirium and a lower likelihood of 7-day mortality.²⁶

The unchanged 30-day hospital readmission rates observed in this study were somewhat surprising in that the literature has supported an association between delirium and hospital readmissions. For example, Eide and colleagues examined 136 patients aged 80 years or greater and evaluated the influence of delirium on 30-day readmission rates in patients undergoing cardiac surgery. Delirium was identified in 76 (56%)

patients; 24 out of 30 (80%) patients who were readmitted within 30 days experienced delirium.¹⁷ The lack of group differences in 30-day readmission rates in this sample may be explained by other factors such as severity of illness, or complications of the disease process, and not delirium.

No improvement in delirium outcomes were noted for the cohort of patients who received iLEAD delirium-informed care, other than a trend for improvements in rates of 30-day readmissions (from approximately 19% in 2017 to 14% in 2018). There are several potential reasons why the iLEAD intervention did not demonstrate effectiveness. Delirium was more frequently identified in the post-implementation cohort, and therefore the poor outcomes associated with delirium were more likely to be detected, potentially confounding the effect of the iLEAD intervention. While the typology of delirium was not captured in this study, patients with hyperactive delirium exhibit restlessness and agitation whereas those with hypoactive delirium generally present as lethargic or sedated and respond slowly to questions or show little spontaneous movements. It is possible that the primary subtype of delirium reported in the pre-implementation cohort was mainly hyperactive, as this type of delirium is readily visible as compared to hypoactive delirium which is more difficult to detect and more common in older adults.

Consequently, while the iLEAD intervention did not show decreased length of stay for patients with delirium in the post-implementation cohort, patients with delirium in the pre-implementation cohort may have been more likely to be discharged before complete recovery from delirium due to lack of education and training. Increased detection rates for hypoactive delirium in the post-implementation cohort likely contributed to the increased SICU length of stay. Literature suggests that bundled interventions, such as the iLEAD protocol, are more likely to reduce the incidence of delirium and provide less robust evidence to support decreasing severity or duration of delirium.³⁸ Alternatively, it

is important to consider that undetectable differences between the pre- and post-implementation cohorts may exist.

Interestingly, 30-day readmissions were not associated with SICU delirium either by study year or presence of delirium. This suggests that readmissions are related to other factors such as severity of illness, or complications of the disease process, and not delirium. Readmissions are both a clinical and financial problem. The Center for Medicare and Medicaid Services (CMS) began penalizing hospitals for 30-day readmissions starting in 2012.¹⁶ According to CMS, the national rate of 30-day all-cause readmissions observed for patients aged 65 and above in 2013 was 16.2%.³⁹ The average cost of a readmission for this age group for any given cause was \$13,800 (U.S. dollars) for those patients on Medicare.³⁹ A portion of these costs are likely attributed to patients with delirium being re-admitted to the hospital. In other reports of the literature, little evidence is available describing the impact of days of delirium on hospital readmissions, a key driver of healthcare costs. The downward trend observed in 30-day hospital readmissions in this study is nonetheless favorable, and perhaps with a greater number of patients receiving iLEAD-informed care, these trends will reach significance.

In both cohorts, rates of mechanical ventilation use among patients with delirium were comparable (65% vs 71%, $p = 0.504$) as were levels of sedation (RASS) ($p = 0.1198$). Unexpectedly, patients in the post-implementation cohort spent a greater number of hours ventilated (66 hours, $p = 0.032$) than patients in the pre-implementation cohort (45 hours). To maintain compliance and comfort for patients on the ventilator, sedative medications, such as propofol and benzodiazepines, are typically used. These medications have potentially psychoactive effects on the central nervous system and have been associated with the development of delirium.⁴⁰⁻⁴⁶ Greater exposure to these deliriogenic medications administered secondary to mechanical ventilation in the post-

implementation cohort may have precluded noting appreciable effects of the iLEAD intervention. The results from the SCCM *ICU Liberation Collaborative* reported that implementation of the ABCDEF bundle was associated with a decreased rates of mechanical ventilation,²⁶ thus once the iLEAD intervention achieves full strength, these results may continue to improve.

Contemporary guidelines, and the iLEAD intervention, promote lighter sedation targets (RASS goals) to minimize the negative consequences of increased exposure to deliriogenic sedatives.²² In critical care patients, literature suggests that maintaining a deep level of sedation is associated with increased ICU length of stay, longer duration of mechanical ventilation, and acquired weakness due to immobility.⁴⁷ A goal of the iLEAD intervention is to reduce the time a patient spends on the ventilator, incorporating the assistance of respiratory therapists, and spontaneous breathing trials. So, while all stakeholders may actively engage in the success of the iLEAD intervention, systems level factors related to respiratory therapist availability may explain some potential shortcomings of implementation. More research is needed to understand the interprofessional team dynamics to achieving successful outcome for these delirious patients.

Admitting diagnoses were utilized as a proxy for severity of illness measures, as more traditional measures of illness severity (*i.e.*, Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) scores) were not exportable for analysis. Overall the two cohorts were comparable ($p = 0.232$) with respect to medical diagnosis on admission. Historically, patients who develop delirium are likely to be more critically ill than non-delirious patients.^{9,48} Therefore, it is possible that improved outcomes were not present due to unmeasured differences related to severity of illness between the two cohorts not captured by admitting diagnosis. Utilizing only the admitting diagnosis did not

allow for changes in medical status and comorbidities developed during the course of the SICU stay to be included in the analysis. These may present additional factors to evaluate in prospective investigations.

Following iLEAD, the number of days where no CAM-ICU assessment was documented was drastically reduced. These results suggest that uptake of the intervention was high and support the analyses of the effect of iLEAD on delirium outcomes. Importantly, while the duration of delirious episode and number of delirious patients was similar per group, the number of patients with delirium-free/coma-free days ($p = 0.0178$) in 2018 increased significantly. Although this is primarily reflective of increased rates of screening, it allows the iLEAD team to understand delirium outcomes more fully among patients in the SICU. Literature reports delirium rates of approximately 50% in ICU populations,² however the incidence in the pre and post iLEAD cohorts were 37% and 33% respectively, suggesting that overall rates of delirium in this population are well below the reported standard. With continued fidelity to the iLEAD intervention, we postulate that rates and duration will continue to decrease.

As noted, implementation of the iLEAD protocol does not direct the nurse to utilize specific delirium interventions, rather allows them to choose from a menu of suggested interventions. Consequently, the lack of iLEAD effects may be related to nurses choosing fewer or less effective activities. At the time of data collection, the individual elements delivered were not captured in the EHR. Furthermore, the entire ABCDEF bundle had not yet been implemented. The interventions for early mobility (E) and family engagement (F) were not yet introduced during the study period. As these elements become implemented, patient outcomes may continually improve.

The results the SCCM *ICU Liberation Collaborative* shows that implementation of the ABCDEF bundle can improve patient and health system-level outcomes. These results

should embolden HUP iLEAD team; with more time and enriched implementation, patient and systems-level outcomes in the SICU, and across all ICU's implementing iLEAD across Penn Medicine, should continue to improve.

Limitations

Being an observational cohort study, patients were not randomized to receive the iLEAD intervention, thus subject to the threats of selection bias. The control group was historical, thus changes over time other than iLEAD implementation may have accounted for the findings. In addition, data collection was limited to that available in the EHR, and inconsistencies in the accuracy of the documentation is another limitation. Any conclusions drawn by this study regarding the contributions of the specific nursing's interventions implemented will require prospective validation in future studies. Lastly, because this study was conducted within a single SICU, the outcomes may not be immediately exportable to other health systems. It is possible that the patient populations and baseline processes of care for delirium management may not be generalizable to other hospitals and health systems.

Future Directions

Literature that specifically addresses delirium management interventions for older adults admitted to the SICU is limited and primarily focuses on comparing pharmacologic approaches. This paper is one of the first to evaluate the patient-centered delirium outcomes following implementation of the nurse-led iLEAD intervention in the SICU. This analysis highlights the contributions of nurses to champion this effort by evaluating the assessment, management and treatment of patients with delirium by utilizing evidence-based nurse-initiated interventions chosen from a validated list of options. The results of this study warrant prospective evaluation of the specific nurse-led iLEAD interventions employed in this study.

Conclusions

Importantly, this work examines the management of delirium among older adult patients admitted to the SICU. To date, few studies have specifically examined this patient population. These results add to the growing body of literature on how to best care for an aging patient with delirium in the critical care setting. Overall, measurable patient outcomes were achievable in the early stages of the iLEAD intervention and may inform prospective systems-level organizational change.

Figures and Tables

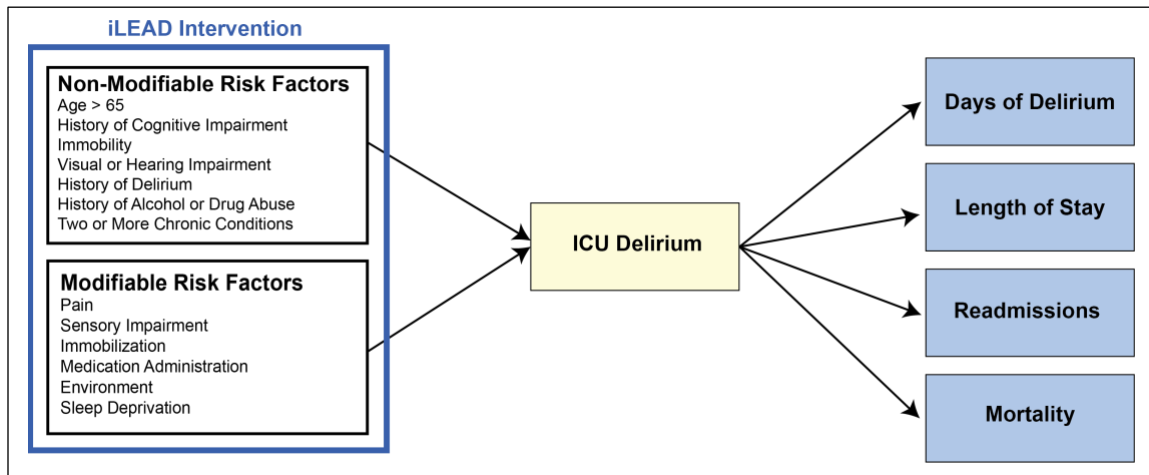


Figure 3.1 Conceptual Model of the Effects of iLEAD on ICU Delirium

This conceptual model illustrates the relationships of risk factors outlined in the iLEAD protocol for delirium to the clinical outcomes of interest. When nurses implement the iLEAD intervention, it was hypothesized that patient outcomes (days of delirium, length of stay, readmissions and mortality) would improve.

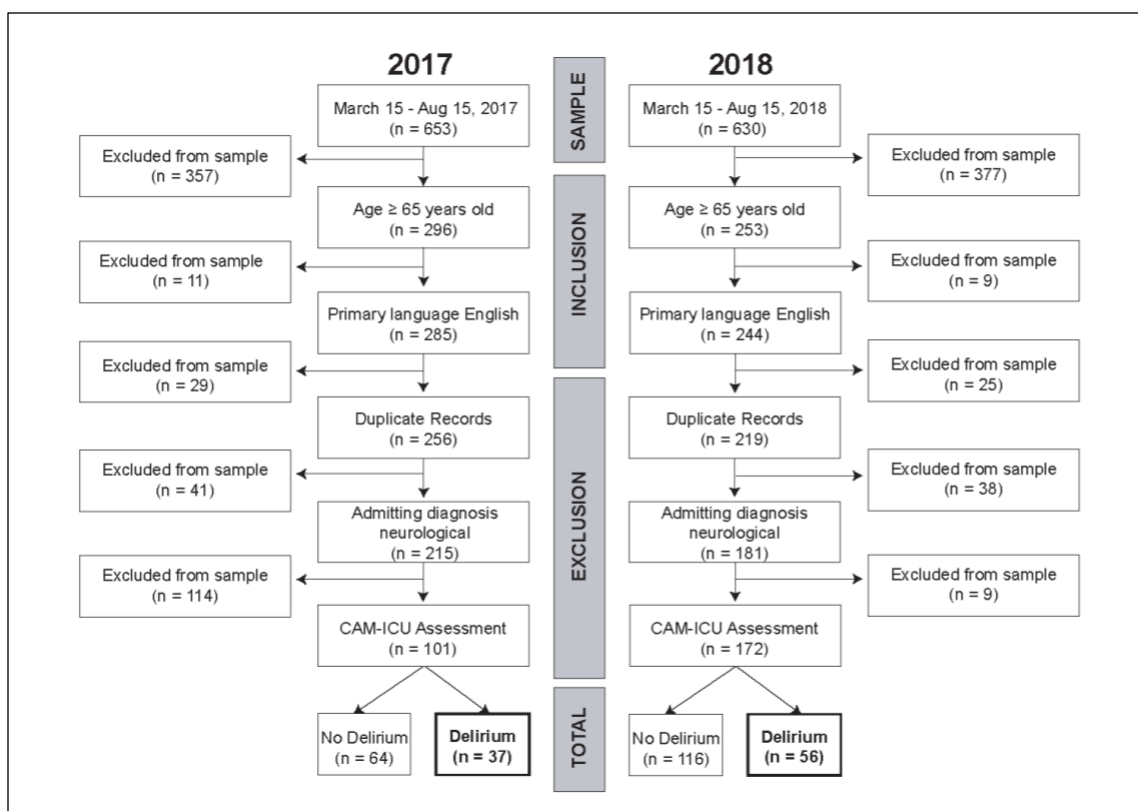


Figure 3.2 Study Sample Consort Diagram

Consort style diagram illustrating the inclusion and exclusion criteria used to evaluate the pre- and post-implementation cohorts. The 2017 sampling pool contained 101 patients and the post-implementation 2018 sampling pool, 172 patients. Of the total sample, 37 and 56 patients screened positive for delirium in the 2017 and 2018 cohorts respectively and were included in the analysis.

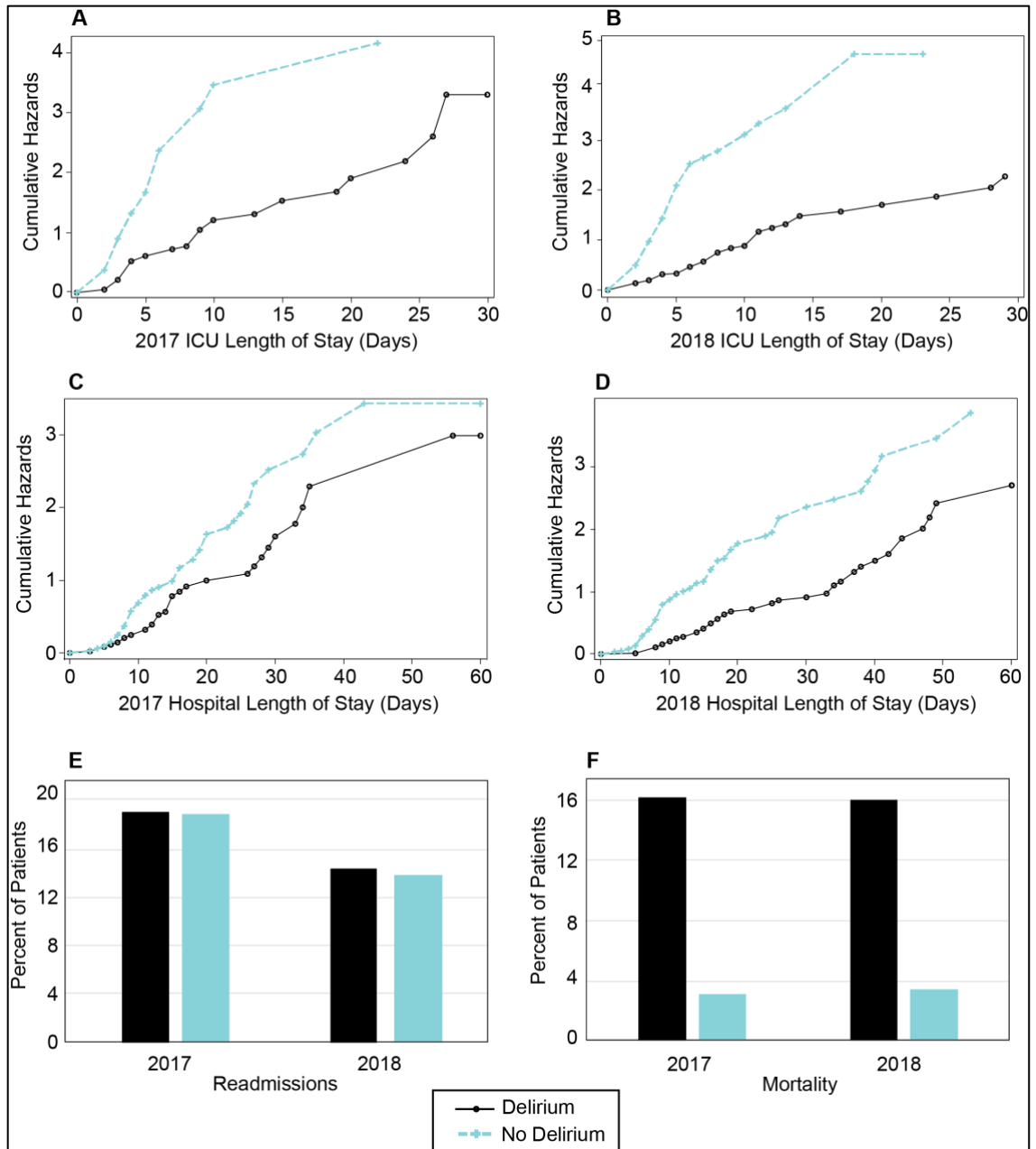


Figure 3.3 Outcomes in Delirious and Non-Delirious Patients

A) ICU Length of Stay 2017 **B)** ICU Length of Stay 2018. **C)** Hospital Length of Stay 2017. **D)** Hospital Length of Stay 2018. **E)** 30-Day Readmission Rates. **F)** 30-Day Mortality Rates.

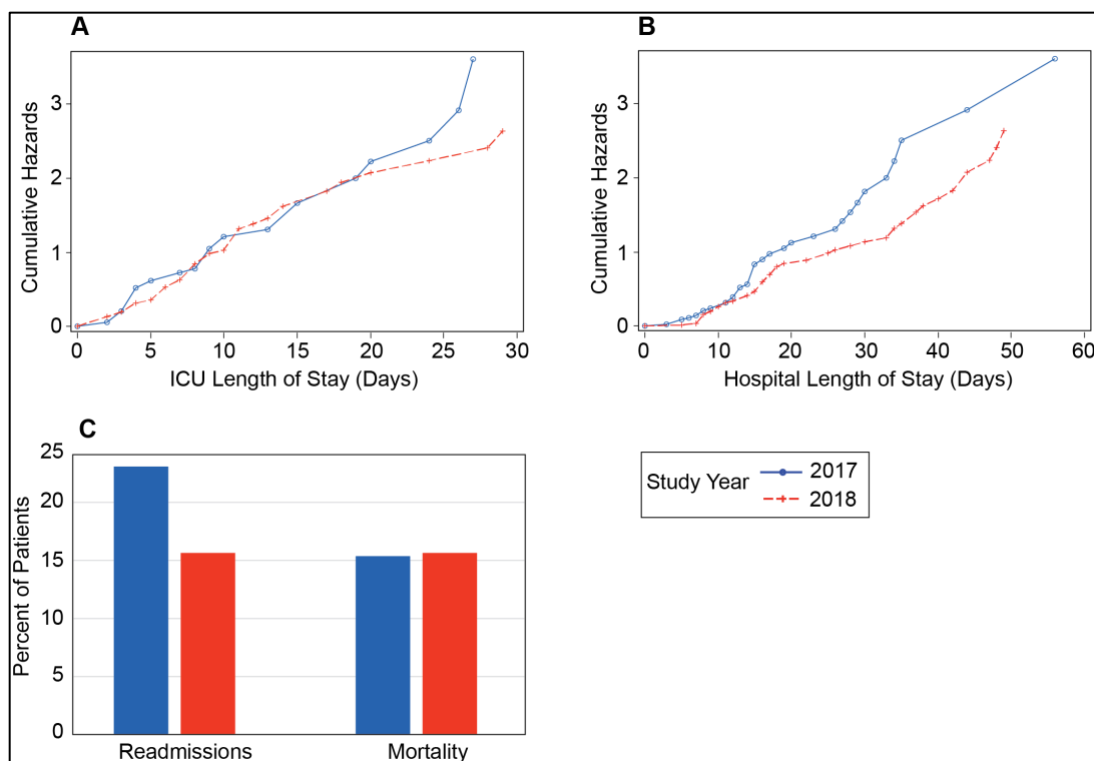


Figure 3.4 Pre-implementation (2017) and Post-implementation (2018) Outcomes of Patients with Delirium

A) ICU Length of Stay. **B)** Hospital Length of Stay. **C)** 30-Day Readmissions and Mortality.

Table 3.1 Characteristics of Sample

	2017 N=101		2018 N=172		
Characteristics	No Delirium	Delirium	No Delirium	Delirium	p-value[#]
Number of Patients	64	37 (37%)	116	56 (33%)	0.511
Age (years), median (range)	72 (65-92)	76 (65-91)	72 (65-92)	73 (65-88)	0.1278
Sex (male), N (%)	40 (63%)	22 (59%)	75 (65%)	33 (59%)	0.959
Weight (kg), median (range)	81 (47 – 129)	77 (50-120)	80 (45-133)	81 (44-172)	0.2457
Race					0.593
Asian	1	0	1	0	
Black or African American	9	4	9	7	
Hispanic	0	1	1	0	
Unknown	1	5	15	6	
White	53	25	90	42	
Other	0	2	0	1	
Mechanical Ventilation % median hours (range)	30% 19 (2-168)	65% 45 (7-168)	25% 18 (1-168)	71% 66 (9 -168)	0.504 0.0320*
RASS, median (range)	0 (-3 to 1)	-1 (-3 to 1)	0 (-4 to 0)	-1 (-2 to 0)	0.1198
ICU Length of Stay, median (range)	3 (2,23)	7 (2, 44)	3 (2,23)	8 (2, 41)	0.7499
Hospital Length of Stay, median (range)	10.5 (3,139)	15 (3, 89)	9 (2,58)	17.5 (5,83)	0.1909
Days of Delirium, mean ± sd	--	2.14 ± 1.4	--	2.60 ± 1.7	0.1660
Admitting Diagnosis (ICD-10-CM Codes)					0.232
A00-B99 Infectious and parasitic diseases	3	1	2	5	0.232
C00-D49 Neoplasms	15	6	27	9	0.985
E00-E89 Endocrine, nutritional and metabolic disease	0	1	1	0	0.398
H60-H95 Diseases of ear and mastoid process	1	1	1	0	0.398
I00-I99 Diseases of circulatory system	4	3	16	11	0.128
J00-J99 Diseases of respiratory system	1	3	3	0	0.06
K00-K95 Diseases of digestive system	18	10	27	14	0.827
L00-L99 Diseases of the skin and tissue	2	0	0	0	--
M00-M99 Diseases of musculoskeletal system	3	2	1	2	1.0
N00-N99 Diseases of genitourinary system	3	2	4	1	0.561
Q00-Q99 Congenital malformations/abnormalities	0	1	0	0	0.398
R00-R99 Symptoms, signs & abnormal labs	10	6	25	11	0.676
S00-T88 Injury, poisoning & other external causes	3	1	6	3	1.0
Z00-Z99 Factors of health status	1	0	2	0	--

*indicates statistical significance. #p-values reflect comparison of patients **with delirium** between 2017 and 2018.

Abbreviations: (sd) standard deviation; (kg) kilograms; (ICD-10-CM) International Classification of Diseases, Tenth Revision, Clinical Modification.

Table 3.2 Daily CAM-ICU Assessments

CAM-ICU Assessment Values	2017	2018	p-value
Positive	0.78 ± 1.33	0.85 ± 1.56	0.7200
No Test Performed	1.1 ± 1.4	0.45 ± 0.65	<0.001*
Negative	2.45 ± 1.66	2.94 ± 1.69	0.0178*
Unable to Assess (Coma)	0.29 ± 0.79	0.27 ± 0.77	0.8873

*indicates statistical significance.

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Chapter 4

Evaluating the relationships among pain, opioid analgesic administration and the onset of delirium in older adults in the surgical intensive care unit

Abstract

Background. Analgesics are among the most commonly administered medications to patients in the surgical intensive care unit (SICU). Literature suggests that both untreated pain and pain management with opioids are each independent precipitating factors for the development of delirium. However, there is limited and mixed evidence to support these assumptions, particularly among older adults in the SICU.

Objectives. This cross-sectional secondary data analysis evaluates the relationships among pain severity, its management with opioids, and the onset of delirium in older adult patients admitted to the SICU.

Methods. A convenience sample of consecutive patients aged 65 or greater admitted to the SICU over a 5-month period were examined (n = 172). Averaged 24-hour pain severity scores and opioid exposure were extracted from the electronic health record and examined with respect to the onset of next day delirium.

Results. Opioids (chi-square [χ^2], 12.60, $P = .0004$), but not pain (χ^2 , 3.61, $P = .0573$) were significant in predicting next-day delirium status. Controlling for pain severity, patients exposed to opioids exhibited odds of developing delirium were 2.5 times those of patients not exposed to opioids (95% Confidence Interval: 0.371-1.485).

Conclusions. Examination of the relative roles of pain and opioid administration on the development of delirium experienced by this population provides evidence that opioids predict the onset of next-day delirium, which has implications for the use of these commonly administered medications to older adults in the SICU setting. In an effort to prevent delirium, future research should focus on both pharmacological and non-pharmacological opioid-sparing pain management approaches.

Introduction

Delirium is believed to occur in approximately 50% of all older hospitalized adults.¹ It is defined as an acute change in cognition and attention not described by a pre-existing condition, established or evolving dementia.² Delirium is a known risk factor for poor outcomes in patients admitted to the surgical intensive care unit (SICU),³⁻⁶ and is associated with longer hospital and intensive care unit (ICU) length of stay,⁷ persistent functional decline^{6,8-13} and mortality.^{3,14-17} Recent studies have shown that outcomes worsen as the duration of delirium increases.^{9,18,19} Further, delirium significantly increases health care costs, ranging from an additional \$16,303 to \$64,421 per patient.²⁰

To date, no single pharmacological intervention has been shown to be effective in treating delirium.⁶ Multiple variables are believed to contribute to the development of delirium, including underlying health conditions, inflammatory processes, neurotransmitter disruptions, physiological stressors, and metabolic derangements,^{6,21-24} however the pathophysiology of delirium remains poorly understood. While numerous risk factors for delirium have been identified,^{17,25-28} many are non-modifiable, such as admission to the ICU, duration of illness, and increased age.²⁵⁻²⁷ Current interventions for the prevention of delirium include ensuring pain, a modifiable risk factor, is adequately managed while minimizing the use of medications to treat pain, such as opioids.^{28,29} The finding that both pain, and its management, can contribute to the onset of delirium suggests that their relative roles in improving delirium outcomes warrant further investigation.

Pain is a potent and common stressor present in approximately 80% of critically ill patients admitted in the SICU,³⁰ and is commonly identified as a precipitating factor for the development of delirium.³¹⁻³⁴ However, there is surprisingly limited evidence to support a causal association between untreated pain and the development of delirium. Several older studies have examined how the presence of postoperative pain may

contribute to the occurrence of delirium, however the findings are mixed.³¹⁻³⁴ Because the relationship between pain and delirium is not well-established, it is unclear that the pharmacological management of pain will prevent delirium in critically ill patients.

Medications are thought to account for 12% to 39% of all cases of delirium.²⁵ Specifically, results from systematic reviews show that opioid analgesics,^{28,29} hypnotics,³⁵⁻³⁸ benzodiazepines,^{37,39} anticholinergic agents,^{25,32} antihistamines,²⁵ and corticosteroids^{7,25} are each associated with the development of delirium. Opioids are the most common analgesics administered to patients following surgery, and morphine, fentanyl, and hydromorphone are those most frequently used.^{28,29} An association has been reported between opioid use and the development of delirium in patients admitted to an ICU²⁶ and with the use of opioids in general across hospital settings.²⁵ However, these studies have limited generalizability and are graded of low to moderate quality evidence.^{25,26,28}

The aim of this investigation was to evaluate the relationships among acute postoperative pain severity, opioid analgesic administration and the onset of delirium among older adults in the SICU. As outlined in the conceptual framework (see **Figure 4.1**), it is hypothesized that pain severity and opioid use are each positively correlated with the onset of delirium, and that opioid administration will decrease pain. These analyses enable comparison of the relative and combined roles of pain severity and opioid administration on delirium onset, providing direction for the management of these delirium risk factors.

Methods

Study Design

Utilizing a longitudinal study design, data were collected from a single hospital SICU to examine the relationships among the onset of delirium, pain severity, and opioid analgesic administration in older adult patients aged 65 years or older. The observation

period was from March 15, 2018 to August 15, 2018. Daily average pain scores, daily worst pain scores, and daily opioid medication exposure were calculated from the time of ICU admission until discharge or up to 7 days and inspected to see how these predicted next-day delirium. Based on other reports in the literature, the sampling period was limited to 7 days as patients whose delirium emerges beyond 7 days may be suffering from an underlying medical abnormality or complications that are not representative of SICU delirium.^{26,40}

All data were extracted from the electronic health record (EHR). The University of Pennsylvania Institutional Review Board approved this exempt research project and granted a waiver of informed consent prior to its initiation. Study design and reporting criteria outlined in the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) were followed.⁴¹

Sample and Setting

Study participants were selected from a 24-bed SICU at the Hospital of the University of Pennsylvania, which is a 795-bed, urban academic teaching hospital. Inclusion criteria were; age ≥ 65 , English speaking, admitted to the SICU for >24 hours, and screened for delirium using the confusion assessment method for the intensive care unit (CAM-ICU) anytime between day 1 and day 7 during their admission to the SICU. Patients were excluded if they had an admitting diagnosis related to neurological or central nervous system injury; for patients readmitted to the SICU, only the index admission was evaluated.

Measures

Delirium. Delirium was identified using the highly reliable and well-validated CAM-ICU tool.⁴²⁻⁴⁴ Delirium was defined as one positive CAM-ICU screening in a 24-hour period calculated beginning at the time of ICU admission through ICU discharge or up to 7 days. Delirium onset was defined as being free of delirium in the preceding 24-hours.

The CAM-ICU assessment was completed by trained nurses every 12 hours and recorded in the EHR.

Pain. The nursing staff completed pain assessments every 4 hours beginning on admission to the SICU. Pain severity was measured using a self-reported 10-point numeric rating scale, where 0 indicates no pain and 10 indicates worst pain ever. Pain scores were extracted from the EHR and averaged for each 24-hour period during days 1-7, providing an average daily pain score; in addition, the highest (worst) pain score recorded each day was extracted for analysis.

Opioid Exposure. Daily opioid use was also extracted from the EHR for analysis. The opioids to which patients were exposed included; acetaminophen-codeine #3, fentanyl, hydromorphone, methadone, morphine, oxycodone, oxycodone-acetaminophen and tramadol. Routes of administration varied by medication and comprised oral, intravenous, epidural and patient controlled analgesia. Exposure was defined as any one instance of opioid administration (any type or route) during a 24-hour period.

In addition, patient characteristics including age, sex, weight, race and admitting diagnosis were extracted from the EHR to describe the population of interest. Use of mechanical ventilation, Richmond Agitation-Sedation Scale (RASS) scores and sedative medications (benzodiazepines and propofol) were also examined as potential covariates.

Statistical Methods

To compare patients who developed delirium with those who did not, student's t-tests for independent groups were used to assess continuous variables and chi-square (χ^2) tests were used to assess categorical variables. P-values of 0.05 or less were considered to indicate statistical significance. Data were closely examined for any systematic patterns of missingness. Pain severity (24-hour average, daily worst) and opioid exposure were assessed as predictors of next-day delirium status using generalized estimating equation

models. The generalized estimating equations method was applied using the Genmod procedure in SAS, which is able to account for correlation within subjects' repeated observations and allows for the assessment of time varying exposure covariates. Daily pain (24-hour average) and opioid exposure were assessed together as predictors of next-day delirium status in a multivariable general estimating equation model. Lastly, daily pain (24-hour average), opioid exposure, propofol exposure, mechanical ventilation and RASS were assessed together as predictors of next-day delirium status in a multivariable general estimating equation model.

Results

The final sample was comprised of 172 patients, 56 of whom experienced delirium during the SICU stay and 116 who did not. Demographically, the two cohorts were comparable (**Table 4.1**) and there were no differences in admitting diagnosis. As noted, both pain (24-hour average) and worst pain scores, averaged across Days 1 to 6, were slightly more severe for patients who did not develop delirium, although not to a statistically significant degree. Delirium was significantly associated with a higher number of days exposed to opioids ($P = .0018$) and propofol ($P < .001$) in comparison to patients who did not develop delirium, however not associated with a number of days exposed to benzodiazepines ($P = .1253$). In addition, patients who developed delirium received mechanical ventilation ($P < .001$) and for a greater number of hours ($P < .001$).

When assessed using generalized estimating equation models, neither average pain score (χ^2 , 1.02, $P = .3135$) nor worst pain score (χ^2 , 0.93, $P = .3353$) were found to be significantly associated with next-day delirium onset (**Table 4.2**). There was however, a statistically significant association between opioid exposure and next-day delirium status (χ^2 , 11.53, $P = .0007$). Specifically, the odds of next-day delirium for a patient treated with opioids were 2.2 times those of a patient not treated with opioids (95% Confidence Interval [CI]: 1.300-3.638). In that propofol was found to be significantly associated with

delirium in the initial descriptive analysis, it was assessed as a predictor of next-day delirium in a generalized estimating equation model. Propofol exhibited a statistically significant association with next-day delirium status (χ^2 , 10.29, $P = .0013$), and the odds of next-day delirium for a patient receiving propofol were 2.7 times those of patients who were not exposed to propofol (CI: 1.457-4.916).

Daily pain severity (average) and opioid exposure were assessed together as predictors of next-day delirium status in a multivariable general estimating equation model (**Table 4.3**). Again, opioids (χ^2 , 12.60, $P = .0004$), but not pain (χ^2 , 3.61, $P = .0573$) were statistically significant in predicting next-day delirium status. When controlling for pain severity, patients exposed to opioids exhibited odds of next-day delirium that were 2.5 times those of patients not exposed to opioids (CI: 0.371-1.485).

Because propofol exposure was a strong predictor of next day delirium in the descriptive analysis, it plus the indications of propofol administration (mechanical ventilation, RASS score), were assessed with daily pain severity (average) and opioid exposure as predictors of next-day delirium status in a multivariable general estimating equation model. Opioids (χ^2 , 5.02, $P = .0251$) remained statistically significant in predicting next-day delirium status; however pain (χ^2 , 0.99, $P = .3189$), propofol exposure (χ^2 , 2.75, $P = .0974$), use of mechanical ventilation (χ^2 , 1.86, $P = .1723$) and RASS (χ^2 , 1.82, $P = .1771$) were not statistically significant in predicting next-day delirium status (**Table 4.4**). In the multivariable model, the odds of next-day delirium for a patient exposed to opioids were 1.9 (CI: 1.0042 – 3.4925) and for patients exposed to propofol 1.9 (CI: 0.9568 – 3.7922) times those of a patient not exposed to either drug respectively.

Discussion

Both untreated pain and opioid analgesics have been implicated in the development of delirium in older adults in the intensive care unit setting.^{31,32,34,45} Our analyses evaluated the relative role of these risk factors in predicting delirium onset in a well-characterized sample of older adult patients in the SICU. The results indicate that medications play a greater role in delirium development than pain and suggest that medication administration may be a modifiable risk factor to mitigate its occurrence.

Pain regularly occurs in adult ICU patients and can impede patients from actively participating in their care (e.g., early mobilization, participation in spontaneous breathing trials, weaning from mechanical ventilation).⁴⁵ The stress response produced by acute pain can lead to negative, both short- and long-term consequences for adults in the ICU. Specifically, acute pain is a risk factor for developing chronic, persistent, often neuropathic pain.⁴⁶ Untreated pain is an oft-cited precipitating factor of delirium; in fact, The Society for Critical Care Medicine identifies pain as a modifiable risk factor for the development of delirium.⁴⁵ Nevertheless, empirical evidence supporting its relationship on the development of delirium is surprisingly limited^{32,34,47} and few studies have examined how the presence of pain contributes to the occurrence of delirium in the SICU population specifically.³⁴

A study of 361 patients undergoing major elective noncardiac surgery evaluated pain at rest, pain with movement, and maximum pain. The authors found that in when stratified by surgical procedure, patients with higher pain scores at rest were at increased risk of developing delirium of the three postoperative days studied (risk ratio 1.2, $P = 0.015$).³² Similarly, Vaurio and colleagues studied 333 older adults scheduled for non-cardiac surgery concluded that severe pain (OR, 3.7; 95% CI 1.5 to 9.0) was independently associated with the development of delirium.³⁴ Newer evidence has not sufficiently drawn definitive conclusions between the relationship of pain and delirium,

which may be related to the practice of aggressively treating pain in the acute care setting.

Our results demonstrated that average and worst pain score were not predictive of next-day delirium status. As noted, weekly averaged pain scores were in the low to moderate range. Although insignificant, patients with delirium had lower pain severity ratings than those patients without delirium, suggesting that opioid provision, although deliriogenic, was also an effective analgesic. The results of this investigation provide additional support that while unrelieved pain may lead to its own detrimental consequences, it may not be predictive of the development of delirium and suggest that pain management with opioids may be responsible for confounding this relationship.

Consistent with the results of a systematic review,²⁵ opioids were a strong predictor of delirium onset, more than doubling the odds of delirium developing the day following opioid administration (**APPENDIX C**). After evaluating the literature, two studies have indicated protective effects of opioids reporting reduced rates of delirium,^{48,49} four studies show no association between opioids and delirium status,⁵⁰⁻⁵³ and seven studies attributed opioid use to the development of delirium.^{25,26,47,54-57} Our results will add to this growing body of literature implicating opioid use as a risk factor for delirium.

Opioids have known psychoactive and depressant effects on cortical function, resulting in diminished cognitive performance, which has been implicated in the decline in cognitive function hallmark of delirium.⁵⁸ Opioid-induced delirium is thought to be the result of underactivity of the cholinergic system.^{1,59} In the central nervous system, cholinergic projections from the basal forebrain to the thalamus and cortex are critical in supporting key cognitive functions, such as maintaining alertness, sustaining attention, and learning and memory.⁶⁰⁻⁶² Opioids appear to impair cognitive processing, leading to the development of delirium, due to obstruction of this vital cholinergic transmission.^{63,64} Inhibition of acetylcholine from morphine has also been implicated in decreasing rapid

eye movement (REM) sleep and disrupt sleep architecture.⁶⁵ These perturbations in sleep architecture may then, in turn, affect arousal and lead to impaired attention, which are early indicators of the development of delirium.⁶⁶

Disruption of the cholinergic system has also been associated with the memory deficits in Alzheimer's disease. A substantial proportion of patients who survive delirium are likely to experience long-term cognitive impairment similar to mild Alzheimer's disease^{6,8-13} for up to one year post-discharge.¹⁹ A recent study placed the odds of requiring of institutional care post-hospitalization at rates 2.4 times higher in patients who suffer from delirium than those who did not,¹⁷ suggesting that opioid exposure in the SICU may not only be associated with delirium onset, but also post-delirium memory deficits. The results of this study add to the growing body of literature reporting an association between opioid use and the development of delirium in patients admitted to an ICU^{25,26,67} and with the use of opioids in general across hospital settings.²⁵

Historically, benzodiazepines (*i.e.*, midazolam and lorazepam) and propofol have routinely been used to provide sedation in the ICU. Older guidelines recommended midazolam for short-term sedation, lorazepam for long-term sedation, and propofol for patients requiring occasional awakenings.⁶⁸ As an emphasis on delirium-related patient centered outcomes have become more prevalent, trials began implicating benzodiazepines as a likely culprit for delirium.^{37,39,69} While this association was not noted in our sample, exposure to benzodiazepine was limited and under-powered to capture this effect (post-hoc power analysis, 33% power to detect statistical significance at the alpha = 0.05 level). Low rates of exposure to benzodiazepines in this sample likely reflect benzodiazepine-sparing practices in the SICU to avoid deliriogenic effects.

The 2018 Society of Critical Care Medicine guidelines now recommend propofol, over benzodiazepines, as first-line sedation for most patients in the ICU.^{45,70} Interestingly, while significantly associated with delirium alone, after controlling for

mechanical ventilation and RASS as covariates, the deliriogenic effect of propofol on next day delirium was weakened. Propofol is routinely used due to its quick onset, short duration of action, and relatively low cost.^{38,63} While exposure to propofol has the potential for sedative and psychoactive effects such as impaired memory and delayed motor performance,⁷¹ the mechanism by which it causes delirium is unclear. A review article by Brown and colleagues cite evidence from *in vitro* studies suggesting that propofol may interact with acetylcholine receptors.⁷² Similar to opioids, this cholinergic deficit may also be responsible for propofol delirium-inducing side effects.

Our finding that propofol exposure was associated with next-day delirium status, support and extend those of other studies that have examined the association between propofol and delirium. The association between delirium and propofol use has been evaluated in 15 studies; three descriptive and 12 comparison studies (**APPENDIX D**). Two out of three descriptive studies⁷³⁻⁷⁵ correlated propofol administration with increased rates of delirium. In a study of 149 patients admitted to the ICU, 69 developed delirium (46.3%) and propofol was administered to 23 patients (33.3%) of these patients, compared to just 6 patients (7.5%) without delirium ($P < .001$).⁷⁴ In a sample of 115 patients, Bryczkowski and colleagues, reported higher average cumulative doses of propofol in patients with delirium (6 mg/kg/d vs. 1 mg/kg/d; $P < .001$).⁷⁵ Finally, a study of 451 patients undergoing spinal surgery found that 42 patients (9.3%) developed delirium, and there was no appreciable difference in the use of propofol between those who developed delirium and those who did not.⁷³

As the hallmark of routine sedation, propofol is often used as an active comparator in clinical trials evaluating alternative medications for the reduction of delirium outcomes in the ICU. When used as a comparator in clinical trials, some, but not all studies confirm that propofol results in worse delirium-related outcomes. Comparators included one study of opioids, one study of benzodiazepines and ten studies utilizing

dexmedetomidine. A retrospective study of 100 patients compared fentanyl sedation ($n = 50$) versus traditional sedation with propofol ($n = 50$) found no difference in the development of delirium between groups ($P = .80$).⁵³ In a sample of 140 patients admitted to the ICU receiving propofol or benzodiazepines for sedation, higher daytime administration of propofol was marginally ($P = .60$) associated with next-day delirium onset.⁷⁶ Of the ten studies evaluating propofol versus dexmedetomidine for the reduction of delirium, no study reported propofol superior to dexmedetomidine for the reduction or prevention of delirium. Four studies reported superiority with dexmedetomidine,^{35,36,77,78} and six studies showed no difference in the incidence of delirium between groups.^{38,79-83} Ultimately, more studies are needed to understand the role of propofol as a precipitating factor in the development of delirium. The results of this investigation add to the growing body of literature, suggesting that even a single exposure to propofol may increase the likelihood for developing delirium in the SICU.

Sedatives, like propofol and benzodiazepines, are regularly used in the ICU to mitigate the agitation associated with mechanical ventilation. Recent literature indicates that both maintaining a deep level of sedation (measured by RASS) and longer duration of mechanical ventilation are associated with the development of delirium, increased ICU length of stay, and acquired weakness due to immobility.⁸⁴ Because propofol exposure was significant in the exploratory analysis, RASS and use of mechanical ventilation were added as covariates to the final model to test their association with the onset of next day delirium status. Notably, patients with delirium spent approximately 66 hours (median) on mechanical ventilation compared to just 18 hours in patients without delirium. In the multivariable analysis, mechanical ventilation did not increase the odds of next day delirium, suggesting that the medication administered to manage mechanical ventilation (propofol), not the ventilation itself, was associated with the development of next-day delirium. Importantly, RASS between the two groups was similar with average scores in

range of light sedation (RASS = 0, -1), and was not significantly associated with the development of next day delirium. These analyses enabled comparison of the relative and combined roles of pain severity, opioid and propofol exposure, mechanical ventilation and RASS on the onset of delirium, providing direction for management of these modifiable delirium risk factors.

The role of opioids and propofol in the development of delirium may be due to interruptions of the natural sleep-wake cycles.^{6,66,70,85} Recent evidence supports the promotion of sleep, aiming to provide at least 4 hours of sleep per night, for the reduction of delirium.⁸⁶ One study has reported that delirium was associated with greater circadian sleep-cycle disruption and increased daytime sleep.⁸⁵ The Society of Critical Care Medicine updated their Pain, Agitation and Delirium (PAD) guidelines were recently updated to now include Immobility (rehabilitation/mobilization), and Sleep (disruption) (PADIS). Importantly, only two of the 37 recommendations are graded as strong; most are conditional (the evidence is conflicting, low quality, insufficient). The specific recommendations related to sleep are conditional, with low to very low evidence. The committee hopes that by adding sleep to the guidelines it will encourage the completion of pragmatic, patient-centered research to answer these important critical care demands.

Limitations

There are several important limitations of this study. Due to limitations in the dataset, only dichotomous medication exposures (opioid, propofol, benzodiazepines) were evaluated. Therefore, potential effects of dose or route of administration were unable to be derived. In addition, no medication exposure or pain score information was available prior to arrival in the ICU, so their predictive role for day 1 delirium status was unable to be evaluated. Also, as noted, aggressive pain management and low rates of benzodiazepine use in the SICU may have precluded a true assessment of the effects of each on delirium onset.

The approach and findings are limited to the data collected during the defined study period. Due to lack of randomization to medication exposure or pain levels, selection bias is a potential threat to the internal validity of the study, and it is possible the observed changes may not be attributed to the medication exposure. It is also possible that the patient populations and baseline processes of care for delirium management at HUP may not be generalizable to other hospitals and health systems.

Future Directions

Literature that specifically addresses the relationships among delirium, pain severity and analgesia and sedation management for older adults admitted to the SICU is growing. In that opioid exposure was the strongest predictor of delirium onset in this study, opioid-sparing approaches may be the best intervention to prevent its development. Pragmatic clinical trials are needed to prospectively evaluate if reduction in opioid administration, and pain control with non-opioid pharmacologic strategies are successful in reducing the onset of delirium. As health care systems respond to the opioid epidemic, opioid-sparing strategies for pain management in acute care settings are encouraged.⁸⁷ Therefore, other types of analgesics and non-pharmacologic pain management approaches may be considered as covariates in future analyses.

Contemporary guidelines, such as *ICU Liberation*, encourage lighter sedation targets to minimize the negative consequences of deep sedation,^{45,70} and consequently, may reduce exposure to propofol. A number of alternative pharmacological strategies to both prevent and treat delirium have been, and continue to be, highly tested including, antipsychotic medications,⁵⁴ acetylcholinesterase inhibitors,⁸⁸ melatonin,⁸⁹ and gabapentin.⁸⁸ Studies purport that dexmedetomidine may reduce or prevent delirium,^{6,22,24,66,77,90-93} and recent studies of intravenous acetaminophen are receiving praise as a possible alternative to opioids due to the analgesic and inflammatory

properties of the drug.⁸³ Thus far, no single strategy has amassed enough evidence to support its role in delirium prevention or treatment.

Conclusions

This study is among the few to characterize the relative relationships among pain, opioid analgesia and sedation with propofol in the onset of delirium in older adults admitted to the SICU. Pain was not found to be a contributor to next-day delirium status however, both opioid and propofol exposure were strong predictors of delirium onset in this sample. Future research should focus on medication-sparing approaches to manage pain and achieve sedation as a means to prevent delirium.

Figures and Tables

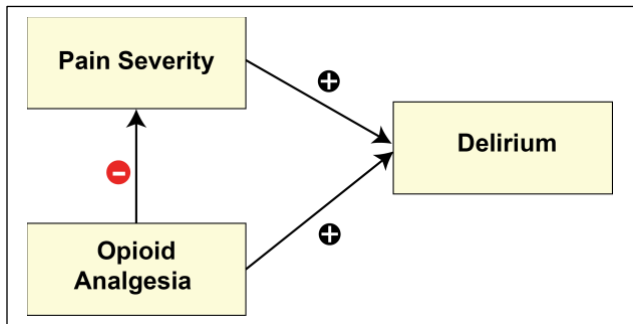


Figure 4.1 Conceptual Model of the Effects of Pain and Opioid Analgesia on Delirium

This conceptual framework postulates that pain severity and opioid use are each positively correlated with the onset of delirium, and that opioid administration will decrease pain.

Table 4.1 Characteristics of Sample

Characteristics	No Delirium	Delirium	p-value
Number of Patients	116	56	0.464
Age (years), median (range)	72 (65, 92)	73 (65, 88)	0.6249
Sex (male), n (%)	75 (65%)	33 (59%)	0.467
Weight (kg), median (range)	80 (45, 133)	81 (44, 172)	0.9980
Race			0.530
Asian	1	0	
Black or African American	9	7	
Hispanic	1	0	
Unknown	15	6	
White	90	42	
Other	0	1	
Medication Exposures, mean days \pm sd			
Opioids	1.2 \pm 1.7	2.0 \pm 2.2	<0.0018*
Propofol	0.2 \pm 0.7	1.1 \pm 1.6	<0.001*
Benzodiazepines	0.2 \pm 0.7	0.4 \pm 1.0	0.1253
Pain Scores (0-10) Days 1 to 6, median (range)			
Average	3.7 (0, 8.7)	2.7 (0, 8.2)	0.2453
Worst	4.2 (0, 9.8)	3.5 (0, 9.3)	0.1936
Mechanical Ventilation %	29 (25%)	40 (71%)	<0.001*
median hours (range)	18 (1-168)	66 (9 -168)	<0.001*
RASS median (range)	0 (-4 to 0)	-1 (-2 to 0)	0.39
Admitting Diagnosis (ICD-10-CM Codes)			0.365
A00-B99 Infectious and parasitic diseases	2	5	0.26
C00-D49 Neoplasms	27	9	0.265
E00-E89 Endocrine, nutritional and metabolic disease	1	0	1.0
H60-H95 Diseases of ear and mastoid process	1	0	1.0
I00-I99 Diseases of circulatory system	16	11	0.335
J00-J99 Diseases of respiratory system	3	0	0.552
K00-K95 Diseases of digestive system	27	14	0.827
M00-M99 Diseases of musculoskeletal system	1	2	0.250
N00-N99 Diseases of genitourinary system	4	1	1.0
R00-R99 Symptoms, signs & abnormal labs	25	11	0.752
S00-T88 Injury, poisoning & other external causes	6	3	0.969
Z00-Z99 Factors of health status & contact health services	2	0	1.0

*indicates statistical significance.

Abbreviations: (kg) kilogram; (sd) standard deviation; (ICD-10-CM) International Classification of Diseases, Tenth Revision, Clinical Modification.

Table 4.2 Odds of Pain and Medication Predicting Next-Day Delirium

	chi-square	p-value	Odds Ratio	95% Confidence Interval
Pain Score - Average	1.02	0.3135	0.95	0.86 - 1.05
Pain Score - Worst	0.92	0.3353	0.96	0.88 - 1.05
Opioid Exposure	11.53	0.0007*	2.2	1.30 - 3.64
Propofol Exposure	10.29	0.0013*	2.7	1.5 - 4.92

*indicates statistical significance

Table 4.3 Predictors of Next-Day Delirium

	chi-square	p-value	Odds Ratio	95% Confidence Interval
Pain Score - Average	3.61	0.0573	0.90	0.81 – 1.00
Opioid Exposure	12.60	0.0004*	2.50	1.45 - 4.42

*indicates statistical significance

Table 4.4 Multivariate Predictors of Next-Day Delirium

	chi-square	p-value	Odds Ratio	95% Confidence Interval
Pain Score - Average	0.99	0.3189	0.95	0.84 – 1.06
Opioid Exposure	5.02	0.0251*	1.9	1.0042 – 3.49
Propofol Exposure	2.75	0.0974	1.9	0.96 – 3.79
Mechanical Ventilation	1.86	0.1723	0.43	0.14 - 1.31
RASS	1.82	0.1771	0.58	0.27 - 1.26

*indicates statistical significance

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Chapter 5

Discussion

Delirium affects more than 2.6 million older adults admitted to the intensive care unit (ICU) each year and can be a life-threatening.¹ Nurses are uniquely prepared to drive solutions to address this clinically significant problem by recognizing risk factors and initiating evidence-based nursing interventions. The Hospital of the University of Pennsylvania created the *ICU Liberation Executing the ABCDEF Bundle Daily* (iLEAD) protocol to implement the ABCDEF bundle and reduce the consequences of delirium in the ICU. The **overall objectives** of this research were to describe the effectiveness of the iLEAD intervention to reduce the burden of delirium and its associated adverse outcomes, and to examine the relative roles of two modifiable risk factors associated with delirium (pain, opioid administration).

Chapter 2 of this proposal served as the groundwork for the research aims and hypotheses by providing an increased understanding of the most current treatment strategies, delirium research methods, and the issues associated with identifying and managing delirium. Appreciative of deficits in delirium identification and management, **Chapter 3** evaluated the efficacy of a new nurse-led preemptive identification, treatment and management strategy (iLEAD) to improve delirium-related patient and clinical outcomes (days of delirium, length of stay, readmissions and mortality). Lastly, **Chapter 4** continued investigation into the link between pain, opioid pain management, and the onset of delirium. Overall, this dissertation research has important implications in moving forward nurse-driven approaches to the clinical care of older adults in critical care environments at risk for experiencing delirium.

This dissertation research contributes to the existing knowledge that delirium is detrimental to the health of older adults. Importantly, the work brings attention to proposed risk factors for delirium in surgical intensive care patients, pain, and its

treatment with opioids. Continued investigation into the relative roles of pain and pain management on the onset of delirium will be invaluable for future delirium research and is vital to improve patient outcomes in older adults.

Major Findings from Chapter 2

There is inadequate, conclusive, evidence supporting pharmacologic interventions for the treatment or prevention of delirium. This integrative review of 16 peer-reviewed publications examined the efficacy of the novel alpha-2 agonist, dexmedetomidine in lowering the incidence of delirium compared to other analgesic and sedation strategies. The results of this analysis suggest that dexmedetomidine administration does not reduce the incidence and/or duration of delirium uniformly across all patient populations studied. However, there was good evidence to support postoperative administration of dexmedetomidine reduces delirium in patients, particularly following cardiac surgical procedures, supporting the results of recent meta-analysis.² Further research is needed to determine the benefits of dexmedetomidine in patients on mechanical ventilation and optimal timing and duration of administration.

As with much of the research in this field, the focus was on evaluating pharmacologic strategies to treat delirium. In future work, non-pharmacologic delirium interventions, pain management, and quality of sleep need to be included in these validation studies. Importantly missing from this literature is the effect of independent nursing interventions on delirium outcomes. Each of these dimensions (pain management, sleep, and medication administration) are areas in which nurses are important stakeholders and should help drive this research forward. As the population continues to age and the incidence of comorbid illnesses grows, addressing the prevention and reduction of delirium is a timely and imperative objective. The results of this integrative review were vital for elucidating the insufficiencies in delirium identification and management addressed in **Chapters 3 and 4**.

Major Findings from Chapter 3

The iLEAD is a nurse-driven protocol aimed at reducing the severity of delirium in the intensive care unit via the implementation of independent nursing interventions. When nurses routinely assess and manage modifiable risk factors for delirium, it was hypothesized that the number of days of delirium would decrease and patient outcomes would improve. Specifically, this retrospective study evaluated the impact of the iLEAD intervention on the number of days with delirium, length of stay in the SICU, overall hospital length of stay, 30-day readmission rates and 30-day mortality experienced by older adults in the SICU with delirium.

Following iLEAD, implementation rates of delirium screening more than doubled, reflecting that nursing staff were highly motivated to address this critical issue facing patients in the SICU. Consistent with previous reports, patients with delirium in this study had increased SICU and overall hospital length of stay, and higher 30-day mortality rates when compared to patients without delirium. Other than a trend for improvements in rates of 30-day readmissions, no statistically significant improvements in delirium outcomes were noted for the patients who received iLEAD delirium-informed care. However, benefits associated with the iLEAD intervention may not have been detected because previously undiagnosed incidents of delirium (pre-implementation) were now identified (post-implementation), increasing measurement of the overall negative outcomes. Despite the lack of statistical significance, the clinical implications remain significant. Reducing delirium-related consequences even by one day may have substantial significance for patients, both in terms of health outcomes and healthcare related costs. As the iLEAD intervention continues to be implemented, patient-centered outcomes may show additional improvement. Delirium continues to be a noteworthy threat to the health of older adults, and dedicated nurse stakeholders are essential in advancing research.

Major Findings from Chapter 4

This cross-sectional secondary analysis study of older adult patients admitted to the SICU evaluated the relationships among pain severity, its management with opioids, and the onset of delirium. Examination of the relative roles of pain and opioid administration on the development of delirium experienced by this population are important contributors to evidence-based guidelines on pain management. Developing approaches that maximize pain relief while minimizing the negative outcomes related to delirium are essential. The results of this investigation show that opioid exposure was the greatest predictor of next-day delirium status, followed by propofol administration. Interestingly, neither daily average nor worst pain score were associated with next day delirium.

As the most commonly administered medications to patients in the SICU, the roles of opioids and propofol in delirium onset requires further explication. Medications are thought to account for 12% to 39% of all cases of delirium.³ The results of this investigation provide additional support that while untreated pain may have detrimental consequences, it may not be predictive of the development of delirium. In the literature, the language surrounding pain and delirium suggests causation, however this may be inappropriate given the potential for the confounding of observational data in a syndrome with intersecting, poorly understood, and underlying pathologic mechanisms. This observational research study cannot demonstrate causality but offers additional description of the relationship between pain and delirium. Too many studies have posited the causal link between pain and delirium with too few studies actually supporting this relationship, and more rigorous evidence is profoundly lacking.

Limitations

It is important to recognize several limitations of this research. First, patients were not randomized to receive the iLEAD intervention. Therefore, selection bias is a possible threat to the internal validity of this study. Second, data collection was limited to the

electronic health record, and inconsistencies in the accuracy and documentation of the assessments performed is another potential limitation to interpretation. Any conclusions drawn by this study regarding the contributions of the specific nursing's interventions implemented will require prospective validation in future studies.

Lastly, due to the retrospective observational nature of these analyses, the ability to demonstrate causation is not possible. It does, however, afford an important opportunity to examine the association between routine screening and patient outcomes for delirium, along with the associations among pain, its management with opioids, sedation and delirium onset. These investigations represent the first studies to evaluate the iLEAD intervention, originally designed as a health systems science initiative. Therefore, this observational approach took advantage of the natural experimental nature of this protocol implementation in effort to provide health systems and organization-level feedback. As such, the outcomes may not be immediately exportable to other health systems. It is also possible that the patient populations and baseline processes of care for delirium management may not be generalizable to other hospitals and health systems.

Implications

Importantly, this investigation is the first evaluation to determine the impact of iLEAD bundled independent nursing interventions to treat the significant and costly problem of ICU delirium. Nurses' clinical expertise and front-line responsibilities make them uniquely qualified to champion these efforts. The implications of this health systems science dissertation research demonstrate that nurse-led interventions for the reduction and prevention of delirium are feasible, and potentially, as time goes on, may be effective.

Close examination of the literature reveals that there is little empirical evidence to support the causal relationship between pain and the development of delirium. Pain severity was not predictive of delirium in this sample, however exposure to the class of

analgesic most commonly used to treat pain, the opioids, made the patient twice as likely to result in next-day delirium. This suggests that opioids, administered to counter pain, contribute to delirium development. The role of pain management with opioids in the development of delirium requires explication. This study is among the few to characterize the relative roles of pain and opioid administration on the onset of delirium in the surgical ICU population.

Sedatives, like propofol and benzodiazepines, are regularly used in the ICU to mitigate the agitation associated with mechanical ventilation. While significantly associated with delirium alone, after controlling for mechanical ventilation and RASS as covariates, the deliriogenic effect of propofol on next day delirium was weakened. The use of mechanical ventilation varied greatly in the sample however, it did not increase the odds of next day delirium, suggesting that propofol administration, not the ventilation itself, was associated with the development of next-day delirium. These analyses enabled comparison of the relative and combined roles of pain severity, opioid and propofol exposure, mechanical ventilation and RASS on the onset of delirium, providing direction for management of these modifiable delirium risk factors.

In summary, this research evaluated the effectiveness of the nurse-led iLEAD intervention to reduce the burden of delirium and its associated adverse outcomes. Further, it examined two modifiable risk factors associated with delirium (pain, opioid administration). Overall, this dissertation research has important implications in moving forward nurse-driven approaches to the clinical care of aging adults in critical care environments at risk for experiencing delirium.

Future Directions

The older adult population is at the greatest risk for developing ICU delirium, and, at present, there is no consensus on best strategies for its prevention or management. Most studies focus on pharmacologic strategies to reduce delirium, while far fewer have

included reports of non-pharmacological interventions (see **Table 1.1**) as part of their reduction strategies. The lack of this information makes it difficult to assess if these non-pharmacologic strategies, incorporated in many ICUs, play a role in the reduction of delirium. Despite limited evidence, use of such supportive measures has nevertheless become standard practice on the basis on clinical experience and lack of adverse effects. Formally evaluating these non-pharmacologic strategies represents a rich opportunity for future research.

In addition, there is significant knowledge to be gained from the Hospital Elder Life Program (HELP), designed by Dr. Sharon Inouye and colleagues. HELP is an evidence-based, patient-care program to maximize independence for older adults post-hospitalization.⁴ The HELP program focuses on consistently reorienting patients to their surroundings, ensuring nutritional goals are met, prioritizing sleep-promoting interventions while encouraging mobility during hospitalization. Rates of delirium in elderly patients have been significantly improved following the HELP program. With more than 200 HELP sites, the program has been successful in returning older adults to their homes (or prior living situations) with preserved or improved cognitive and physical function. A community hospital employing the HELP program evaluated 595 patients 70 years of age or older admitted to a general medicine floor, and reported a 40% reduction in delirium incidence resulting in a cost savings of \$841,000 over 9 months.⁵ The HELP program relies on the support of highly trained and supervised volunteers to enable one-to-one support and delivery of personalized interventions to achieve optimal outcomes. While many large-scale health systems may find it difficult to achieve this level of personalized care, the associated cost savings may provide financial incentive to incorporate these strategies.

The short-term consequences of pharmacologic pain management strategies may contribute to the development of delirium. Pragmatic clinical trials are needed to

prospectively evaluate if reduction in opioid administration, and pain control with non-opioid pharmacologic strategies, are successful in reducing the onset of delirium. A number of alternative pharmacological strategies to both prevent and treat delirium have been, and continue to be, highly tested. Thus far, no single strategy has amassed enough evidence to support its role in delirium prevention or treatment. While dexmedetomidine has shown promise, additional studies are needed.

A possible explication for the role of opioids and propofol in the development of delirium may be due to interruptions of the natural sleep-wake cycles. Recent evidence supports the promotion of sleep, aiming to provide at least 4 hours of sleep per night, for the reduction of delirium.⁶ Dexmedetomidine is an attractive choice for delirium therapy or prevention, as it is believed to mimic natural sleep architecture and reduce pain. If sleep is a potential curative or preventative measure for reducing the incidence of delirium, nighttime administration of dexmedetomidine may be advantageous in aligning patients with their natural circadian rhythms to facilitate more restful and restorative sleep. Validation studies are needed to evaluate day-time versus nighttime drug administration. In addition, metrics of quality of sleep should be included in other prospective evaluations of delirium, including those using opioids and propofol as active comparators.

Conclusions

In conclusion, this dissertation research contributes to the current understanding of the consequences of delirium among older adults in the surgical intensive care unit. This work described the effectiveness of the nurse-led iLEAD intervention to reduce the burden of delirium and examined two modifiable risk factors associated with delirium (pain, opioid administration). This dissertation research expands knowledge of delirium-related patient and clinical outcomes (days of delirium, SICU length of stay, hospital length of stay, 30-day readmissions and 30-day mortality) and facilitates continued

investigation into the link between pain, opioid analgesics and the onset of delirium.

Overall, this dissertation research has important implications in moving forward nurse-driven approaches to the clinical care of aging adults in critical care environments at risk for experiencing delirium.

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APPENDIX A

iLEAD

Identification of Risk Factors

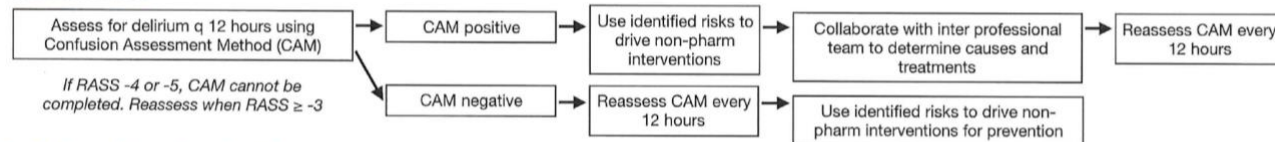
Risk Factors Assessed on Admission to the ICU

- Age > 65
- History of dementia or cognitive impairment
- History of baseline functional or mobility impairment
- Visual or hearing impairments
- History of delirium
- History of alcohol or drug misuse
- Two or more chronic health conditions

Risk Factors Assessed Every 12 Hours

- Active pain
- Surgery within the past 7 days
- High-risk medications
- New oxygen demands
- Mechanical ventilation
- Limited mobility
- Invasive tubes, lines, and drains
- Constipation
- Acute oliguria
- Poor nutritional intake or tolerance
- Sleep deprivation
- New metabolic/electrolyte abnormalities

Assessment



Collaborative Evaluation

For patients with positive CAM:

- Review delirium risk factors
- Evaluate for new infection, cardiac or neurological event, or medical emergency
 - Consider sending laboratory tests for chemistry, CBC, LFT, UA, toxicology, and ABG
- Complete inpatient and home medication review
 - High-risk medications include anticholinergics, antihistamines, benzodiazepines, corticosteroids, and opioids
- Ensure that all tubes, lines, and drains are patent
- Evaluate for urinary retention, fecal impaction
- Consider psychiatry consultation

Interventions for Prevention and Management of Delirium

Non-Pharmacological Interventions			Pharmacological Intervention
Manage pain	Expose to sunlight	Adjust room temperature	
Use communication tools	Provide physical activity	Manage stimuli from tubes, lines, and drains	
Eyeglasses or hearing aid available at bedside (check batteries are working)	Encourage family to bring familiar items from home	Manage bowel, bladder	
Ensure adequate nutrition, Assist with feeding	Avoid physical restraints	Provide cognitively stimulating activities	
Consistently provide reorientation	Provide music therapy	Manage thirst sensation	
Provide sleep hygiene, 2-4 blocks of minimal interruption; Noise minimization			

For more information refer to Penn medicine critical care committee website <http://criticalcare/> and Dorsata Penn Pathways to access critical care nursing delirium guidelines and the Penn Medicine Formulary to access Guidelines for Use of Antipsychotics

Protocol

APPENDIX B

Study Variables and Operational Definitions

Type	Variable	Definition	Measured by	Units/Range/Frequency	Data Type
Independent	iLEAD (Specific Aim 2)	A nurse-led intervention assessing and managing risk factors for delirium.	Time period	Pre vs. Post	Dichotomous
Independent	Pain scores (Specific Aim 3)	A measure a patient's pain intensity.	Numeric Pain Scale	0 - 10 Every 4 hours	Numeric continuous, ratio
Independent	Opioid exposure (Specific Aim 3)	Opioids administered to treat pain.	Exposure	Yes/No	Dichotomous
Dependent	Days of Delirium	A positive CAM-ICU score in 24-hour period equals one day of delirium.	Days	Positive/Negative Every 12 hours	Numeric continuous, ratio
Dependent	Length of stay (SICU)	Number of days of SICU stay	Days	Days (24 hrs)	Ratio
Dependent	Length of stay (Hospital)	Total number of days hospitalized	Days	Days (24 hrs)	Ratio
Dependent	30-day Readmission	A subsequent hospital admission within 30 days following discharge.	EHR	Incidence of readmission	Dichotomous
Dependent	30-day Mortality	Death (all-cause) occurring 30 days following hospital admission.	EHR	Incidence of death	Dichotomous
Covariate	Age	The number of years a person has lived.	EHR	Years	Continuous
Covariate	Sex	The physiological state of being male or female.	EHR	Male/Female	Nominal, categorical
Covariate	Admitting Diagnosis	The condition identified by the physician at the time of admission.	EHR	Type	Nominal, categorical
Covariate	Mechanical Ventilation	A device that helps patients breathe	EHR	Use and duration (hrs)	Dichotomous/ Continuous
Covariate	Richmond Agitation-Sedation Scale (RASS)	A measure of a patient's level of sedation.	EHR	-5 to +4 Every 4 hours	Continuous, ratio
Covariate	Propofol Exposure	Propofol administered for sedation	Exposure	Yes/No	Dichotomous
Covariate	Benzodiazepine Exposure	Benzodiazepines administered for sedation	Exposure	Yes/No	Dichotomous

APPENDIX C

Opioids and Delirium: Table of Evidence

A literature search was conducted with National Library of Medicine Medical Subject Headings (MeSH) terms opioid AND delirium AND intensive care. Studies published between 1995 and 2019 were reviewed by using the PubMed database. Inclusion criteria included: 1) articles written in English; 2) search terms found in the title or as keywords; 3) study sample defined as adult population; 4) delirium as a primary or secondary outcome; and 5) intensive care unit setting. Exclusion criteria included: 1) articles related to the pediatric critical care setting; 2) mixed adult/pediatric studies; 3) case studies, commentaries, expert consensus, editorials and grey literature; 4) cancer pain populations and; 5) studies pertaining to general anesthesia management. The search strategy yielded 78 articles. After title and abstract review, 15 articles met inclusion criteria and were retained and evaluated for scientific rigor of study design, methods and analysis. Our literature search, article selection, and evaluation were guided by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) for quality of reporting for systematic and meta-analyses. Using the Johns Hopkins Nursing Evidence-Based Practice Research Appraisal Guidelines, the design and quality of evidence of the articles were assigned an evidence level of I, II, III, IV or V and graded A (high quality) B (good quality) or C (low quality or major flaws) (see **Table 2.1**). The Table has been organized as to whether or not the findings supported an association between opioids and delirium, and the articles are summarized below.

First Author, Year, Country	Study Aim	Methodology, Study Design	Sample Characteristics	Major Findings/Outcomes	Evidence Level & Grade
Opioids Reduce Risk of Delirium					
Liu, 2017, China	To investigate the influence of opioids and midazolam sedation on delirium and outcomes in critically ill patients and to analyze the risk factors of delirium.	<p>Single center, prospective randomized controlled trial</p> <p>Patients were randomly divided into three groups: 1) remifentanyl and midazolam, 2) fentanyl and midazolam, and 3) the control group received only midazolam.</p> <p>Delirium assessed using the CAM-ICU.</p>	<p>Patients admitted to the surgical intensive care unit who required sedation and were undergoing mechanical ventilation for longer than 24 hours.</p> <p>Sample Size: 105 Age, mean (SD)</p> <p>Remifentanyl and midazolam (n = 35) 66 yrs (11.94 yrs)</p> <p>Fentanyl and midazolam (n = 35) 62 yrs (9.96 yrs)</p> <p>Control Group - Midazolam (n = 35) 64.49 yrs (10.01 yrs)</p>	<p>40% of patients developed delirium. Significant differences were noted in delirium rates among the three groups ($P = 0.014$), 22.9% for the remifentanyl group, 40% for the fentanyl group, and 57.1% for the control group.</p> <p>Compared to the control group, remifentanyl had a significantly lower rate of delirium ($P = 0.007$).</p> <p>The logistic regression analysis demonstrated that remifentanyl (OR 0.230, 95%CI 0.074±0.711, $P = 0.011$) is <u>independent protective factor</u> for delirium.</p>	Level I Grade B
Agarwal, 2010, United States	To evaluate the prevalence of delirium in ventilated burn patients and to identify delirium risk factors.	<p>Retrospective, observational cohort study</p> <p>Burn patients often experience longer periods of mechanical ventilation and ICU care, making this a population at risk for developing delirium and its associated complications.</p> <p>Delirium assessed using the CAM-ICU.</p>	<p>Adult burn patients receiving mechanical ventilation.</p> <p>Sample size: 82 Age median (IQR): 48 yrs (38-62 yrs)</p>	<p>The prevalence of delirium was 77% (63 of 82 patients) with a median duration of 3 (1-6) days.</p> <p>Exposure to intravenous opiates (0.5 [0.4-0.6], $P < .001$) and methadone (0.7 [0.5-0.9], $P = .02$) were associated with a lower risk of delirium.</p> <p>Opiates and methadone reduced the risk of developing delirium, possibly through reduction of pain in these patients.</p>	Level III Grade A

Opioids Not Associated with Delirium					
Sieber, 2011, United States	To determine the relationship between opioid consumption and cognitive impairment following hip fracture repair.	Prospective study of consecutive patients. Pain, opioid consumption, and postoperative delirium was recorded. Delirium assessed using the CAM.	Patients ≥65 years old undergoing hip fracture repair Sample Size: 236 Age mean (SD): 81 yrs (7.1 yrs) Delirium (n = 60) 83 yrs (6.9 yrs) Non delirium (n=176) 81 yrs (7.1 yrs)	There was no association between the use of any postoperative opioid and incident delirium (P = 0.615) Opioid dose (P ≥ 0.591) on postoperative days 1 and 2 was not predictive of incident delirium.	Level III Grade A
Tedders, 2014, United States	To compare the efficacy and safety of fentanyl versus traditional sedation with propofol in critically ill patients receiving mechanical ventilation.	Retrospective, observational cohort study Patients greater than 18 years of age receiving mechanical ventilation for a minimum of 24 hours were eligible for inclusion in this study. Delirium assessed using the CAM-ICU.	Patients admitted to the ICU Sample Size: 100 Age years, median (IQR) Fentanyl (n=50) 70yr (59yr–83yr) Propofol (n=50) 63yr (57yr–78yr)	No difference in the rate of intensive care unit delirium was noted between groups (fentanyl 23% vs propofol 27%, p=0.80).	Level III Grade B
Panharipande, 2006, United States	To determine whether sedative and opioid analgesic medications independently increased the probability of daily transition to delirium.	Cohort study Markov regression modeling (adjusting for 11 covariates) was used to determine the probability of daily transition to delirium as a function of sedative (midazolam, propofol) and analgesic (fentanyl, morphine) dose administration during the previous 24 h. Delirium assessed using the CAM-ICU.	Mechanically ventilated patient admitted to the medical or coronary ICUs Sample Size: 198 Age, mean (SD): 56 yrs (17.0 yrs)	Lorazepam was an independent risk factor for daily transition to delirium (OR, 1.2; P 0.003), although the four medications were associated with trends toward significance (midazolam OR, 1.7; P = 0.09; fentanyl OR, 1.2; P = 0.09; morphine OR, 1.1; P = 0.24; propofol OR, 1.2; P = 0.18).	Level III Grade A
Shehabi, 2009, Australia and New Zealand	To assess the characteristics of dexmedetomidine compared with morphine-based regimen after cardiac surgery at equivalent levels of sedation and analgesia.	Randomized, double-blind, controlled trial Study drug infusions were started in the ICU. The infusion was continued until the removal of chest drains, when patient was ready to discharge from ICU, or for up to 48 hours of mechanical ventilation. Delirium assessed using the CAM-ICU.	Cardiac surgery patients > 60 years Sample size: 306 Age, Median (IQR) Dexmedetomidine (n=152) 71.5 yrs (66 – 76 yrs) Morphine (n= 147) 71 yrs (65 – 75 yrs)	The incidence of delirium within 5 days was 11.7% (35 of 299) with 8.6% occurring in the dexmedetomidine group and 15% occurring in the morphine group (RR 0.571, 95% CI 0.256-1.099, p = 0.088).	Level I Grade A

Opioids Increase Risk of Delirium					
Dubois, 2001, Canada	To establish risk factors for the development of delirium in the ICU.	<p>Prospective study.</p> <p>Delirium was assessed by the intensivist and confirmed by formal psychiatric assessment.</p>	<p>Consecutive patients aged 18 or older admitted to the ICU for > 24 hours.</p> <p>Sample Size: 198 Age, mean (SD)</p> <p>Delirium (n=38) 63 yrs (13.9 yrs)</p> <p>No Delirium (n = 160) 66 yrs (13.4 yrs)</p>	<p>19% of patients developed delirium.</p> <p>In a multivariate analysis, morphine, in all dosages, was significantly linked to the development of delirium (OR between 6 and 9.2).</p>	Level III Grade A
Marcantonio, 1994, United States	To examine the role of medications with known psychoactive properties in the development of postoperative delirium.	<p>Nested case-control study within a prospective cohort study.</p> <p>Exposures to opioids, benzodiazepines, and anticholinergics were recorded for the 24-hour period before delirium developed in the 91 cases and for the same 24-hour postoperative period for the 154 matched controls.</p> <p>Delirium assessed using the CAM.</p>	<p>One or two controls were matched to each case of delirium.</p> <p>Sample Size: 245 Age, mean (SD)</p> <p>Delirium (n=91) 73 yrs (8 yrs)</p> <p>Controls (n=154) 73 yrs (8 yrs)</p>	<p>Delirium was significantly associated with postoperative exposure to meperidine (odds ratio [OR], 2.7; 95% confidence interval [CI], 1.3 to 5.5).</p> <p>Opioids as a class of medication (OR, 1.4; 95% CI, 0.5 to 4.3) were not significantly associated with delirium.</p>	Level III Grade A
Clegg, 2011, United Kingdom	To identify prospective studies that investigated the association between medications and risk of delirium	<p>Meta-analysis</p> <p>Systematic review of randomized controlled trials, prospective cohort studies and case-control studies that reported on medications and delirium in hospital patients or long-term care residents.</p>	<p>Fourteen studies were included. Seven studies included opioid use across multiple settings (ICU and Hospital).</p>	<p>Pooling data from two studies, delirium risk is increased with opioid administration (odds ratio [OR] 2.5, 95% CI 1.2-5.2).</p>	Level I Grade B
Pisani, 2009, United States	The objective of this study was to examine the impact of benzodiazepine or opioid use on the duration of ICU delirium in an older medical population.	<p>Prospective cohort study.</p> <p>Recorded use of opioids (fentanyl and morphine), benzodiazepines (lorazepam and midazolam), and propofol on a daily basis.</p> <p>Delirium assessed using the CAM.</p>	<p>Consecutive patients age 60 and older admitted to the medical ICU.</p> <p>Sample Size: 304 Age, mean (SD): 75 yrs (8 yrs)</p> <p>Delirium (n=239) Benzodiazepine or Opioid Use (n=247)</p>	<p>Delirium occurred in 79% of patients.</p> <p>The median duration of ICU delirium was 3 days with a range of 1-33 days.</p> <p>Receipt of an opioid (rate ratio [RR] 1.64, 95% confidence interval [CI] 1.27-2.10) was associated with increased delirium duration.</p>	Level III Grade A

Buray, 2017, Canada	Investigate the relationship between benzodiazepines, propofol, opioids and delirium	<p>Prospective observational study</p> <p>During ICU admission, no patient was managed with a standardized sedation protocol (i.e., propofol, benzodiazepine).</p> <p>Delirium assessed using the Intensive Care Delirium Screening Checklist</p>	<p>Critically ill adult patients admitted \geq 24h to 6 different intensive care units</p> <p>Sample Size: 520 Age, mean (SD)</p> <p>No Delirium (n = 260) 58 yrs (17.8 yrs)</p> <p>Delirium (n = 260) 62 yrs (16.2 yrs)</p>	<p>Delirium was detected in 260 (50%) patients. The median (IQR) duration of delirium was 2 (1-5) days.</p> <p>Patients with delirium received more opioid (P=0.0008) drugs than patients without delirium.</p>	Level III Grade A
Pisani, 2010, United States	To identify factors associated with persistent delirium in an older medical intensive care unit (ICU) population.	<p>Prospective cohort study</p> <p>Persistent delirium was defined as delirium occurring in the ICU and continuing upon discharge to the ward.</p> <p>Delirium assessed using the CAM.</p>	<p>Consecutive admissions to the medical ICU patients 60 years or older</p> <p>Sample Size: 173</p> <p>Persistent delirium 58% (n = 100) Age > 75 (n=49)</p> <p>Non-persistent delirium 42% (n = 73) Age > 75 (n=24)</p>	<p>In a multivariable logistic regression model, factors significantly associated with persistent delirium included age more than 75 years (odds ratio [OR], 2.52; 95% confidence interval [CI], 1.23-5.16), and opioid (morphine equivalent) dose greater than 54 mg/d (OR, 2.90; 95% CI, 1.15-7.28).</p>	Level III Grade A
Sosa, 2017, Argentina	To describe the incidence of and risk factors for delirium in the intensive care unit .	<p>Prospective observational study</p> <p>The PRE-DELIRIC model assesses 10 risk factors for delirium that are readily observable within the first 24 hours following ICU admission.</p> <p>Delirium assessed using the CAM.</p>	<p>Patients admitted to the ICU</p> <p>Sample Size: 178 Age mean (SD) 64.3 yrs (17.9 yrs)</p> <p>No Delirium (n=129) 60.9 yrs (18.4 yrs)</p> <p>Delirium (n=49) 74.4 yrs (9.4 yrs)</p>	<p>27.5% of patients developed delirium.</p> <p>Predictive factors for the development of delirium were increased age, prolonged ICU stay, and opioid use (OR 4.32; P = .003; CI: 1.64 – 11.38).</p>	Level III Grade A

APPENDIX D

Propofol and Delirium: Table of Evidence

A literature search was conducted with National Library of Medicine Medical Subject Headings (MeSH) terms propofol AND delirium. Studies published between 1995 and 2019 were reviewed by using the PubMed database. Inclusion criteria included: 1) articles written in English; 2) search terms found in the title or as keywords; 3) study sample defined as adult population; 4) delirium as a primary or secondary outcome; and 5) intensive care unit setting. Exclusion criteria included: 1) articles related to the pediatric critical care setting; 2) mixed adult/pediatric studies; 3) case studies, commentaries, expert consensus, editorials and grey literature; 4) chronic or cancer pain populations and; 5) studies pertaining to general anesthesia management, not intensive care unit sedation. The search strategy yielded 51 articles. After abstract review, 15 articles met inclusion criteria and were retained and evaluated for scientific rigor of study design, methods and analysis. Our literature search, article selection, and evaluation were guided by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) for quality of reporting for systematic and meta-analyses. Using the Johns Hopkins Nursing Evidence-Based Practice Research Appraisal Guidelines (see **Table 2.1**), the design and quality of evidence of the articles were assigned an evidence level of I, II, III, IV or V and graded A (high quality) B (good quality) or C (low quality or major flaws). The Table has been organized according to comparators: propofol and delirium, opioids, benzodiazepines and dexmedetomidine. The articles are summarized below.

First Author, Year, Country	Study Aim	Methodology, Study Design	Sample Characteristics	Major Findings/Outcomes	Evidence Level & Grade
Propofol and Delirium					
Jiang, 2017, China	To analyze various risk factors for postoperative delirium after spine surgery in the middle- and old-aged patients.	Retrospective cohort study Delirium assessed using cognitive tests consisting of Clinical Dementia Rating and Global Deterioration Scale.	Patients who underwent spinal surgery. Sample Size: 451 patients Age, mean (SD), years: 65 (18.3) years	A total of 42 (9.3 %) patients were diagnosed with delirium. Delirious and non-delirious patients had no difference in use of propofol.	Level III Grade B
Mori, 2016, Brazil	To identify the incidence of delirium, compare the demographic and clinical characteristics of patients with and without delirium.	Prospective cohort study Delirium assessed using the CAM-ICU.	Patients admitted to the Intensive Care Unit Sample Size: 149 Age years, median (IQR) With Delirium (n=69) 65 (22.0 yr) Without Delirium (n=80) 54 (24.3 yr)	Of the total 149 patients in the sample, 69 (46.3%) developed delirium during ICU stay. Propofol was utilized in 33% of patients with delirium compared to just 7.5% of patients without delirium ($p < 0.001$).	Level III Grade A
Bryczkowski, 2014, United States	This study aimed to identify modifiable factors that would predict delirium in an older trauma population admitted to the SICU.	Prospective cohort study Delirium assessed using the CAM-ICU.	Consecutive patients older than 50 years, admitted to the SICU. Sample Size: 115 Age, mean (95% CI) With Delirium (n=69) 68yr (65yr – 71yr) Without Delirium (n=46) 65yr (62yr – 68yr)	The average propofol dose in patients with delirium was 6 mg/kg/d compared to 1 mg/kg/d in patients without delirium ($p < 0.001$). Significant risk factors influenced by clinical treatment included doses propofol.	Level III Grade C

Comparison Studies – Opioids					
Tedders, 2014, United States	To compare the efficacy and safety of fentanyl versus traditional sedation with propofol in critically ill patients receiving mechanical ventilation.	Retrospective, observational cohort study Patients greater than 18 years of age receiving mechanical ventilation for a minimum of 24 hours were eligible for inclusion in this study. Delirium assessed using the CAM-ICU.	Patients admitted to the ICU Sample Size: 100 Age years, median (IQR) Fentanyl (n=50) 70yr (59yr–83yr) Propofol (n=50) 63yr (57yr–78yr)	No difference in the rate of intensive care unit delirium was noted between groups (fentanyl 23% vs propofol 27%, p=0.80).	Level III Grade B
Comparison Studies – Benzodiazepines					
Seymour, 2012, United States	To determine whether benzodiazepine and propofol doses are increased at night and whether daytime and nighttime sedative doses are associated with delirium, coma, and delayed liberation from mechanical ventilation.	Single-center, prospective cohort study Hourly doses of benzodiazepine and propofol exposure were measured during the daytime (7 AM to 11 PM) and nighttime (11 PM to 7 AM) for 5 days. Delirium assessed using the CAM-ICU.	Adult patients receiving mechanical ventilation for >12 hrs. Sample Size: 140 Age, median (IQR): 66yr (55yr–75yr)	Higher daytime propofol doses were marginally associated with delirium (p = .06), whereas nighttime change in propofol dose was not associated with delirium the following day (p = .27).	Level III Grade B
Comparison Studies – Dexmedetomidine					
Maldonado, 2009, United States	Investigated the effects of postoperative sedation on the development of delirium in patients undergoing cardiac-valve procedures.	Randomized, open-label, controlled trial After weaning from bypass, patients were randomly assigned to postoperative sedation regimens. Patients were extubated while still on the medication and were kept on the maintenance infusion as deemed clinically necessary for a maximum of 24 hours. Delirium assessed by a trained neuropsychiatrist.	Patients schedule for elective cardiac valve operations. Sample size: 118 randomized, 90 analyzed. Age, mean (SD) Dexmedetomidine (n= 40) 55yr (16yr) Propofol (n= 38) 58yr (18yr) Midazolam (n= 40) 60yr (16yr)	Using a per-protocol analysis, the incidence of delirium for the entire study population was 34% (31/90). The incidence of delirium was statistically different between the three groups (p < 0.001): Dexmedetomidine = 3% (1/30) Propofol = 50% (15/30) Midazolam = 50% (15/30)	Level I Grade A

Subramaniam, 2019, United States	To evaluate the effect of postoperative intravenous (IV) acetaminophen vs placebo combined with IV propofol vs dexmedetomidine on postoperative delirium among older patients undergoing cardiac surgery.	Randomized, placebo-controlled trial Patients were randomized to one of four groups; postoperative analgesia with acetaminophen or placebo (0.9% saline) and postoperative sedation with dexmedetomidine or propofol. Delirium assessed using the CAM-ICU.	Patients undergoing cardiac surgery. Sample size: 120 patients Age; median (IQR) Acetaminophen and dexmedetomidine (n = 29) 64yr (63yr-72yr) Placebo and dexmedetomidine (n = 30) 69yr (63yr-74yr) Acetaminophen and propofol (n = 31) 70yr (66yr-75yr) Placebo and propofol (n = 30) 71yr (64yr-79yr)	Delirium was reported in 21% of patients receiving propofol vs 17% of patients receiving dexmedetomidine. No significant difference in delirium between groups was reported ((difference, -4%) p = .54).	Level I Grade A
Chuich, 2019, United States	This study evaluates the effects of the intraoperative and postoperative use of dexmedetomidine versus propofol infusions.	Retrospective observational study Patients received either dexmedetomidine or propofol infusion in addition to general anesthesia intraoperatively and as a postoperative sedative. Delirium assessed using the CAM-ICU.	Patients undergoing cardiac surgery. Sample size: 278 patients Age; median (range) Dexmedetomidine (n = 69) 63yr (56yr-71yr) Propofol (n = 209) 67yr (58yr-74yr)	There was no significant association between use of dexmedetomidine or propofol and incidence of delirium (p = 0.27) after adjusting for covariates.	Level III Grade A
Liu, 2017, United States	To compare the effects of dexmedetomidine and propofol sedation on outcomes in adult patients after cardiac surgery.	Meta-analysis	Patients undergoing cardiac surgery. Sample size: 969 8 studies met the selection criteria 4 studies (Liu 2016; Corbett 2005; Djaiani 2016; Maldonado 2009) used propofol as a comparator with a total number of 393 accrued participants.	Pooling of data from 4 studies showed the incidence of delirium to be 23.5% in the propofol group compared to 9.3% in the dexmedetomidine group (p < 0.001). Meta-analysis showed that the dexmedetomidine sedation significantly decreased postoperative delirium (POD; RR, 0.40; 95% CI, 0.24-0.64; P = .0002).	Level I Grade A

Liu, 2016, United States	To compare the effects of dexmedetomidine and propofol on sublingual microcirculation in patients after cardiac surgery.	Prospective, randomized, single-blind study Patients were assigned randomly to receive either dexmedetomidine or propofol upon admission to the ICU. Delirium assessed using the CAM-ICU.	Patients undergoing cardiac surgery. Sample Size: 61 Age, median (range) Propofol (n = 32) 55yr (48yr-62yr) Dexmedetomidine (n = 29) 53yr (48yr-63yr)	Incidence of delirium was 6% in the propofol group, compared to 0% in the dexmedetomidine group (p = 0.493).	Level I Grade C
Jiang, 2016, United States	To assess the prevalence of delirium in mechanically ventilated patients sedated with dexmedetomidine or propofol.	Retrospective cohort study Patients received either dexmedetomidine or propofol for 24 hours or more for sedation. Delirium assessed using the CAM-ICU.	Patients admitted to the medical or surgical intensive care units. Sample Size: 111 Age, years (range) Dexmedetomidine (n= 56) 73yr (50yr-94yr) Propofol (n = 55) 68yr (22yr-93yr)	The rates of delirium were similar in both groups, with 20% in propofol-treated patients vs. 16% in the dexmedetomidine group (p = 0.63).	Level III Grade B
Djaiani, 2016, Canada	To assess if dexmedetomidine in comparison to propofol sedation after cardiac surgery would reduce the incidence of postoperative delirium.	Single-blind, prospective, randomized controlled trial Upon arrival to ICU, sedation was initiated. The infusion was continued for a maximum period of 24 hours. Delirium assessed using the CAM-ICU.	Patients undergoing cardiac surgery. Sample size: 185 Age, mean (SD) Dexmedetomidine (n= 91) 73yr (6.4yr) Propofol (n= 92) 73yr (6.2yr)	A total of 17.5% and 31.1% of patients in the dexmedetomidine and propofol groups respectively, developed delirium (p = 0.028).	Level I Grade A
Wanat, 2014, United States	This study compares sedation with dexmedetomidine versus propofol in mechanically ventilated patients after cardiovascular surgery.	Retrospective cohort study Sedation orders were based on individual physician ordering upon arrival to the ICU. Delirium assessed using the CAM-ICU.	Patients admitted to the ICU after cardiovascular surgery. Sample size: 352 Age, mean (SD) Dexmedetomidine (n= 33) 63yr (14.1yr) Propofol (n= 319) 68yr (11.2yr)	CAM-ICU scores were reported in 79% of dexmedetomidine patients and 84% of propofol patients (p = 0.411). Incidence of delirium (any vs. none) was similar between both groups (9.09% vs. 7.52%, p = 0.747).	Level III Grade B

Xia, 2013, China	To assess the influence of dexmedetomidine and propofol sedation on adverse events for adults in the intensive care unit.	<p>Meta-analysis</p> <p>The primary outcomes of this study were length of ICU stay, duration of mechanical ventilation, and risk of ICU mortality. Secondary outcomes included risk of delirium.</p>	<p>Ten randomized controlled trials, involving 1202 patients, were included.</p> <p>Three studies (Maldonado 2009; Corbett 2005; Jakob 2012) comprised of 658 patients, reported the incidence of delirium.</p>	Delirium rates were significantly lower with dexmedetomidine compared with those with propofol (RR, 0.40; 95% CI, 0.22-0.74; p = 0.003).	Level I Grade A
Corbett, 2005, United States	To assessed patient-perceived satisfaction with coronary artery bypass graft surgery after administration of dexmedetomidine or propofol for sedation.	<p>Prospective, randomized clinical study</p> <p>Patients were randomized to either dexmedetomidine or propofol.</p> <p>Delirium was assessed by a modified Hewitt-sedation questionnaire was administered by the study investigator.</p>	<p>Patients in the surgical ICU following cardiac surgery.</p> <p>Sample size: 89 Age mean (SD)</p> <p>Dexmedetomidine (n = 43) 64yr (10.1yr)</p> <p>Propofol (n = 46) 63yr (10.7yr)</p>	One episode of delirium occurred in the dexmedetomidine treatment arm and one episode occurred in the propofol treated patients.	Level I Grade C