Chapter 14
Treatment Strategies for Delirium

Noll L. Campbell and Babar A. Khan

Key Concepts

1. The lack of evidence for treatment of delirium, outside of critically ill populations, limits the ability to make recommendations in other populations or care environments.
2. Non-pharmacologic approaches are the only universally recommended treatment for delirium.
3. Pharmacologic treatment options have not yet provided sufficient evidence to be recommended in any population or care environment.
4. Reducing potential harm through deprescribing or medication-sparing principles is reasonable.

N. L. Campbell (✉)
Department of Pharmacy Practice, Purdue University College of Pharmacy, West Lafayette, IN, USA

Center for Health Innovation and Implementation Science, Regenstrief Institute, Indianapolis, IN, USA

Indiana University Center for Aging Research, Regenstrief Institute, Indianapolis, IN, USA
e-mail: campbenl@iupui.edu

B. A. Khan
Center for Health Innovation and Implementation Science, Regenstrief Institute, Indianapolis, IN, USA

Indiana University Center for Aging Research, Regenstrief Institute, Indianapolis, IN, USA

Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, USA

C. G. Hughes et al. (eds.), *Delirium*, https://doi.org/10.1007/978-3-030-25751-4_14

Introduction

The last 30 years of delirium research has informed many aspects of delirium treatment; nevertheless this field is currently described more by the gaps in knowledge than by the evidence supporting current recommendations. Most of the literature describing delirium treatment has been derived from heterogeneous populations of critically ill adults, with little or no high-quality research to make recommendations on potential treatments in disparate populations. While the critically ill population represents the majority of participants included in delirium treatment trials, other populations at high risk of delirium such as older adults with and without dementia, those in post-acute care facilities, children, and populations at the end of life have been poorly studied and as such have little or no evidence for which to make clinical recommendations. Similarly, current literature fails to evaluate a diverse battery of treatment approaches (non-pharmacologic and pharmacologic) and clinically relevant delirium-associated outcomes.

The underlying heterogeneity in the etio-pathology of delirium creates a challenge to develop uniform therapeutic interventions efficacious for diverse patient populations. Additionally, the very same heterogeneity afforded by the myriad of etiologies and clinical phenotypes may lead to differential delirium duration and severity, relationship with mortality, and long-term cognitive and psychological sequelae. As such, the heterogeneity of delirium pathology may require a similar degree of heterogeneity in treatment approaches. Taking into consideration the advancements in understanding delirium pathophysiology and focusing on desirable treatment outcomes of delirium duration, severity, downstream mortality, and delirium-associated cognitive impairment, therapeutic interventions are likely to require personalization in both their design and delivery.

In this chapter, we will discuss the current pharmacologic and non-pharmacologic treatment strategies for delirium management focusing on patient populations and treatment approaches that have been studied to date. Because much of the evidence published to date reflects trials conducted in critically ill or surgical populations, recommendations cited herein should be applied only to those populations in which trials were conducted. While in this chapter we review the current literature and where it applies, we also note that the absence of particular treatment approaches reflects the absence of investigation as delirium treatments. For example, melatonin and ketamine have been studied in the prevention of delirium, but there is no study evaluating the treatment of delirium, and as such are not discussed in this chapter. Therefore, recommendations made in this chapter intend to highlight available research with applications for clinical practice and appreciate the existing gaps in delirium treatment.

Non-pharmacologic Approaches to Delirium Treatment

Non-pharmacologic approaches to delirium treatment borrow from delirium prevention literature in both hospitalized and critical care populations and address risk factors for delirium common across different patient populations. The approaches

include orientation strategies, supporting and normalizing sleep/wake cycles, and mobility and sensory (visual and auditory) support [1–6]. Studies utilizing non-pharmacologic strategies for delirium prevention have identified variable results, with some showing as much as a 50% reduction in delirium incidence [1, 4–6], while others show no difference [2, 3]. In a study by Inouye and colleagues, although the severity and recurrence rates of delirium were not different between intervention and usual care, there was a significant reduction in the total number of hospital days with delirium (105 vs. 161 days, $p = 0.02$). Among critically ill subjects, a combination of aggressive early physical and occupational therapy provided to patients receiving daily awakening protocols with reduced sedation exposure resulted in a 50% decrease in delirium duration (2 days versus 4 days, $p = 0.03$) [7].

Recently, attention has been focused on the ABCDE bundle (awakening and breathing coordination, delirium monitoring/management, and early exercise and mobility) among critically ill patients. The ABCDE bundle is a promising non-pharmacologic approach to decrease delirium burden in the ICU setting pulling together components that make intuitive sense to reduce delirium burden [8–11]. Implementation of the bundle in the ICU was found to be significantly associated with a lower incidence of delirium (49% vs. 62%, OR 0.55; 95% CI 0.33–0.93) in a before-after study [12]. A newer expanded version of the bundle, the ABCDEF bundle (with "A" modified to assess and manage pain and "F" for family engagement), was evaluated in a larger, multicenter, before-after, cohort study. Improvements in bundle compliance were significantly associated with reduced mortality and more ICU days without coma or delirium [13]. A recent pre-/post-implementation project showed that complete ABCDEF bundle implementation could decrease odds of delirium the next day (AOR 0.60, 95% CI 0.49–0.72). However, complete bundle performance was limited; only 8% of all ICU days reached full adherence, reflecting the challenges of multicomponent interventions in the ICU [14].

Based on the current literature on non-pharmacological treatment of delirium in the ICU setting, the Society of Critical Care Medicine (SCCM) and 2018 Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption (PADIS) guidelines suggest use of multicomponent non-pharmacologic interventions such as the ABCDEF bundle for delirium management although acknowledging the low quality of evidence [15]. Similarly, the American Geriatrics Society's Clinical Practice Guideline for Postoperative Delirium in Older Adults (published in 2015) recommends that healthcare professionals "consider" multicomponent interventions in older adults diagnosed with postoperative delirium (based on a weak level of evidence available at the time) [16].

Value of Future Research: Non-pharmacologic Approaches

While non-pharmacologic interventions for delirium treatment are suggested, key elements of multicomponent interventions are still needed from rigorous clinical trials to improve application and implementation of such interventions. First,

developing consistent definitions and protocols for each element of multicomponent intervention would improve rigor in both comparing results of clinical trials and implementing in clinical practice. Second, understanding which element(s) of multicomponent interventions contribute to the improvements in clinical outcomes could improve efficiency of work force efforts and perhaps improve understanding of mechanisms of disease. Lastly, understanding if and how families can support non-pharmacologic strategies during episodes of delirium would also improve adherence to delirium prevention and treatment strategies.

Pharmacologic Approaches to Delirium Treatment

Although a number of theories exist that explain potential etiologies of delirium [17, 18], the neurotransmitter imbalance hypothesis serves as the primary justification for pharmacologic treatments evaluated to date. Neurotransmitter imbalances may be derived from a number of sources, including hypoxemia, inflammation, endocrine disturbances, and concomitant medications. The neurotransmitter hypothesis initially developed as an explanation for presumed cholinergic deficiency states [19–23] and subsequently expanded to include a state of heightened dopaminergic transmission [24, 25]. In addition to acetylcholine deficiency and dopaminergic excess, the most commonly described neurotransmitter imbalances associated with delirium include norepinephrine and glutamate pathways. Additionally, decreases or increases in serotonin, histamine, and gamma-aminobutyric acid (GABA) may also contribute to neurotransmitter imbalances depending on the population and comorbid medical factors.

In some cases, neurotransmitter imbalances can be aligned with symptom presentations, with cholinergic deficiency explaining symptoms of inattention and dopaminergic imbalance explaining hyperactive states and hallucinations. Dopaminergic effects may be a result of direct dopaminergic activity or by potentiating excitotoxic effects of glutamate [24, 26]. While these theories provide a framework through which to justify treatments, clinical trials have failed to provide a valid treatment effect to date. Potential explanations for treatment failures must include flawed hypotheses; however it is important to note again that the available evidence is drawn from critically ill populations, with heterogeneity in cause of illness and pathophysiologic disease processes. Therefore, recommendations for or against treatment must be made based on results of existing clinical trials and the populations in which they were conducted. Whether unique populations within those trials could benefit from a treatment, or different treatment approaches result in benefit in future trials, remains to be determined. As such, recommendations made by available clinical guidelines [16, 27] state clearly the intent to apply the guidelines only to those patients for which data are included (i.e., guidelines for delirium treatment in *all* critically ill patients published by the Society of Critical Care Medicine).

Failed Pharmacologic Approaches to Delirium Treatment

Antipsychotics

As antagonists at dopaminergic receptors, both typical and atypical antipsychotics have been evaluated as treatments of delirium in critically ill, surgical, and palliative populations [28–33]. While typical (first-generation) antipsychotics are primarily used to reduce hyperactive neurotransmission at dopaminergic receptors (though have lesser affinity for other receptors at higher doses), atypical (second-generation) antipsychotics have a more diverse profile of activity that includes dopaminergic receptors as well as serotonin, histamine, and muscarinic receptors.

Despite evidence from delirium prevention trials suggesting that atypical antipsychotics may prevent delirium in surgical populations, neither typical nor atypical antipsychotics have consistently improved delirium or other clinical outcomes as a treatment approach in critically ill or palliative populations. Five randomized controlled trials have compared either typical or atypical antipsychotics to placebo, and one randomized trial compared a typical antipsychotic as part of a multicomponent pharmacologic intervention with usual care (see Table 14.1). One trial comparing haloperidol to placebo did not show any reduction in the duration of delirium, duration of mechanical ventilation, length of stay in the ICU, or mortality [31]. While one small pilot study comparing quetiapine to placebo did reduce duration of delirium [34], findings from the analysis have been debated [35], and a second pilot trial of quetiapine failed to show differences in delirium severity compared with placebo in hospitalized older adults [36]. Additionally, two larger trials comparing the atypical antipsychotic ziprasidone with haloperidol and placebo also failed to show a difference in the duration of delirium and other important outcomes [28, 29].

Addressing the multicomponent neurotransmitter abnormalities hypothesized to contribute to delirium, Khan and colleagues attempted a multicomponent pharmacological intervention including low-dose haloperidol, along with deprescribing interventions for benzodiazepines and anticholinergic medications in critically ill adults admitted to a mixed medical and surgical ICU. While this trial again found no differences in duration of delirium, it was unique in its assessment of delirium severity and found a small but statistically significant improvement in the intervention group. The impact of this finding on delirium severity and reproducibility from other trials is not yet known. As such, guidelines from both the Society for Critical Care Medicine [27] and the American Geriatrics Society [16] *recommend against the routine use of antipsychotics in the treatment of delirium in all critically ill adults and postoperative older adults.*

Although the randomized trials evaluating antipsychotics in the treatment of delirium were conducted in both medical and surgical patients who were critically ill, each used open-label antipsychotic rescue medication for agitation or hallucinations. Administration of open-label medication particularly in the placebo group may bias the results toward the null hypothesis. Fortunately, and as a result of generally lower doses and short duration of use, tolerability assessments from delirium

Table 14.1 RCTs comparing antipsychotics with placebo or usual care in the treatment of delirium

Author/ title	Population	Intervention	Delirium outcome	Secondary outcomes
Girard et al. MIND [28]	Mixed medical and surgical ICU, $n = 102$	Adjusted-dose haloperidol vs. ziprasidone vs. placebo up to 14 days	No difference in delirium duration	No difference in ventilator-free days, LOS, or mortality
Page et al. HOPE-ICU [31]	Mechanically ventilated ICU, n-141	Fixed-dose haloperidol vs. placebo up to 14 days	No difference in delirium duration	No difference in ventilator-free days, LOS, or mortality
Devlin et al. [34]	Mixed medical and surgical ICU, $n = 36$	Adjusted-dose quetiapine vs. placebo up to 10 days	Shorter duration of delirium in quetiapine group (36 h vs. 120 h; $p = 0.006$)	Shorter time to delirium resolution, less agitation. No difference in ICU LOS or mortality
Girard et al. MIND-USA [29]	Mixed medical and surgical ICU, $N = 566$	Adjusted-dose haloperidol vs. ziprasidone vs. placebo up to 14 days	No difference in coma-free days alive without delirium	No differences in duration of mechanical ventilation, length of stay, or mortality
Khan et al. PMD [32]	Mixed medical and surgical ICU, $N = 350$	Fixed-dose haloperidol, deprescribing of benzodiazepines and anticholinergics	No difference in coma-free days alive without delirium	Intervention group had a small but statistically significant reduction in delirium severity; no differences in LOS or mortality
Agar et al. [30]	Inpatient hospice or palliative care $N = 247$	Adjusted-dose risperidone vs. haloperidol vs. placebo	Higher delirium symptoms in treatment arms	More extrapyramidal symptoms and higher rate of mortality in both active treatment groups

treatment trials have not found significant increases in adverse effects, namely, movement-related disorders such as extrapyramidal symptoms and cardiac arrhythmias including QTc prolongation. However, given a lack of benefits in delirium or other clinical outcomes, recommendations to avoid use of antipsychotics in the treatment of delirium are intended to prevent potential adverse events including risk of prolonged use after discharge from the ICU or hospital.

Antipsychotics in the Management of Agitation (Symptoms of Hyperactive Delirium)

While current guidelines recommend against routine use of antipsychotics in the treatment of delirium, some patients experience distressing thoughts, symptoms, or behaviors as a result of delirium. These may include anxiety, hallucinations, delusions, and agitation. As a result, delirious patients may become physically harmful to themselves or others. Such patients may benefit from short-term use of

haloperidol or an atypical antipsychotic until these distressing symptoms resolve. When using pharmacologic agents to manage behaviors, the following strategies are recommended based on expert opinion:

1. Initiate at lowest dose possible and titrate as needed.
2. Evaluate efficacy and tolerability continuously, allowing appropriate time for clinical effect based on pharmacokinetic principles and onset of effect.
3. Avoid unnecessary continuation by setting stop date parameters (48-h symptom-free, discharge from acute care, discharge from hospital) to avoid inappropriate continuation.

As many as 30% of patients in whom an antipsychotic for delirium is initiated in the ICU are at risk of continuing these medications unnecessarily after discharge [37–40]. Continued exposure to antipsychotic medications after discharge from the ICU or hospital can result in significant morbidity and financial cost. Additionally, recommendations from the American Geriatrics Society regarding the management of agitation in postoperative older adults include the avoidance of benzodiazepines [16]. The AGS guideline states practitioners may use antipsychotics at the lowest effective dose for the shortest possible duration to treat patients who are severely agitated or distressed and are threatening substantial harm to themselves and/or others. In all cases, treatment with antipsychotics should be employed only if behavioral interventions have failed or are not possible, and ongoing use should be evaluated daily with in-person examination of patients.

Acetylcholinesterase Inhibitors

Responding to the well-recognized cholinergic deficiency theory, cholinesterase inhibitors have been tested in the treatment of delirium in both ICU and hospitalized older adult populations. While two pilot trials identified no differences in the severity or duration of delirium (total sample size of both pilots was 31 participants) [41, 42], two larger randomized, placebo-controlled trials of acetylcholinesterase inhibitors failed to show improvements in delirium outcomes [43, 44]. In fact, one study of adults admitted to the ICU was stopped after only 35% of the planned population was recruited due to longer duration of delirium and higher mortality rates in those randomized to the intervention group [44]. As a result, the American Geriatrics Society [16] recommends against using acetylcholinesterase inhibitors in the treatment of delirium in postoperative older adults, and this recommendation is generally accepted among other populations as well.

Statins

Statins, in addition to decreasing cholesterol synthesis, have complex pleiotropic effects [9]. These pleiotropic effects might prevent or attenuate delirium in critical illness by acting on causative mechanisms including neuroinflammation,

blood-brain barrier injury, neuronal apoptosis, ischemia, hemorrhage, and microglia activation [45–47]. Despite evidence from two observational studies suggesting statin users were less likely to experience delirium in the ICU [48, 49], two randomized trials of critically ill adults failed to show improvements in delirium outcomes including incidence and duration of delirium [50, 51]. As such, the SCCM guidelines [27] *recommend against* the routine use of statins as a treatment of delirium, though note that the quality of evidence supporting this recommendation was low.

Unclear Role of Pharmacologic Approaches in Delirium Treatment

Dexmedetomidine

Dexmedetomidine is an alpha-2 receptor agonist with sedative and analgesic properties used as an adjuvant for general surgery and as a sedative in mechanically ventilated populations. Only one randomized trial has evaluated dexmedetomidine as a treatment for delirium particularly in mechanically ventilated adults in whom agitation precludes extubation. This study fell short of its planned sample size due to financial limitations despite screening over 21,000 intubated patients from 15 ICUs [52]. Compared with placebo, the dexmedetomidine group experienced a small but statistically significant increase in ventilator-free hours in the first 7 days after study randomization (17.3 h.; 95% CI, 4.0–33.2) and reduction in delirium duration (24 h; 95% CI 6–41 h); however dexmedetomidine did not influence ICU or hospital LOS, or disposition location at hospital discharge [52]. As with studies of other pharmacologic interventions, patients were allowed to receive open-label dexmedetomidine 48 h after randomization and were also allowed to receive antipsychotics to manage agitation, which may have contaminated the comparator groups, biasing results toward the null hypothesis. Given this single study, the SCCM guideline [27] recommends (based on a low quality of overall evidence) the use of dexmedetomidine in the specific population of mechanically ventilated adults where agitation is precluding weaning/extubation. Whether dexmedetomidine can be used to reduce delirium and other clinically relevant outcomes in patients with delirium but not agitation or in those with delirium and agitation who are not mechanically ventilated has yet to be determined.

Table 14.2 summarizes the applicable guidelines in the acute care of patients at risk of or with delirium. These guidelines represent recommendations generated from expert consensus panels that take into account the quality of evidence as well as the application to routine use of pharmacologic options in all patients. As noted elsewhere in this chapter, these recommendations cite a low quality of evidence, largely driven by the heterogeneity of populations included in clinical trials and delivery of various pharmacologic interventions and protocols.

Table 14.2 Summary of guideline recommendations regarding pharmacologic treatment of delirium in ICU or postoperative populations

	SCCM (2013, 2018) critically ill adults [15, 27]	AGS (2015) postoperative older adults [16]
Antipsychotics	Recommended against use	Recommended against use
First- or second-generation		
HMG-CoA reductase inhibitors	Recommended against use	Not evaluated
Statins		
Acetylcholinesterase inhibitors	Not evaluated	Recommend against use
Dexmedetomidine	Unable to make recommendation	Not evaluated

AGS American Geriatrics Society, *SCCM* Society of Critical Care Medicine

Pharmacologic Risk Factor Reduction in Delirium Prevention and Treatment

Medications including benzodiazepines and anticholinergics may be risk factors for delirium and should be discontinued or used sparingly in those with or at risk of delirium. Benzodiazepines are well-recognized to increase the risk of delirium [53–55], while anticholinergics have been associated with cholinergic deficiency delirium in several studies [20]. Deprescribing strategies in those at risk of delirium have not been well developed or studied in ICU populations; available literature includes two studies unable to significantly reduce exposure to benzodiazepines and anticholinergics compared to usual care [32, 33]. Recommendations against the new use of benzodiazepines and anticholinergics in those with delirium are included in both SCCM and AGS guidelines; however no evidence is available to weigh the risks and benefits of deprescribing benzodiazepines or anticholinergics among prevalent users with delirium in any care environment [16, 27].

Despite rigorous evidence that deprescribing classes of medications with adverse cognitive effects improves outcomes in those with delirium, collaboration with transdisciplinary practitioners in the execution of risk factor reduction can improve efficiency of such interventions; however the optimal approach has not been evaluated with rigorous scientific or implementation approaches.

Value in Future Research: Pharmacologic Approaches

Despite failures of current delirium treatment approaches to improve clinical outcomes, many valuable lessons have been learned that will guide next steps toward treatment of delirium. Guidelines qualify current recommendations largely with low or low-to-moderate quality of evidence given the heterogeneity in delirium etiology and monotherapy approaches attempted. The next phase of research in delirium treatments is challenged with both reducing the heterogeneity in trial participants

and diversifying approaches tested with a personalized treatment regimen. Further work with promising agents including melatonin, ketamine, valproic acid, and dexmedetomidine is also warranted. Of particular importance to any pharmacologic intervention found effective (and safe) in delirium treatment trials are appropriate system approaches to prevent harm from such treatments, which include study into the appropriate duration and cessation of treatment to prevent unnecessary and prolonged exposure.

Additional considerations to optimally defining and measuring the outcomes important in guiding research and clinical practice in the treatment of delirium are important in order to reduce variability across settings and populations. Currently, there is no systematic approach to the selection and reporting of outcomes and their measures in these studies resulting in reporting of numerous and varied study outcomes and measures. Rigorous consensus processes involving key stakeholders including patients and caregivers are ongoing and will develop standardized definitions of core outcome sets to be used in multiple populations and care settings. Lastly, evaluation of a key outcome of extreme importance among those experiencing delirium, long-term functional and cognitive impairment, has been grossly absent from delirium treatment trials. Whether delirium treatment may impact short-term outcomes may be equally as important as their influence on long-term outcomes among delirium survivors.

Summary

It is important to emphasize, again, that gaps in existing knowledge of delirium treatment are prevalent and compromise the ability to make recommendations for or against delirium treatments in many care environments. As such, most recommendations in available guidelines are made with low quality of evidence and may change as rigorous research becomes available. In critically ill and surgical populations, where delirium is perhaps most prevalent, existing evidence does not support the use of pharmacologic approaches to manage delirium. As noted in other chapters of this text, the final common pathway of delirium pathogenesis, if one exists, is currently unclear and is possibly unique to a population or specific etiology. As such, it is unlikely that a one-size-fits-all treatment approach will be effective. The most important actions that clinicians must employ when treating delirium are the identification and correction of underlying causes, along with supportive non-pharmacologic care and management of emergent behaviors as needed. Future research will undoubtedly provide confirmatory evidence to current recommendations or improve clarity into which populations may receive short-term (acute delirium outcomes) or delayed (reduced risk of chronic cognitive impairment or mortality) benefit from pharmacologic or non-pharmacologic treatments of delirium.

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