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Future Directions of Delirium Research and Management

Christopher G. Hughes, MD¹, Nathan E. Brummel, MD², Eduard E. Vasilevskis, MD³, Timothy D. Girard, MD, MSCI⁴, and Pratik P. Pandharipande, MD, MSCI⁵

¹Assistant Professor, Department of Anesthesiology, Division of Critical Care, Vanderbilt University School of Medicine

²Clinical Fellow, Department of Medicine, Division of Pulmonary and Critical Care Medicine and the Center for Health Services Research, Vanderbilt University School of Medicine

³Assistant Professor, Geriatric Research, Education and Clinical Center, Clinical Research Training Center of Excellence, Department of Veterans Affairs Medical Center, Tennessee Valley Healthcare System; Department of Medicine, Division of General Internal Medicine and Public Health and the Center for Health Services Research, Vanderbilt University School of Medicine

⁴Assistant Professor, Department of Medicine, Division of Pulmonary and Critical Care Medicine and Center for Health Services Research, Vanderbilt University School of Medicine; Geriatric Research, Education and Clinical Center Service, Department of Veterans Affairs Medical Center, Tennessee Valley Health Care System

⁵Associate Professor, Anesthesia Service, Veterans Affairs Medical Center, Tennessee Valley Health Care System and Department of Anesthesiology, Division of Critical Care, Vanderbilt University School of Medicine

Abstract

Delirium is a prevalent organ dysfunction in critically ill patients associated with significant morbidity and mortality, requiring advancements in the clinical and research realms to improve patient outcomes. Increased clinical recognition and utilization of delirium assessment tools, along with clarification of specific risk factors and presentations in varying patient populations, will be necessary in the future. To improve predictive models for outcomes, the continued development and implementation of delirium assessment tools and severity scoring systems will be required. The interplay between the pathophysiological pathways implicated in delirium and resulting clinical presentations and outcomes will need to guide the development of appropriate prevention and treatment protocols. Multicenter randomized controlled trials of interventional therapies will then need to be performed to test their ability to improve clinical outcomes. Physical and cognitive rehabilitation measures need to be further examined as additional means of improving outcomes from delirium in the hospital setting.

Keywords

delirium; risk factors; pathophysiology; drug therapy; rehabilitation

Corresponding Author: Christopher G. Hughes, MD, 1211 21st Ave South 526 Medical Arts Building Nashville, TN 37212 United States christopher.hughes@vanderbilt.edu P: 615-936-2454 F: 615-343-6272.

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Introduction

The last decade has seen an explosion in the medical literature on brain dysfunction associated with acute illness, with the focus of these studies primarily on determining the prevalence of delirium as well as its associated risk factors and outcomes.^{1, 2} The very high prevalence of delirium in the setting of acute illness has led researchers and clinicians alike to use validated delirium screening tools performed by non-psychiatrist practitioners to diagnose delirium in the hospital setting, from the emergency department to the intensive care unit (ICU).^{3, 4} To improve patient outcomes and decrease the burden of this costly complication of acute illness, numerous advances in research and clinical management must occur (Table 1). Delirium assessment tools must be adopted clinically to promote widespread recognition of delirium as well as change in the culture of many hospitals, which entail heavy use of some sedatives that may contribute to delirium. Since delirium is a constellation of symptoms that is the clinical manifestation of an underlying pathology, the epidemiology of the different types of delirium (e.g., sepsis associated delirium, sedation associated delirium, etc.) needs to be elucidated. Delirium assessment tools must be further developed, validated, and implemented, including the ability to not only diagnose delirium but measure severity and distinguish delirium subtypes. Prediction models must also be developed and extensively studied. The interplay between the pathophysiological pathways implicated in delirium and the effects of these pathways on clinical presentation needs to be elucidated. After utilizing pathophysiological data to guide the development of appropriate prevention and treatment protocols, multicenter randomized controlled trials of interventional therapies will need to be performed to test their ability to improve clinical outcomes. Finally, further development and initiation of physical and cognitive rehabilitation programs need to be investigated as additional means of improving outcomes from delirium in the hospital setting.

Advances in Delirium Assessment and Prediction

The last decade has seen a rapid growth in the number of tools that have been developed and validated to screen for delirium. Prior to the availability of these tools, delirium was a subjective diagnosis that was often missed when relying upon the clinical intuition of physicians and nurses at the bedside.^{5, 6} Symptoms of delirium, especially the hypoactive form, would be incorrectly attributed to dementia, depression, or sedation. As described in detail earlier in this issue, delirium monitoring instruments now provide highly sensitive and specific assessments for delirium, with the two instruments most commonly used in the ICU being the Confusion Assessment Method for the ICU (CAM-ICU)³ and the Intensive Care Delirium Screening Checklist (ICDSC).⁴

The CAM-ICU is a rapid, structured screening tool made up of objective patient assessments for use with nonspeaking, mechanically ventilated patients.³ The tool tests for four primary features of delirium: 1) Acute changes in or fluctuating mental status, 2) Inattention, 3) Altered level of consciousness, and 4) Disorganized thinking. Delirium is diagnosed in patients that exhibit features 1 and 2 and either feature 3 or 4. The ICDSC is a structured tool made up of eight subjectively assessed items observed over a period of time.⁴ The patient is evaluated by their nurse (or clinician with serial contact) for inattention, disorientation, hallucination, delusion or psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep-wake cycle disturbance, and fluctuation of the above symptoms. Each respective item is scored as absent or present (0 or 1) based on standard definitions, and the present items are summed. The scale is completed based on information obtained during the prior nursing shift, with a score of 4 or greater indicating the presence delirium. Additional tools have been validated, but there is limited published experience as they have been tested only in smaller numbers of patients; larger studies with broader

generalizability are needed before these tools, which include the NEECHAM scale⁷ and the Nursing Delirium Screening Scale (Nu-DESC),⁸ can be recommended for widespread use.

Delirium screening instruments have been essential to advance research in the understanding of the pathophysiology, risk factors, and outcomes of delirium. Delirium screening tools, however, should not be viewed solely as tools for research since their use at the bedside can be a pivotal component in the care of patients. In fact, these tools are increasingly being implemented into the routine course of clinical care. Multiple large scale implementation trials have shown the feasibility of this approach. Pun et al demonstrated in the medical ICUs of two large institutions that nurses could use the CAM-ICU routinely with high levels of compliance and reliability,⁹ and similar compliance has been shown in the trauma ICU setting.¹⁰ Importantly, Vasilevskis et al demonstrated that compliance and reliability of CAM-ICU measurements at the bedside could be sustained over multiple years, well after the initial time period of implementation.¹¹ A study by van Eijk et al also demonstrated the feasibility of CAM-ICU implementation, with lower sensitivity than the former study but extremely high specificity, diagnosing delirium with almost near certainty.¹²

The value of “real-world” implementation of delirium tools cannot be understated; these assessments should be incorporated into the routine neurological examination of ICU and hospital patients, not just those on mechanical ventilation. Without valid, reproducible delirium assessment tools, providers lack the skills, confidence, and language to assess and communicate the presence of delirium. With valid tools at their disposal, clinicians are assessing ICU patients for delirium and using their findings to help guide prevention and treatment decisions; delirium screening has already been integrated into many pain and sedation protocols and linked with standard practices aimed at reducing sedative exposure (e.g., spontaneous awakening trials).¹³ Skrobik et al, for example, added a nursing checklist evaluation for delirium using the ICDSC and linked antipsychotic administration to threshold ICDSC scores as part of an analgesia/sedation/delirium protocol associated with reduced rates of subsyndromal delirium.¹⁴ Finally, validated delirium assessments are being used to evaluate the impact of quality improvement interventions. Needham et al assessed cognitive outcomes of an early mobility quality improvement intervention by means of standard delirium assessments.¹⁵ Using delirium as an outcome is effective, patient-centered, and should be considered for future quality improvement efforts.

Utilizing these delirium assessment tools, advances in risk factor identification have led to a variety of hypotheses regarding the pathophysiological basis of delirium. In addition, this new knowledge is a critical factor for the development of robust risk prediction models that will aid clinicians to identify patients at highest risk for delirium and guide prevention strategies prior to the development of delirium. The Prediction of Delirium in ICU Patients (PRE-DELERIC) model is the first delirium prediction model developed specifically for the ICU and has demonstrated excellent discrimination and calibration.¹⁶ Compared to clinician predictions, the model was far superior, but this model’s performance outside ICUs has yet to be tested. Importantly, the severity of illness in this population was relatively low (median APACHE II score of 14), which may explain in part the delirium incidence (25.5%) observed in the PRE-DELERIC validation study, an incidence that is low compared with other studied cohorts characterized by higher severity of illness.^{3, 17}

The benefits of risk-prediction are most likely to be found in the targeting of high risk individuals with risk-tailored, non-pharmacologic and/or pharmacologic interventions. For example, although the impact of antipsychotic medication in delirium prevention has been mixed,^{18, 19} it is possible that with improved targeting these medications may demonstrate clinical benefit that has not been clearly demonstrated in a general population. Moving forward, it will be important to link risk predictions with interventions and learn if these

strategies improve the utilization of limited resources (e.g., early mobility teams) and increase the benefit of proposed interventions.

Subtypes of Delirium

Despite significant advances in delirium monitoring in the ICU, available diagnostic methods detect only symptoms of delirium and do not consider factors such as delirium severity, clinical subtype, etiology, or mechanism, any of which are likely to play a pivotal role in determining a delirious patient's risk for adverse outcomes. As studied to date, for example, the CAM-ICU reliably and accurately classifies a patient as delirious or not, but the tool has not been validated as a measure of delirium severity or as a method by which patients can be classified into different subtypes of delirium. The ICDSC has been shown in one study to identify delirium and subsyndromal delirium,²⁰ an intermediate state between normal mental status and fully developed delirium, but no other data exist regarding the use of this tool to measure delirium severity or delineate delirium subtypes. Thus, studies are now needed to validate approaches to measuring delirium severity and to distinguishing various delirium subtypes.

As with other forms of organ dysfunction, delirium can range in severity from mild to severe. Despite the fact that a delirium severity tool has yet to be validated for use in the assessment of acutely ill patients, some features of severe delirium are readily apparent. Prolonged delirium is more severe than short periods of delirium, as proven in several studies showing that duration of delirium independently predicts both mortality and long-term cognitive impairment up to one year following critical illness.^{1, 2, 21} In addition, the full syndrome of delirium (i.e., as defined by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders [DSM])²² is more severe than subsyndromal delirium,²⁰ wherein some of the features of delirium are present but not enough of them to warrant a diagnosis of delirium per DSM criteria. Apart from recognizing that fully developed, prolonged delirium is associated with worse outcomes than subsyndromal and/or short-lived delirium, practitioners are currently left without validated tools to delineate mild, moderate, and severe delirium. Future studies are thus needed to develop and validate measures of delirium severity.

Currently available delirium assessments tools are not designed to ascertain other potentially important aspects of delirium, including motoric subtype or etiology. Though pure hyperactive delirium (characterized by agitation and increased psychomotor activity) is rare during critical illness,^{23, 24} both hypoactive delirium (characterized by a reduced level of consciousness) and mixed (intermittently hyper- or hypoactive) subtype delirium are common and may portend different prognoses or susceptibilities to interventions. Previous investigations^{24, 25} used delirium assessment tools in tandem with sedation scales, such as the Richmond Agitation-Sedation Scale,²⁶ to classify patients according to motoric subtypes of delirium, but no study has validated this or any other approach to discriminating hyperactive from hypoactive delirium. Additionally, available delirium assessment tools do not distinguish delirium due to different etiologies. Neither the CAM-ICU nor the ICDSC differentiates an ICU patient demonstrating inattention and somnolence due to septic encephalopathy from one demonstrating the same symptoms due to sedatives, such as benzodiazepines. The physiology underlying such symptoms in various patients is likely very different; therefore, outcomes and responses to therapy could be expected to be different as well. No research to date has sought to determine the contribution of different etiologies of delirium to the development of adverse outcomes (e.g., long-term cognitive impairment after critical illness). Future studies are needed to illuminate these relationships in order to pave the way for preventive and therapeutic interventions intended to reduce brain dysfunction by ensuring that future studies are focused on patients at highest risk.

Elucidation of Delirium Pathophysiology

While the multifactorial pathophysiology of delirium remains unclear, multiple clinical risk factors have been identified and numerous pathophysiologic pathways have been hypothesized based on these observed clinical associations. However, these mechanisms have not been clearly associated with the varying subtypes or severity of delirium witnessed clinically. Sedative medications, in particular the γ -aminobutyric acid (GABA)-ergic benzodiazepines, were some of the first iatrogenic therapies to be implicated in delirium development in a wide range of patient populations.^{27–29} GABA receptors in the brain contribute to an inhibitory tone and likely reduce synaptic connectivity, and it remains to be proven if iatrogenic administration of GABA-ergic medications such as benzodiazepines contributes to further inhibition of neural pathways.³⁰ Neuroinflammation, one of the leading hypotheses for delirium pathophysiology, drives upregulation of GABA_A receptors, potentially working synergistically with administered medications to produce a pronounced inhibitory tone in the central nervous system.³⁰

In addition to GABA modulation, infiltration of leukocytes and cytokines into the central nervous system, producing ischemia, neuronal apoptosis, and brain edema, form the basis of the neuroinflammation hypothesis.^{31–34} Microglial activation, oxidative injury, and additional neurotransmitter imbalances also occur.^{32, 35} The risk of delirium development attributed to the GABA receptor versus microglial activation versus apoptosis has not been delineated and is likely significantly different amongst different patient populations. For example, patients with prior cognitive disease likely already have ongoing inflammatory changes, including microglial priming, predisposing them to delirium with only minor clinical insult.^{32, 35}

Anticholinergic medications have also been associated with delirium,³⁶ and cholinergic deficiency can be present for numerous reasons in hospitalized patients, including critical illness itself or medication administration (e.g., opioids, general anesthetics).³⁷ A significant overlap also exists between cholinergic projections from the subcortical to the cortical regions and neuroimaging lesions associated with delirium.³⁷ Furthermore, the cholinergic pathway attenuates the systemic response to inflammatory insults, including brain acetylcholinesterase activity controlling systemic cytokine release.^{38, 39} Microglia also express acetylcholine receptors, and reduced cholinergic inhibition may potentially lead to their overactivation and subsequent neurodegeneration.³⁵ Decreased availability of acetylcholine during inflammatory disease states, therefore, likely leads to decreased counter-regulatory nervous system activity and worsening neuroinflammation, a key component to the cholinergic deficiency hypothesis of delirium. In addition, the physiological responses to dopamine, norepinephrine, and serotonin are modulated by the cholinergic pathway, likely contributing to the varying clinical presentations of acute brain dysfunction.³⁷ However, it is unclear whether it is the actual cholinergic deficiency or the resulting subsequent changes from neuroinflammation or neurotransmitter imbalances that drives clinical symptomology or if this risk varies by patient characteristics.

There is a complex cortical relationship between norepinephrine and dopaminergic and cholinergic pathways, and disturbances in the native balance may underlie delirium pathophysiology. According to the monoamine axis hypothesis, dopamine, norepinephrine, and serotonin excess and their respective amino acid precursors have been associated with brain dysfunction. Dopamine excess has traditionally been thought of as a cause of hyperactive delirium, as dopamine agonists can induce psychosis while antipsychotic agents with dopamine antagonist properties may resolve delirium.⁴⁰ Meanwhile, excess norepinephrine activity has been associated with impaired attention, anxiety, mood, and, specifically, hyperactive delirium, and elevated serotonin levels have been associated with

impaired learning and memory.³⁷ In addition, selective serotonin reuptake inhibitors have been associated with delirium.³⁷ Finally, altered plasma levels and cerebral uptake of tryptophan (serotonin precursor) or phenylalanine and tyrosine (dopamine and norepinephrine precursors) compared to the other large neutral amino acids may lead to changes in the production of specific neurotransmitters, affecting their function in the brain and contributing to the development of delirium.⁴¹

Thus, numerous hypotheses involving different yet intertwined pathophysiologic pathways have been proposed as etiologies for delirium. However, large scale studies in humans have not yet been performed due to the difficulty of directly evaluating these neurological pathways in alive patients as well as the difficulty in obtaining adequate patient and biological samples to study multiple systems that either work independently or in concert with one another. Furthermore, the roles of these pathways in specific patient cohorts, delirium types, and delirium presentation have not been determined. In the future, additional large cohort studies and randomized trials will be necessary to test modulation of these pathways as a means to improve delirium outcomes, but in the meantime, animal models of delirium examining these different pathways will be required.

Interventional Trials of Potential Therapies

Cohort studies over the last 10–15 years have helped us understand some common risk factors of delirium, and we have just begun to understand elements in the pathogenesis of delirium. Thus, interventional trials have focused on iatrogenic risk factors, such as sedatives, analgesics, and sleep, and on potential pathogenesis mechanisms, such as cholinergic deficiencies, attenuation of inflammation, and tryptophan depletion. A broader approach has examined the development of non-pharmacological protocols and the use of antipsychotic medications (both typical and atypical) to attenuate the manifestations of delirium.

The MENDS study (a randomized controlled trial of the α_2 agonist dexmedetomidine versus lorazepam) provided evidence that sedation with dexmedetomidine can decrease the duration of brain organ dysfunction, with a lower likelihood of delirium development on subsequent days.⁴² The SEDCOM study compared dexmedetomidine with midazolam and demonstrated a reduction in delirium prevalence with dexmedetomidine.⁴³ Another recent randomized controlled trial, the DEXCOM study, compared dexmedetomidine with morphine and showed that dexmedetomidine reduced the duration but not the incidence of delirium after cardiac surgery as compared to morphine-based therapy.⁴⁴ These studies attest to the fact that reducing benzodiazepine exposure by using alternative sedation paradigms improves brain dysfunction outcomes. In a recently published study, dexmedetomidine was compared to midazolam (MIDEX) and propofol (PRODEX) for light to moderate sedation in patients requiring mechanical ventilation for greater than 24 hours.⁴⁵ Arousability, communication, and patient cooperation were improved with dexmedetomidine sedation. Delirium rates were similar but were measured at just one time point (48 hours after stopping sedation); thus, little about the impact of sedation on delirium rates can be ascertained from this study. Propofol and dexmedetomidine appear to be becoming the cornerstones of ICU sedation. While fewer patients are being sedated overall, future studies comparing outcomes, including cost and brain dysfunction, between propofol and dexmedetomidine are necessary. In the end, these studies may be restricted to the most critically ill patients, such as those with severe sepsis and acute respiratory distress syndrome, in whom sedative use may still be justified. Mechanistic studies should be undertaken to better understand the differences in these agents with regards to their contribution to delirium and poor outcomes.

A number of studies have suggested that patients with delirium have cholinergic deficiencies. These have been supported by cohort studies that have shown an association between elevated serum anticholinergic drug levels or serum anticholinergic activity and delirium.^{36, 37} More recently, a large randomized controlled trial evaluating rivastigmine, a cholinesterase inhibitor, failed to show any benefit, and the study was prematurely stopped due to adverse events.⁴⁶ Thus, existing or new medications that would target an increase in cholinergic activity, either globally or via selective cholinergic subtype receptors, still need to be evaluated.

Attenuation of inflammation and reducing microglial activation is an area of significant interest given their implication in delirium. Furthermore, it is possible that patients with endothelial dysfunction or injury may be more prone to blood brain barrier permeability disorders, making patients more vulnerable to systemic inflammatory perturbations and neuroinflammation. It is in this context that there has been a significant interest in the pleotropic effects of statin medications.³³ Studies are underway evaluating the role of statins in delirium, but these will need to be followed by others designed to determine optimal dose and duration of therapy, type of statin medication, whether all patient populations and types of delirium would be equally responsive, and to better understand the mechanisms via which statins would confer the beneficial effects (if any).

As previously discussed, lower levels of serum tryptophan have been associated with delirium in postoperative elderly patients. One randomized controlled trial (NCT00865202) is underway to assess the role of postoperative supplementation of L-tryptophan on the duration and incidence of delirium. Similarly, tryptophan depletion could lead to reduction in serotonin and, consequently, melatonin levels. Melatonin levels themselves may be associated with poor sleep hygiene and, subsequently, delirium. Studies underway will need to focus on dose and duration of melatonin therapy to reduce delirium and will have to incorporate whether this effect is mediated either partially or completely through improved sleep quality.

A landmark study of medical patients reduced the development of delirium by 40% by focusing on several key goals, including regular provision of stimulating activities, a non-pharmacological sleep protocol, early mobilization activities, appropriate and early removal of catheters and restraints, optimization of sensory input, and attention to hydration.⁴⁷ Similar studies have shown a decrease in the duration and severity of delirium without impacting overall incidence;^{48, 49} others have shown benefit only in subgroups of patients⁵⁰ or have not shown any benefit at all.⁵¹ Unfortunately, little data exists about the efficacy of these strategies in ICU patients, and studies need to be undertaken to assess their feasibility and effectiveness.

Pharmacologic therapy to manage delirium should be attempted only after correcting any contributing factors or underlying physiologic abnormalities. Numerous studies have examined the effects of antipsychotic medications on delirium, though large randomized controlled trials comparing the efficacy of typical and atypical antipsychotics to placebo are still lacking. In one of the first studies in critically ill patients, olanzapine and haloperidol were shown to be equally efficacious in reducing the severity of delirium symptoms.⁵² In a small study of patients with delirium and orders to receive as needed haloperidol, quetiapine was shown to be more efficacious than placebo in time to resolution of delirium.⁵³ Prakanrattana et al conducted a randomized controlled trial and showed that a single dose of risperidone sublingually after cardiac surgery reduced the incidence of delirium compared to placebo.⁵⁴ The MIND study, however, compared an atypical antipsychotic with a typical antipsychotic and placebo and found no differences in brain dysfunction outcomes.⁵⁵ Thus, large scale placebo controlled trials are required to determine best antipsychotic agents, dose

and duration of therapy, and to ascertain which population in particular may benefit. Additionally, it would be important to determine if antipsychotic medications would have a differential impact on hypoactive versus hypoactive subtypes of delirium.

Physical and Cognitive Rehabilitation Programs

Among the sequela associated with delirium, functional disability and cognitive impairment, in particular, have been the focus of rehabilitation efforts to improve long-term outcomes. The association between delirium and functional disability is well described in both ICU and non-ICU populations.^{56–59} Functional disability refers to the inability of patients to carry out basic activities of daily living (ADLs) such as bathing, toileting, and dressing and/or instrumental activities of daily living (IADLs) such as taking medication, managing finances, and housework. The interplay between the brain and the body is complex, and there is a growing body of literature indicating pro-cognitive effects of physical activity. Thus, physical and occupational therapy of patients may serve as a means to not only improve functional outcomes but cognitive outcomes as well.

Critically ill patients were once believed to be too ill to undergo physical rehabilitation. Bailey and colleagues challenged this paradigm and demonstrated the safety and feasibility of performing early mobility in a population of mechanically ventilated patients.⁶⁰ Building on these data, Morris and colleagues used a mobility team to perform early physical rehabilitation in ICU patients which led to patients being out of bed on average 6 days sooner than patients receiving usual care.⁶¹ Additionally, intervention patients had shorter ICU and hospital length of stays. Follow-up of this cohort indicated that receiving early physical rehabilitation was protective against hospital readmission and death during the year following critical illness.⁶² Schweickert and collaborators randomized patients to early physical and occupational rehabilitation beginning in the first 72 hours after intubation or to usual care.⁶³ Patients undergoing early rehabilitation were more likely to return to their baseline functional status (e.g., free of ADL and IADL impairments). Additionally, early physical and occupational therapy was associated with a 50% reduction in the duration of delirium in the ICU and in the hospital, suggesting an association between early rehabilitation and improved cognitive outcomes.⁶³ Further data linking early physical rehabilitation to cognitive outcomes was reported following a quality improvement project emphasizing functional rehabilitation and reducing heavy sedation, where the number of days patients spent alert and free of delirium was significantly increased compared to the pre-project rates.¹⁵ These studies highlight the efficacy of early physical rehabilitation for improving brain dysfunction outcomes, suggest an interconnection between the brain and the body, and indicate that the beneficial effects of early physical and occupational therapy are not limited to the body.

Cognitive impairment following delirium is also common, effecting memory, executive functioning, attention, and processing speed and manifesting across a spectrum ranging from minor impairments to frank dementias.⁶⁴ Duration of delirium is associated with cognitive impairment 1 year following critical illness.¹ Similarly, the presence of delirium was found to be associated with self-reported worse cognition 18 months following critical illness.⁶⁵ Interventions focusing on cognitive rehabilitation as a means of rehabilitating post-ICU cognitive impairment are limited. Jackson and colleagues performed a randomized, feasibility study of outpatient cognitive and physical rehabilitation.⁶⁶ Patients undergoing a 12-week, in-home rehabilitation program emphasizing rehabilitation of executive function as well as physical function had improved scores on a test of executive functioning and reported less impairment of IADLs compared to patients managed with usual care. These data suggest the feasibility of outpatient cognitive and functional rehabilitation of hospital survivors but will require determination of efficacy in a larger trial. A randomized trial of

rehabilitation of memory, reasoning, and processing speed conducted in elderly outpatients demonstrated domain specific improvements in the intervention groups.⁶⁷ While these data did not specifically address post-delirium cognitive impairment, they do suggest neurocognitive domains in addition to executive function may be amenable to rehabilitation. Finally, whether critically ill patients can undergo early cognitive rehabilitation in the same manner as they undergo early physical and occupational rehabilitation is an area of ongoing study.⁶⁸

Functional disability and cognitive impairment are adverse outcomes associated with delirium that may be amenable to rehabilitation. Reductions in duration of delirium associated with early physical and occupational rehabilitation requires further study to determine the underlying mechanisms, including directionality, that link the brain and the body. The effects of early physical and occupational therapy on long-term outcomes remains to be evaluated. Limited studies suggest rehabilitation of cognitive impairment is feasible but will require additional study to determine efficacy. Nevertheless, rehabilitation of functional disability and cognitive impairment serves as an attractive intervention aimed at reducing delirium and its associated morbidity.

Conclusion

Clinical assessment of varying presentations in differing patient populations, therapeutic risk stratification, detangling the complex pathophysiology, and evaluation of prevention and management protocols are examples of the future directions required in the clinical and research realms to improve patient outcomes associated with delirium.

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Practice Points

- Delirium assessment tools must be adopted clinically to promote widespread recognition of delirium.
- Altering sedation paradigms and reducing benzodiazepine exposure can improve brain dysfunction outcomes.
- Early physical rehabilitation is safe, feasible, and reduces delirium duration.

Research Agenda

- The epidemiology of the different types of delirium needs to be elucidated and prediction models developed.
- Delirium assessment tools must be further developed, validated, and implemented, including the ability to not only diagnose delirium but measure severity and distinguish delirium subtypes.
- The contribution of different etiologies of delirium to the development of adverse outcomes will need to be determined.
- Research will be required to examine modulation of the proposed pathophysiologic pathways of delirium, including animal models of delirium.
- Interventional therapies aimed at reducing brain dysfunction will need to be tested by multicenter randomized controlled trials.
- The evaluation of physical and cognitive rehabilitation measures will need to continue to determine their effects on short- and long-term cognitive outcomes.

Table 1

Clinical and Research Opportunities to Improve Delirium Outcomes

Knowledge Gap	Future Direction	Potential Application
Delirium recognition	Widespread adoption of assessment tools	Increased recognition, prevention, and treatment of delirium
Epidemiology of delirium severity and subtypes	Development and validation of severity and subtype assessment tools	Flexible prevention and treatment protocols determined by delirium type
Delirium pathophysiology	Animal models and large trials of pathway modulation	Therapeutic modulation of pathways depending on delirium type
Delirium treatment	Multicenter randomized controlled trials of interventional therapies	Appropriate therapeutic protocols for different delirium presentations
Cognitive rehabilitation	Further implementation of early rehabilitation and trials of cognitive rehabilitation	Reduced morbidity by rehabilitating functional and cognitive impairment