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REVIEW

Precision-based approaches to delirium in critical illness: A narrative review

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Abstract

Delirium occurs in critical illness and is associated with poor clinical outcomes, having a longstanding impact on survivors. Understanding the complexity of delirium in critical illness and its deleterious outcome has expanded since early reports. Delirium is a culmination of predisposing and precipitating risk factors that result in a transition to delirium. Known risks range from advanced age, frailty, medication exposure or withdrawal, sedation depth, and sepsis. Because of its multifactorial nature, different clinical phenotypes, and potential neurobiological causes, a precise approach to reducing delirium in critical illness requires a broad understanding of its complexity. Refinement in the categorization of delirium subtypes or phenotypes (i.e., psychomotor classifications) requires attention. Recent advances in the association of clinical phenotypes with clinical outcomes expand our understanding and highlight potentially modifiable targets. Several delirium biomarkers in critical care have been examined, with disrupted functional connectivity being precise in detecting delirium. Recent advances reinforce delirium as an acute, and partially modifiable, brain dysfunction, and place emphasis on the importance of mechanistic pathways including cholinergic activity and glucose metabolism. Pharmacologic agents have been assessed in randomized controlled prevention and treatment trials, with a disappointing lack of efficacy. Antipsychotics remain widely used after "negative" trials, yet may have a role in specific subtypes. However, antipsychotics do not appear to improve clinical outcomes. Alpha-2 agonists perhaps hold greater potential for current use and

future investigation. The role of thiamine appears promising, yet requires evidence. Looking forward, clinical pharmacists should prioritize the mitigation of predisposing and precipitating risk factors as able. Future research is needed within individual delirium psychomotor subtypes and clinical phenotypes to identify modifiable targets that hold the potential to improve not only delirium duration and severity, but long-term outcomes including cognitive impairment.

KEYWORDS
biomarkers, critical care, critical illness, delirium, intensive care units, phenotypes, precision medicine

1 | INTRODUCTION

Delirium is common in critical illness and is characterized by an acute and fluctuating disturbance in a patient's attention, awareness, and cognition.[1] It is a frequently encountered form of organ dysfunction and the most prevalent form of acute brain dysfunction in critically ill adults. Around half of intensive care unit (ICU) patients will develop delirium at some point during their critical illness, with a higher prevalence reported in those receiving mechanical ventilation.[2] Importantly, delirium translates to worsened clinical outcomes, ranging from prolonged time on mechanical ventilation to increased mortality, with poorer trajectories seen in those with prolonged durations of delirium.[2–4] Survivors of critical illness are not immune from complications of delirium and commonly exhibit long-term issues, such as cognitive impairment and functional decline.[5] This is reported in both old and young patients, regardless of the burden of baseline coexisting conditions.

The presence of delirium is reported to be in decline since Ely et al.[3] seminal publication in 2004, which reported an 81.7% incidence of delirium in mechanically ventilated patients (this same study highlighted delirium as an independent predictor of 6-month mortality). The 2018 MIND-USA study, conducted at the same site, as well as 15 other institutions in the United States, reported an incidence of 48% in a similar high-risk patient population.[6] While specific pharmacologic prophylaxis or treatment strategies have been lacking in terms of reproducible efficacy, this decrease in incidence is likely due to the improved multi-dimensional care provided in ICUs today, such as the A-to-F Bundle (found at www.icudelirium.org), thus highlighting the importance of adopting and ensuring ongoing compliance with evidence-based, best-practice treatments in critically ill patients.[7,8] This decline in delirium incidence has likely halted or slowed since the coronavirus disease 2019 (COVID-19) pandemic.[9] The change is multifactorial and has been associated with an increase in factors such as prolonged time on a ventilator and deeper levels of sedation, greater exposure to deliriogenic medication, lack of adherence to daily awakening trials, decreased mobility, and isolation—especially from a patient's family, due to onerous visitation policies.

Multiple causes are implicated in the etiology of delirium, with a host of neurobiological processes that contribute to delirium pathogenesis, including neuroinflammation, brain vascular dysfunction, altered glucose metabolism, neurotransmitter imbalance, and impaired neuronal network connectivity.[10] Evidence supports an association between neuronal axonal injury and delirium. These, and many other pathophysiologic processes that contribute to the development and persistence of delirium, make the lack of evidence for a single therapeutic drug or drug class that is effective in all delirium unsurprising. While more precision (i.e., a pharmacogenomic approach) regarding medication therapy for delirium could be warranted in the future, the understanding of an individual's genetic profile to predict alterations in drug metabolism and the risk of adverse effects would only have value once a therapy is established to be effective for an indication. In light of the broad array of contributing factors, and complimentary to the classical psychomotor descriptions of delirium as hyperactive, hypoactive, or mixed, novel classification strategies are perhaps needed to further optimize care in the critically ill population.[11] Clinical phenotypes described in a recent study included delirium driven by hypoxic, septic, sedative-associated, or metabolic (renal or liver dysfunction) causes; each of these was shown to occur in different frequencies, both individually and in overlap, and could potentially lead to differences in long-term outcomes.[12] The complex interaction between sedation and delirium is further emphasized in a study by Kenes et al.,[13] which demonstrated a low incidence (17.3%) of rapidly-reversible, sedation-related delirium (i.e., delirium resolving shortly after a daily awakening trial). Interestingly, rapidly-reversible delirium was not associated with worsened clinical outcomes compared with patients exhibiting delirium that persisted after awakening trials. Clearly, delirium presenting during critical illness is multifactorial and as such, we describe in this narrative review a precision-based approach to this complex syndrome.

2 | METHODS/SEARCH TERMS

A search strategy was designed by all authors and was conducted in MEDLINE and Embase in August of 2022, and repeated in December of 2022. The strategy was limited to English and 2004 onwards. The following Medical Subject Headings (MeSH) headings initially were utilized in the search: delirium, critical care, critical illness, intensive care units, precision medicine, and/or biomarkers. An extensive literature review by the authors reported a paucity of published evidence

on precision and critical care delirium. Therefore, all three authors conducted a narrative review of ICU delirium utilizing the terms: predisposing and precipitating risk factors; precision medicine, biomarkers, phenotypes, and delirium; pharmacological therapy and delirium. Literature that reported previously conducted clinical trials and/or the references of retrieved literature were examined for inclusion in this narrative review. Despite the paucity of strong pharmacologic options for the prevention and treatment of ICU delirium, this review seeks to provide a framework for a detailed, patient-specific understanding of risk and insight into potential prevention and treatment options that are currently available or may be explored in the future.

3 | PREDISPOSING RISK FACTORS

An early step in patient-focused prevention and/or treatment of delirium in critical illness is an understanding and mitigation of risk factors in the patient presenting to the ICU. These risk factors are classically described as predisposing (i.e., background patient characteristics) and are present on ICU admission, and precipitating (i.e., acute modifications from baseline), which are factors that occur during critical illness (Table 1).[14] While predisposing factors may be less amenable to modification in the ICU setting, their recognition and understanding are important for in-patient assessment and treatment when delirium occurs. For example, low baseline vitamin D (i.e., 25-OH-D) levels have been associated with an increased risk of delirium, however, the impact of correcting or repleting the deficiency in the acute setting is unknown.[15] Future work is needed to clarify the impact of modifying predisposing risk factors in the ICU such as chronic deficiency in nutritional status, including vitamin D and thiamine (B1), and their ability to affect the incidence or trajectory of ICU delirium. Additionally, amelioration of predisposing factors, when feasible, should be a priority for survivors of critical illness and could help to highlight the role of post-ICU recovery clinics.

In terms of chronic medication use and ICU delirium risk, there has been much focus in recent years on medications with an anticholinergic burden and their deleterious impact on delirium and dementia. This is emphasized especially in advanced-aged populations where organ function or drug elimination may be impaired, polypharmacy with drug interactions occur frequently, and a blood–brain barrier which may be disrupted. All of these factors will lead to an increased risk of adverse drug effects.[16] Clinical pharmacists must remain diligent in identifying the burden of medications as a root cause for delirium and the need for not just discontinuation, but also resumption because of either actual or potential deliriogenic risk. Continued discussion of re-initiation of medications is therefore critical, despite the paucity of clear guidance.

4 | PRECIPITATING RISK FACTORS

Over 100 precipitating risk factors for ICU delirium have been investigated to varying degrees.[14,17,18] However, given the heterogeneous nature of delirium, one must be mindful of the specific population reported, which likely influences specific findings: advanced aged, post-surgery, or acuity setting, reason for ICU admission, inclusion and exclusion criteria of individual patients, the specifically reported delirium outcome (e.g., incidence, prevalence, duration of delirium, etc.), and delirium assessment tool used (i.e., Confusion Assessment Method for the Intensive Care Unit [CAM-ICU], Intensive Care Delirium Screening Checklist [ICDSC], and so forth). Despite these challenges, there remain several overarching precipitating factors that are common in critical illness. In 2015, Zaal et al.[18] reported 11 putative risk factors for delirium (both predisposing and precipitating). There was high certainty of evidence that age, dementia, hypertension, emergency surgery or trauma, severity of illness, mechanical ventilation, metabolic acidosis, delirium on the day prior, and coma are risk factors for delirium. Additional precipitating factors including sepsis and infection, dysglycemia, stroke, hepatic or renal failure (either due to the inciting cause, reduced clearance of endogenous toxins and medications, or subsequent volume and hemodynamic effects), or metabolic and respiratory derangements are important

TABLE 1 Risk Factors for Delirium in Critical Illness.[14]

Predisposing risk factors	Precipitating risk factors
• Advanced age (i.e., ≥ 65 years of age) • Alcohol (i.e., ≥ 2 units per day) or tobacco use • Cognitive impairment (dementia, developmental delay) • Frailty • High comorbidity burden (cerebrovascular, cardiovascular, renal, hepatic disease) • History of delirium • Home opioid or benzodiazepine use • Illicit drug use • Lower educational level • Poor nutritional status • Psychiatric illness (depression and psychosis) • Polypharmacy, especially medications with a high anticholinergic burden • Seizure disorder • Visual and hearing impairment	• Acute physiologic derangements and severity of illness (e.g., increasing Acute Physiology and Chronic Health Evaluation II score) • Exposure to benzodiazepines, opioids, anticholinergics, and psychoactive medications • Early deep sedation • Immobility and physical restraints • Infection • Invasive devices • Lack of communication with family • Longer duration of mechanical ventilation and ICU and hospital length of stay • Pain • Prolonged ileus • Sleep deprivation and day-night disorientation

to consider when evaluating patients with, or at risk for, delirium. Resolution of these acute pathophysiological changes often coincides with delirium resolution (either partial or complete resolution). ICU patients with more severe or longer delirium duration are more likely to develop longstanding neurocognitive deficits.[5]

The PRE-DELIRIC prediction model, evaluating 10 different risk factors (all mentioned above), has the promising ability to predict patients' risk of developing delirium during an ICU stay (area under the receiver operator characteristic curve [AUC] in original calibration of 0.87 [95% confidence interval [CI]: 0.85, 0.89]; recalibrated in 2018 to 0.74 [95% CI: 0.71, 0.76]) and has the potential to be applied in conjunction with preventative therapies for at-risk patients.[19,20] The concept of risk-stratification, as demonstrated by the PRE-DELIRIC score, will likely facilitate the ability to provide precision-targeted interventions or risk-factor mitigation. That said, PRE-DELIRIC is composed of a minority of factors that are modifiable: coma and opioid use. These factors could also arguably be considered interdependent.

4.1 | Sedation depth

Depth of sedation, especially early deep sedation (generally a Richmond Agitation Sedation Scale [RASS] −3 to −5 within the first 48 h of intubation) versus light sedation, notwithstanding a lack of uniform definitions for each, has been shown to be strongly predictive of delirium.[21–23] This effect may in fact outweigh the clinical impact of a single medication or medication class. Despite this understanding, a 2021 systematic review and meta-analysis by Aitken et al.[24] encompassing 7865 patients from 26 studies reported an inconsistent relationship, especially in randomized controlled trials (RCT), with sedation depth and clinical outcomes; the authors were unable to establish a linear relationship between sedation depth and delirium. The authors acknowledged that substantial heterogeneity existed and few studies identified an a priori outcome specifically in relation to sedation depth; instead, this was tangentially examined in most included studies which sought to examine the effect of specific sedatives or interventions and the subsequent impact on clinical outcomes. The 2018 PADIS clinical practice guidelines separately examined eight RCTs that met their criteria for examination of this question: light sedation was not associated with 90-day mortality but was associated with shorter time to extubation (mean difference −0.77 days; 95% CI: −2.04, −0.50) and reduced tracheostomy (relative risk [RR] 0.57; 95% CI: 0.41, 0.80).[21] Importantly, the guideline authors highlight that studies describing daily spontaneous awakening trials were not included in the assessment of benefit of light sedation as, by definition, they include lightening at a single point in time rather than over an entire 24-h period. This could be a meaningful distinction and warrants further exploration to solidify the benefit of daily awakening for patients already maintained at a light level of sedation. The pausing of sedatives during a protocolized awakening trial, to allow for elimination within the central nervous system (CNS) space and receptor, is beneficial and may lead to the avoidance of harmful effects, such as the development of withdrawal, regardless of the level of arousal. Importantly, no evidence of harm with light sedation was found in these two analyses of the existing literature. Further studies are needed to solidify recommendations in this area and to improve understanding of the benefit of evolving practices, such as a potential synergistic impact of light sedation paired with daily awakening trials.

4.2 | Benzodiazepines and opioids

Medications used in the ICU can be associated with the development of ICU delirium, especially those acting on the CNS. Benzodiazepines are classically associated with delirium, dating back to observational studies first published in 2006, however, one could argue the (over-) sedating effect of the medication class is what primarily drives the risk for delirium.[21,25] In these early studies, both lorazepam and midazolam, commonly used in large doses during mechanical ventilation in the early 2000s, exhibited a near-ubiquitous association with delirium. In the seminal study by Panharipande et al.,[25] the baseline risk of delirium for patients started around 60%, increasing almost linearly to essentially 100% for patients receiving 20 mg of lorazepam per day. However, in a 2007 randomized, double-blind, placebo-controlled trial, lorazepam did not result in a higher prevalence of delirium compared with dexmedetomidine (82% vs. 79%, respectively; $p = 0.65$), although patients randomized to dexmedetomidine did require significantly more fentanyl than those randomized to lorazepam.[23] Importantly, lorazepam was associated with a higher prevalence of the composite outcome of brain dysfunction, including both coma, defined as a RASS of −4 to −5, and delirium (98% vs. 87%, respectively; $p = 0.03$); comatose patients cannot be assessed for the presence or absence of delirium.

In a secondary analysis of the 2015 SLEAP trial by Mehta et al.[26] examining risk factors for delirium, an association between delirium risk and benzodiazepine use was found (hazard ratio [HR] 0.998, 95% CI: 0.997 to 1.0; $p = 0.049$), however, the discordance with previous work could be explained by the interplay between delirium and potential indications for benzodiazepines, as well as the observation that all patients in the study were receiving benzodiazepines and/or opioid infusions at baseline. However, a separate study published in 2015 by Zaal et al.[27] again demonstrated an increased risk of next-day delirium for benzodiazepines (odds ratio [OR] 1.04 per 5 mg of midazolam equivalent, 95% CI: 1.03–1.05); separately, this increased risk was only seen with continuous as opposed to intermittent administration.

Use of benzodiazepines in the critically ill should, therefore, be limited to select indications (i.e., status epilepticus, substance, and alcohol dependence, and potentially in the management of iatrogenic withdrawal or those hemodynamically unstable or requiring deep sedation).[21,28] It could be argued to reinstate a smaller dose of a benzodiazepine for a patient who chronically takes a high dose benzodiazepine and is thus predisposed to iatrogenic withdrawal, agitation, and delirium. Nevertheless, re-initiation of therapy should

be individualized to the patient, while affording the lowest dosage possible and mitigating negative effects of medication reinitiating.

Opioid use has also been associated with the development of delirium however the relationship between opioid use and presence of pain, either treated or untreated, is unclear.[29] Opioids may be deliriogenic in certain patients, but delirium can affect a patient's ability to appropriately describe or self-report pain. This relationship is complex, likely varies based on individual patient factors that change throughout the course of illness and recovery, and has yet to be fully understood.[30] A recent study of 4075 mixed medical-surgical-cardiovascular-neurologic ICU patients demonstrated a dose-dependent increase in the risk of next-day delirium with increasing opioid use (i.e., a 2.4% increased risk for each daily 10 mg intravenous morphine-equivalent dose), which was found to be independent of reported severe pain.[31] Clearly, the relationship between opioids and benzodiazepines, the two classes of medications with arguably the highest deliriogenic risk while commonly utilized in the ICU, and delirium in the individual patient is complex and can be difficult to generalize.

5 | SELECT MEDICATIONS THAT MAY IMPACT ICU DELIRIUM

While opioids and benzodiazepines have historically received much scrutiny within the ICU delirium literature arena, several other medications and medication classes can have an interaction with delirium for the critically ill patient. Medications with cholinergic and anticholinergic properties should be avoided, or at minimum used cautiously in the ICU, as they may precipitate delirium or worsen other clinical outcomes.[21] Anticholinergics are classically associated with confusion and delirium across the health care spectrum.[32] This relationship is often complex and difficult to navigate in the ICU; even prehospital anticholinergic burden has been associated with increased delirium within the hospital, regardless of inpatient use.[33] Several scoring tools have been developed to quantify the risk of adverse outcomes with cumulative anticholinergic burdens. These scales encompass settings generally in older patients and often outside of the ICU.[34] Other classes of medications that have been associated with ICU delirium include dihydropyridine calcium channel blockers.[35] Again, the relationship between the underlying disease state (i.e., hypertension, either controlled or uncontrolled), effective medication therapy, and delirium warrants further exploration. While baseline anxiety and depression are known strong risk factors for the development of delirium, a secondary analysis of the BRAIN-ICU study recently demonstrated that the use of selective serotonin reuptake inhibitors (SSRIs) was associated with a decreased risk of delirium and coma.[36,37] These findings warrant further exploration to determine the association between baseline mental illness, effective chronic treatment (i.e., SSRI therapy) versus new initiation during critical illness, and subsequent impact on delirium.

While avoidance of deliriogenic medications is the focus of much work regarding delirium risk factors, it is notably only half of the work needed when seeking to gain a full understanding of risk factor mitigation concerning medications. Withdrawal, even withdrawal of deliriogenic medications, can be a frequent and strong risk factor for the development of delirium. Alcohol withdrawal syndrome is a common cause of altered mental status and delirium within the ICU. This requires initiation of benzodiazepines or other gamma-aminobutyric acid (GABA)-acting medications for treatment.[38] Withdrawal from medications including opioids or even gabapentinoids carries a strong risk of precipitating delirium, secondary to iatrogenic withdrawal.[29] The confirmed or suspected use of any CNS-acting medications should lead to an evaluation of the potential deliriogenic effect of holding versus any harm in resuming. As alluded above regarding a potential benefit for SSRI use in the ICU, abrupt discontinuation of antidepressants, even those outside of the SSRI class, can precipitate a hyperactive delirium, more commonly known as antidepressant discontinuation syndrome.[39] While statins were assessed in a RCT for the treatment of delirium, investigators discovered that withholding a patient's long-term statin actually increased the odds of developing delirium.[40] While much emphasis has been placed on the deliriogenic risk of *initiation* of medications in the ICU setting, the lack of continuation of chronic therapy is often just as critical.

6 | IMPACT OF THE COVID-19 PANDEMIC ON ICU DELIRIUM

The COVID-19 pandemic has highlighted the importance of risk factor mitigation in the prevention and treatment of delirium. A large, international, observational trial of COVID-19 ICU patients reported a median of 5 days alive without delirium or coma within a 21-day period.[9] Mechanical ventilation, use of restraints, lack of family visitation (in person or virtual), benzodiazepine, opioid, and vasopressor infusions, and antipsychotic receipt were each associated with a higher risk of delirium. Therapies or risk factor mitigations that have proven difficult such as mobility and exercise, light sedation with daily awakening, frequent reorientation and personal interaction, and bedside family presence were demonstrated to be beneficial prior to COVID-19 and were becoming common in clinical practice, yet have received significant focus for their widespread abandonment during the pandemic, potentially in part, to difficulties with isolation precautions.[9,41,42]

7 | PRECISION, PHENOTYPES, BIOMARKERS, AND DELIRIUM IN CRITICAL ILLNESS

7.1 | Delirium subtypes and clinical phenotypes

In 2018, Krewulak et al.[2] reported a systematic review and meta-analysis summarizing the existing literature on the incidence and prevalence of delirium subtypes in the ICU. The authors reported additional variables that contributed to the heterogeneity of the ICU population.

Studies that used the RASS and CAM-ICU defined hypoactive delirium as a positive CAM-ICU assessment associated with a RASS score of 0 to −3. Hyperactive delirium was defined as a positive CAM-ICU associated with a daily RASS score of +1 to +4. Mixed delirium was defined as a positive CAM-ICU assessment and a daily RASS score that fluctuated between hypoactive and hyperactive delirium. Incidence was defined as new cases of delirium in intensive care and prevalence was defined as existing cases.[2] The pooled incidence of delirium psychomotor subtypes was reported in 18 studies: hyperactive (4% [95% CI, 2–6; I^2 (measure of study heterogeneity) = 92%]), hypoactive (11% [95% CI, 8–17; I^2 = 97%]), and mixed (7% [95% CI, 4–11; I^2 = 97%]). Thirty-one studies reported delirium prevalence; delirium psychomotor subtypes were hyperactive (4% [95% CI, 3–6; I^2 = 94%]), hypoactive (17% [95% CI, 13–22; I = 97%]), and mixed (10% [95% CI, 6–16; I^2 = 99%]). The pooled prevalence of hypoactive delirium in a sicker subset (as defined by higher severity of illness and receipt of mechanical ventilation) was higher than the pooled prevalence of hypoactive delirium among the entire study population (35% [95% CI, 23–55%] I^2 = 93% versus 29% [95% CI, 18–46%] I^2 = 95%, respectfully). Additionally, Krewulak et al. identified that some of the heterogeneity was attributed to the proportion of mechanically-ventilated patients, proportion of females, frequency of delirium assessment, and study location.

In Bowman et al.'s 2021[11] review in *Critical Care*, they argue that while there is an exponential rise in delirium research, understanding of the underlying physiological processes remains low. Could the emphasis on psychomotor classification, simply characterized by the degree of global sedation or arousability at the bedside (i.e., RASS scale), inhibit future research?[43] As Bowman describes, accepted psychomotor phenotypes were proposed in 1989 and perhaps over emphasis on these misleads the critical care community. We should instead focus on a personalized patient approach with attention to clinical phenotypes, predisposing risk factors, and precipitating causes within the ICU.[11] An example of this could be the analgesic, sedative, and possible anticholinergic properties of opioid infusions in critical care, which effectively suppress hyperactivity in critical care patients. An emphasis on utilizing opioids in an analgesia first or analgosedation strategy may have resulted from a lack of consideration of the full risk/benefit profile in modern sedation practices. While untreated pain can be detrimental to an ICU patient and should be identified and appropriately addressed, many do not need the tremendous analgesic support provided by opioid infusions. The risk of this approach includes the likely committal to the deliriogenic and sleep-altering effects of opioids, as well as the significant potential for the development of tolerance, withdrawal, and induced hyperalgesia and allodynia, which are exacerbated from prolonged, excessive, and uninterrupted use.[29] Furthermore, the recent scrutiny of common terms including acute encephalopathy and delirium by Slooter et al.[1] in 2020, and recommendation for commonly agreed terminology, goes someway to challenging the current dogma and misleading categorizations. These recommendations include avoiding terms such as acute brain failure and altered mental state.

Bowman goes on to suggest that the term subsyndromal delirium—originally devised as an objective way to identify "high-risk" patients to target for pharmacologic prophylaxis trials—is a condition falling on a continuum between no delirium and confirmed delirium.[11] Subsyndromal delirium may be considered part of a spectrum of delirium severity when using core delirium diagnostic features, however, lacks literature supporting its association with clinical outcomes in the ICU, and is unknown if identification would be practical or clinically useful. Delirium overall then becomes a mixture of sub-phenotypes including risk factors, symptoms, precipitants, and mechanisms.

In 2018, Girard et al.[12] published a secondary analysis of the BRAIN-ICU and MIND-USA studies, which performed rigorous cognitive assessments at 3 and 12 months. The authors reported of the 1040 participants, 708 (68%) survived to 3 months of follow-up and 628 (60.4%) to 12 months. Delirium was common, affecting 740 (71%) patients. A single delirium phenotype was present in only 1355 (32%) of all 4187 participant-delirium days, whereas two or more phenotypes were present during 2832 (68%) delirium days. Sedative-associated delirium (predefined as any receipt of benzodiazepine, propofol, opioid, or dexmedetomidine) was most common (present during 63% of delirium days), and a longer duration of sedative-associated delirium predicted a worse global cognition score after adjusting for covariates (difference in score comparing 3 days vs. 0 days: -4.03, 95% CI: −7.80 to −0.26). The authors did not distinguish whether the individual sedative agent or dose influenced cognitive outcome (Table 2).

Similarly, longer durations of hypoxic delirium (−3.76, 95% CI: −7.16 to −0.37), septic delirium (−3.67, 95% CI: −7.13 to −0.22), and unclassified delirium (−4.70, 95% CI: −7.16 to −2.25) also predicted worse cognitive function at 12 months, whereas metabolic delirium duration did not (1.14, 95% CI: −0.12 to 3.01).[12] Girard et al. go on to recommend that clinicians consider that sedative-associated, hypoxic, and septic delirium often co-occur, that they are distinct indicators of "acute brain failure" (noting terminology), and that clinicians should seek to identify and mitigate potential risk factors that may impact long-term cognitive impairment—especially those that are iatrogenic and modifiable, such as sedation (Table 2).

In an additional post hoc analysis of a RCT, Lindroth et al.[44] sought to categorize delirium phenotypes based on severity (as defined by CAM-ICU-7, a 7-point scale, scored directly from the CAM-ICU) and timing of delirium resolution. Clearly, one would expect that more severe (i.e., more "points" awarded from each of the CAM-ICU aspects) and a longer duration delirium would predict worse clinical outcomes than delirium that is less "intense" and resolves quickly—and is exactly what the authors demonstrated. This builds upon work by Kenes et al.[13] from 2017 demonstrating that persistent delirium after a spontaneous awakening trial portends worsened clinical outcomes, compared with delirium that quickly resolves with cessation of sedation. While the work by Lindroth et al. is important in demonstrating the natural delirium course among the severity spectrum, we are currently lacking in evidence of how to apply this knowledge to a precision-based pharmacotherapeutic approach. Future interventional trials aimed at treating delirium should be mindful of the ongoing work to further classify and assess delirium, in a more granular manner,

TABLE 2 Proposed clinical delirium phenotypes and clinical impact.

Proposed clinical phenotype[12]	Hypoxic	Septic	Sedative-associated	Metabolic	Unclassified
Definitions	SaO_2 < 90% in ≥2 15-min intervals or MAP <65 mmHg in ≥2 15-min intervals or Lactate >4.4 mmol/L with lowest mean arterial pressure < 65 mm Hg	Known or suspected infection and ≥2 systemic inflammatory response syndrome (SIRS) criteria	Any receipt of a benzodiazepine or propofol or opioid or dexmedetomidine	BUN >50 mg/dL or Glucose <45 mg/dL or INR >2.5 and [AST or ALT] >200 U/L or Sodium < 120 mEq/L or Sodium >160 mEq/L	Absence of hypoxic, septic, sedative-associated, or metabolic
Prevalence among participants in Girard et al. study[12] ($N = 1040$)[a]	56%	51%	64%	25%	22%
Long-term cognitive outcomes (RBANDS global cognition at 3 and 12 months in Girard et al.[12] study)[b]	−3.85 (−7.07 to −0.64) and −3.76 (−7.16 to −0.37)	−2.65 (−6.05 to 0.75) and −3.67 (−7.13 to −0.22)	−6.52 (−9.66 to −3.37) and −4.03 (−7.80 to −0.26)	0.15 (−1.52 to 1.81) and 1.44 (−0.12 to 3.01)	−4.72 (−6.93 to −2.51) and −4.70 (−7.16 to −2.25)
Treatment and mitigation options[c]	Potential area for future research. Both hypoxia and hyperoxia have been associated with worsened clinical outcomes	Early, goal-directed treatments (i.e., antimicrobials, volume resuscitation, and vasopressors, as indicated) Ensuring early and aggressive antimicrobial dosing to optimize pharmacokinetic-pharmacodynamic parameters, while adjusting for organ dysfunction, as warranted	Identify and treat/prevent potential medication or substance withdrawal Maintain light sedation with daily spontaneous awakening trials (especially early light sedation) Consider opioid and sedation weaning strategies in long-term patients	Provide supportive care and adjust medications appropriately for organ dysfunction Carefully correct serum electrolytes or other laboratory abnormalities	Determine potential causes and risk factors for delirium, with future avoidance or minimization, as able

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BUN, blood urea nitrogen; INR, international normalized ratio; MAP, mean arterial pressure; RBANDS, Repeatable Battery for the Assessment of Neuropsychological Status; SaO_2, oxygen saturation.

[a]Importantly, in the study by Girard et al.,[12] delirium phenotypes were not mutually exclusive, i.e., patients could be classified as having several types of delirium on the same study day. Delirium was seen with a prevalence of 71% among all study participants.

[b]RBANDS global cognition reported as point estimates (95% confidence interval) at 3 and 12 months, comparing 3 versus 0 days of the exposure variable (delirium clinical phenotype).

[c]Minimize deliriogenic medication, when feasible, including anticholinergic burden.

compared with the historic practice of simply describing psychomotor phenotypes, and correlate severity scores with long-term cognitive decline.

7.2 | Biomarkers and delirium

There is a vast array of biomarker literature in post-operative and critical care delirium. Biomarkers that have been reported in a critical care population including neurofilament light protein (NfL), serum C-reactive protein (CRP), interleukin (IL)-1, IL-6, IL-8, and IL-10, plasma tau, neuron-specific enolase (NSE), and most recently acetylcholinesterase, which was reported by Hughes et al. in 2022.[10,45]

Chan et al.[46] conducted a meta-analysis of ICU delirium biomarkers in 2021. They based their alignment with the National Institute on Aging-Alzheimer's Association (NIA-AA) Research Framework for diagnostic biomarkers; 38 studies were included with 8 suitable for the meta-analysis. In the pooled analysis, significant associations were found between ICU delirium and amyloid β-peptide 1–40 (standard mean difference [SMD], 0.42; 95% CI: 0.09–0.75), IL-1 receptor antagonist (SMD, 0.58; 95% CI: 0.21–0.94), and IL-6 (SMD, 0.31; 95% CI: 0.06–0.56). No significant association was observed between ICU delirium and other biomarkers, but points to potential overlapping mechanisms between delirium and Alzheimer's disease and other related dementia. The authors recommend that critical care providers consider integrating diagnostic approaches used in Alzheimer's disease and other related dementia in their assessment of post-ICU cognitive dysfunction.

In 2022, Page et al.[47] reported a secondary analysis of the Modifying Delirium Using Simvastatin (MoDUS) trial, an RCT of simvastatin versus placebo in ICU delirium, in which the aim was to assess the association, if any, between NfL levels and days in delirium. Higher NfL levels were associated with delirium or coma, and the AUC for NfL levels predicting 6-month mortality was 0.81 (95% CI: 0.7, 0.9). Based on their findings, the authors concluded that NfL measurement within the first 3 days of admission may be useful to identify those patients with worse clinical outcomes and serve as a valuable tool for investigating future delirium interventions. In 2022, Hughes et al.[45] reported a landmark delirium biomarker study where they hypothesized that higher acetylcholinesterase (AChE) activity would be an indication of delirium presence in ICU. The authors enrolled 272 ICU patients and compared AChE activity in patients with delirium versus normal mental state. A higher absolute AChE level was reported in those with delirium versus normal mental status on the same day (OR 1.64, 95% CI: 1.11, 2.43; $p = 0.045$). However, AChE normalized per gram of hemoglobin (AChE/Hgb) and butyrylcholinesterase levels were not associated with delirium. Additionally, none of the markers were associated with long-term cognitive dysfunction or quality of life after ICU discharge. This study was the first to report an association between AChE and delirium in the ICU setting and adds support to the theory that the cholinergic pathway may be key in delirium.

7.3 | Functional connectivity, the electroencephalogram (EEG), and delirium

Delirium presents, finally, as an alteration in brain network integration, described as functional connectivity. In terms of mechanistic origin, there is evidence of both reduced cerebral glucose metabolism and neurotransmitter imbalance in delirium pathophysiology, but work remains to solidify our understanding of this complex arena.[10] In 2021, a systematic review by Boord et al.[48] investigating how EEG measures associated with delirium concluded that delirium is consistently associated with reduced functional brain integration and EEG slowing. Wiegand et al.[49] report that the measurement of functional connectivity differs significantly between ICU patients with and without delirium. This systematic review of EEG in delirium assessment reviewed 31 studies; all showed a certain degree of qualitative or quantitative EEG alterations in delirium. The quantitative measure in the EEG that discerns between delirium and not delirium is the phase lag index (PLI). The PLI is a computer-generated quantitative measure of alpha-band dysconnectivity and theta- and delta-band hyperconnectivity.[50] Overall, this body of work summarizes that EEG slowing and reduced functional connectivity discriminate between those with and without delirium and that a normal routine or continuous EEG makes the presence of delirium very unlikely. The PLI importantly may also be altered in conditions such as Alzheimer's Disease or Lewy Body Dementia and could be used to differentiate cognitive impairment in patients with Parkinson's Disease. Altered functional connectivity (defined as a change in PLI) consistently occurs in delirium in critical illness, and with further investigation, may allow EEG assessments to serve as a precise biomarker for ICU delirium with specific utility in identifying vulnerability, incidence and severity, and long-term effects.

8 | PHARMACOLOGICAL THERAPY AND DELIRIUM

Because of the high burden of delirium in critical illness, there is often considerable overlap between pharmacological treatment and prevention. However, this overlap, or transition, can often be difficult to objectively categorize and pinpoint in large clinical trials (i.e., a patient may be diagnosed with delirium based upon the validated and guideline-recommended ICDSC assessment which occurs over an 8–24 h period, but may fluctuate into and out of delirium during this time). Additionally, as discussed below, enrollment procedures for trials can have a significant interaction in this space. In this section, the authors have critically appraised pharmacological therapies that are considered treatment before considering prevention strategies.

Despite several well-conducted RCTs assessing the efficacy of several pharmacotherapies in delirium prevention and treatment, the vast majority of RCTs continue to report negative or mixed results.[51] There have been only two placebo-controlled trials to show the effectiveness of any drug therapy in critically ill patients with delirium.[21,52,53]

There are many theories and hypotheses as to why RCTs results report negative or mixed findings. First, it is imperative to acknowledge the contribution of heterogeneity in the trial populations. Essentially, labeling all presentations of delirium in critical illness as a single entity (detected by a positive delirium screen) could hamper our ability to differentiate for different delirium subtypes and/or phenotypes.[11,51] There is an urgent need for personalized management strategies for delirium, yet this is hampered by our overall understanding of pathophysiological mechanisms behind a presentation of delirium. Our understanding of the pathobiology and mechanistic causes of delirium continue to grow as hypotheses are developed and examined; these warrant thorough exploration and examination of potential therapies—recently reported research proposes glucose hypometabolism as a potential final common pathway in delirium, which could lead to exploration of different therapeutic approaches in the prevention and treatment of delirium.[10] Consequently, simple psychomotor subtypes (hyperactive, hypoactive, and mixed) are often utilized and simply reported in a table of subject demographics when the overarching term of "delirium" likely requires further categorization and assessment.[11]

8.1 | Alpha-2 agonists—dexmedetomidine

In a 2019 Cochrane Review, Burry et al.[54] reviewed pharmacological interventions for the treatment of delirium in critically ill adults. The authors reported that dexmedetomidine may decrease delirium duration when pharmacological classes were compared with placebo. While this was not reported at the network meta-analysis level, this small effect was seen in the pairwise analyses based on the results of one study (ratio of means 0.58, 95% CI: 0.43–0.79; 71 participants). This single study was the Dexmedetomidine to Lessen ICU Agitation (DahLIA) study.[53]

The DahLIA study randomized 74 patients (71 patients included in the analysis) across 15 ICUs in Australia and New Zealand to dexmedetomidine or placebo, initially at a rate of 0.5 μg/kg/h and titrated by the bedside nurse (from 0 to 1.5 μg/kg/h) to the sedation goal set by the medical staff.[53] This study reported that in mechanically-ventilated patients exhibiting agitated delirium which was precluding extubation, adding dexmedetomidine to standard care compared with placebo (standard care alone) increased ventilator-free hours at 7 days (median 144.8 h vs. 127.5 h, respectively; median difference between groups, 17.0 h [95% CI: 4.0–33.2 h]; $p = 0.01$). There was no difference in ICU or hospital length of stay in either group. However, this study was terminated prior to reaching the planned sample size of 96 patients as the sponsoring pharmaceutical company declined ongoing funding beyond the earlier agreed completion date. In addition to being underpowered, it is important to note that to randomize the 74 patients, about 21,500 patients were screened. Information regarding why these patients were not randomized is interesting and may, in addition to other factors, limit the generalizability of the positive results of this trial. The positive data from this RCT (and subsequent limitations) is reflected in the *Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (2018)*, with a suggestion that dexmedetomidine be considered in mechanically-ventilated patients with delirium (specifically in agitated/hyperactive delirium), where the level of agitation precludes extubation.[21]

In 2019, Shehabi et al.[55] reported the SPICE III study, an international RCT enrolling 4000 patients in which early dexmedetomidine was assessed against standard care. The primary outcome was ICU mortality and there was no difference between either group. The dexmedetomidine arm did have one less day on the ventilator and one less day with delirium or coma, however, these secondary outcomes were unadjusted for multiple comparisons, restricting their interpretation. Importantly, a predefined subgroup analysis found an increase in mortality in patients less than or equal to 63.7 years of age randomized to dexmedetomidine compared with usual care of propofol, midazolam, and other sedatives; the significance or rationale for this difference remains unknown. A post hoc analysis of these findings was reported in *Intensive Care Medicine* in 2021, with Shehabi et al.[56] stating that the risk of mortality was greatest in patients with a higher Acute Physiology and Chronic Health Evaluation (APACHE II) score and with a non-surgical ICU admission, while the study corroborated the findings of a high probability of increased mortality in patients less than 65 years of age, with reduced mortality in patients older than this cutoff. These post hoc analyses should be interpreted with care—while these findings may caution some providers against using dexmedetomidine in this population, the same results of increased harm have not been demonstrated in similar RCTs.[22,23] It is also important to take into consideration the large proportion of patients in both arms of the SPICE III trial that exhibited RASS scores in the deep-sedation range (−5 to −3; 40% and 45.6%, *p*-value not reported), which is arguably not able to be obtained with the sole receipt of dexmedetomidine.[55] In the dexmedetomidine arm of the trial, during the first 2 days post-randomization, 64.7% of patients received propofol, 6.9% received midazolam, and 2.9% received both propofol and midazolam as supplemental sedation; this increased to 86% of patients assigned to dexmedetomidine receiving propofol and 23.3% receiving midazolam in the entire 28-day study period. This finding is contrasted by 11.5% of those assigned to usual care having received dexmedetomidine during the study period. The results of the study demonstrated increased mortality in subpopulations within the trial must be interpreted with this significant cross-contamination.

The most recent RCT conducted in this arena was published in 2021 when Hughes et al.[22] reported the result of the double-blinded MENDS-2 trial, conducted at 13 sites across the U.S. and randomizing 432 patients. Mechanically-ventilated adult patients with sepsis were randomized to dexmedetomidine or propofol and dosed according to sedation targets set by medical staff, with the infusion rate titrated to target by the bedside nurse (all others were blinded to treatment allocation, which included the use of covered infusion bags and tubing). The primary outcome was days alive without delirium or coma and there was no difference

between groups. In the context of a lack of detectable difference in clinical outcomes between groups, it is worthy to note that the rates of sedatives administered to achieve goal arousal levels in this study were small with a median of dexmedetomidine 0.27 μg/kg/h and propofol 10.21 μg/kg/min, coupled with essentially 100% compliance to daily spontaneous awakening and breathing trials. The incidence of deep sedation (as reported in the SPICE III trial) was not reported in the MENDS-2 manuscript or supplement, however, the MENDS-2 study protocol listed instructions for medication titration for "oversedation" (defined as more than 1 RASS level deeper than the sedation target). Oversedation in MENDS-2 was reported to be the reason for a temporary medication hold in 14% of dexmedetomidine patients compared with 20% of propofol patients, which we believe suggests a lighter level of sedation in this study population compared with SPICE III. This amount of medication exposure may (or may not) be different from local ICU practice and further highlights the importance of sedation depth, which according to this study, may be more important than individual sedative agents used for most patients.

8.2 | Alpha-2 agonists—other

Despite clonidine being a frequently utilized alpha-2 agonist in the critically ill in certain regions of the world or in clinical settings where dexmedetomidine cannot be utilized, robust head-to-head data comparing it to dexmedetomidine for sedation and/or delirium in critical illness is currently lacking. The A2B study, currently recruiting in the United Kingdom, compares dexmedetomidine versus clonidine versus standard care (propofol) (NCT03653832).[57] This is a sedation study with a primary outcome of time to extubation, but delirium incidence and long-term cognitive assessment are secondary outcomes. The Clodex trial is also currently recruiting subjects and seeks to compare clonidine with dexmedetomidine in the setting of agitated delirium in intensive care patients (NCT04758936).[58] The results of these two trials are needed to help inform clinicians on the appropriate use of clonidine in the ICU for the indications of sedation and delirium.

Placebo-controlled trials utilizing guanfacine (alpha-2 agonist with both an enteral and intravenous [IV] bolus option) are also being conducted (NCT04742673, NCT04578886).[59,60] Given the potential benefits of dexmedetomidine for delirium in the critically ill, and the fact that guanfacine has a high selectivity for the alpha-2A receptor in the CNS, it is postulated that the delirium-sparing benefits may be enhanced with guanfacine while decreasing other effects which can be seen with dexmedetomidine (because of significant action at all three alpha-2 receptor subtypes).[61]

Finally, with regard to alpha-2 agonists, while not a critical care study, a RCT of sublingual dexmedetomidine versus placebo for acute agitation in bipolar disorder reported a significant reduction in agitation, although excess sedation was reported in more patients compared with placebo.[62] Notwithstanding safety concerns and the need for hemodynamic monitoring, this non-IV formulation could potentially allow for the use of dexmedetomidine in patient care areas outside of the ICU or in those without IV access. However, more research in diverse settings, including the ICU, is needed to define the role of non-intravenous formulations of this agent.

8.3 | Antipsychotics

Antipsychotic medications (typical and atypical) have been widely used and studied to treat delirium in critical illness. Of all RCTs, only a single placebo-controlled trial reported a positive outcome.[52] This RCT by Devlin et al. included 36 adult ICU patients across three sites in the U.S. and Canada, with patients being randomized to 50 mg quetiapine every 12 h or placebo; quetiapine doses were increased every 24 h if greater than one dose of as-needed haloperidol was administered in that block. This study showed that quetiapine added to as-needed haloperidol was associated with a shorter time to first resolution of delirium (1 [IQR 0.5–3] vs. 4.5 days [IQR 2–7]; $p = 0.001$), a decrease in agitation and increased rate of discharge to rehabilitation or home. However, no large RCTs have reported a treatment benefit.[21] Additionally, even though larger than the Devlin et al. investigation,[52] the sample sizes of antipsychotic studies in critical illness are relatively small, thus unfavorable effects may be unclear; antipsychotic rescue medication is also common in these trials and giving such therapy to the placebo group could potentially bias the findings in the direction of the null hypothesis. While some might argue for the benefit of first-generation (i.e., haloperidol) versus second-generation antipsychotics, there remains a lack of demonstrable benefit from either subclass; the decision to utilize a specific agent for a patient can often be attributed toward not only provider familiarity and availability of a desired dosing form, but the differing side effect profile and the desire to take advantage or avoid these specific effects given the heterogeneity in receptor activities.[63] These considerations regarding antipsychotics are reflected in the PADIS guideline, where the routine use of this class of medication is discouraged.[21] The PADIS guideline authors do note that the short-term use of an atypical antipsychotic or haloperidol may be needed in those who experience substantial distress and may cause physical harm to themselves or staff.

In 2022, Andersen-Ranberg et al.[64] published the AID-ICU trial, where 1000 patients were randomized to haloperidol or placebo. For the primary outcome at 90 days post-randomization, the mean number of days alive and out of the hospital was 35.8 (95% CI, 32.9–38.6) in the haloperidol group and 32.9 (95% CI, 29.9–35.8) in the placebo group, with an adjusted mean difference of 2.9 days (95% CI, −1.2 to 7.0; $p = 0.22$). There was also no difference in the secondary outcome of days alive without delirium or coma with an adjusted mean difference of 5.1 days (95% CI, −1.2 to 11.3; p-value not reported). These two composite outcomes were driven largely by a difference in the secondary outcome of mortality at 90 days experienced by 36.3% in the haloperidol group versus 43.3% in the placebo group (adjusted absolute difference, −6.9%; 95% CI: −13.0,

−0.6). However, most consider this to be a negative trial and, taken together with the negative findings of MIND-USA (a multicenter RCT comparing haloperidol, ziprasidone, and placebo for the treatment of ICU delirium), the likely end to the evaluation of antipsychotics for "all comers" in the ICU with delirium.[6] As Marcantonio points out in his editorial, another important aspect of the AID-ICU trial that differs from previous antipsychotic trials, notably MIND-USA, is the enrollment procedure.[65] MIND-USA obtained written informed consent prior to the onset of delirium (screening 20,914 patients to enroll 566 in the trial); AID-ICU subjects were referred to study team members for evaluation for enrollment and informed consent only after screening positive for delirium (data on those with a positive screen referred for inclusion but not enrolled was not provided). This may limit the generalizability of the results as study staff could preferentially enroll patients they thought would benefit the most from therapy and induce selection bias. Potentially related to this enrollment procedure, it is worthwhile to note that AID-ICU enrolled a larger proportion of patients with hyperactive delirium, the psychomotor subtype least commonly detected, compared with previous trials (44.7% vs. 10% in MIND-USA). Regardless of any potential benefit or lack thereof, the use of antipsychotics in these large RCTs was not associated with an increase in adverse effects (despite a QTc segment threshold of 550 msec in MIND-USA compared with potentially lower "standard" thresholds in clinical practice) when used over the short-term for critically ill patients with delirium.[6]

Despite the limited evidence for use in critically ill patients with delirium, antipsychotics continue to be administered. In a point prevalence study conducted across 44 Australian and New Zealand ICUs in 2019, 12% of patients (74/627) received an antipsychotic drug on the study day, with quetiapine the most frequently given antipsychotic.[66] It is again important to note as previously mentioned, that while many antipsychotic studies to date have had negative or mixed outcomes, many of these studies have included a majority of patients with hypoactive delirium.[6,63] It is biologically plausible that antipsychotic medications could treat hyperactive (agitated) delirium, but less so for patients experiencing hypoactive delirium, where the patient may be apathetic and withdrawn. Consequently, there are arguments that any future antipsychotic studies should focus on patients with hyperactive or mixed delirium.

8.4 | Melatonin

Wilbrow et al.[67] recently reported the results of the Pro-MEDIC multicenter, double-blinded, randomized trial of early (within 48 h of ICU admission) 4 mg melatonin liquid at 2100 (for 14 nights or until discharge from ICU) versus placebo for delirium prevention; melatonin is generally given prophylactically each night to maintain/reinstitute normal circadian rhythm as opposed for as-needed treatment, some may still view this as treatment. Unfortunately, despite the rigorous methodology and outcomes examined, melatonin did not result in any detectable improvements compared with placebo.

8.5 | Rivastigmine

It was hypothesized that altered cholinergic transmission may play a role in delirium. Rivastigmine, a cholinesterase inhibitor, had been assessed in a RCT as a potential treatment for delirium based on the impaired cholinergic neurotransmission hypothesis for delirium, but ultimately was found to increase not only the duration of delirium, but mortality as well, leading to the abandonment of further investigation.[68] This is less surprising given the current emphasis on the anticholinergic burden and its association with delirium and dementia.[45]

8.6 | Statins

Given the theory that neuroinflammation could be a significant mechanism in the development of delirium and the previously discussed risk for delirium in patients who are withheld their chronic statin therapy, it has been hypothesized that the new initiation of statins may decrease delirium as a result of their anti-inflammatory properties.[69] The MoDUS trial, published in 2017, included 142 patients at a single site in a randomized, double-blind, placebo-controlled study investigating whether the early administration of simvastatin 80 mg daily in mechanically ventilated patients reduced the time that critical illness survivors experienced delirium or coma, but were unable to find a significant difference in days alive without delirium and coma at day 14 ($p=0.66$). The negative results of MoDUS were potentially thought to have been affected by its tight inclusion criteria, which meant a recruitment rate of just over 12% (1164 patients screened to randomize 142 patients). Prior to the publication of the MoDUS study, an ancillary study within the SAILS trial reported that rosuvastatin did not decrease delirium in ICU or cognitive impairment during the 12-month follow-up period.[70] In line with trial data, the PADIS guidelines recommend not routinely initiating statins to treat delirium.[21]

8.7 | Thiamine

Thiamine has an important role within the CNS. In its active form, it is essential for normal glucose metabolism and is also the cofactor in the transformation of glutamate to GABA and the synthesis of acetylcholine (ACH); neurotoxicity with glutamate and depletion of ACH and glucose hypometabolism is reported in delirium.[71] A systematic review and meta-analysis of IV thiamine supplementation in critical illness was reported by Sedhai et al. in 2021.[72] Their review included 18 studies (8 RCTs and 10 cohort studies). Thiamine supplementation resulted in a 42% lower odds of developing ICU delirium (OR 0.58, 95% CI: 0.34–0.98). A reduction in mortality was also observed on performing fixed effect model analysis, but was not statistically significant on random effect model analysis (OR 0.78, 95% CI: 0.59–1.04). Given that thiamine plays an essential role in both glucose metabolism and neurotransmitter synthesis, has demonstrated success in available studies, and is relatively safe and affordable, it

holds promise in delirium treatment and prevention and should be a target for future research.

8.8 | Valproic acid

Given the desire to maintain patients at appropriate sedation goals without deliriogenic agents, there is increasing interest in the role of valproic acid in the treatment of hyperactive or mixed delirium presentations, but with no available RCTs, evidence for use is solely based on case series and retrospective studies.[73]

9 | PHARMACOLOGICAL PREVENTION OF DELIRIUM

There have been several studies exploring drug therapies to prevent delirium in critical illness, but most studies have had disappointing results—this could be because delirium prevention may be more about what we remove (including the risk factors we minimize) as opposed to the initiation of therapy.[74] Additionally, without medication therapies that effectively treat delirium, a personalized approach is needed regarding the choice of therapy to investigate initiating for prevention. Another challenge is determining a suitable high-risk patient population to expose to a potentially dangerous therapy. Antipsychotics, and even agents like dexmedetomidine are not benign and carry considerable risk, especially in patients who may be predisposed to medication adverse effects; these patient groups and patient groups at high risk for delirium may often overlap. Utilizing prediction models, such as PRE-DELIRIC, as well as identifying patients at risk for specific delirium phenotypes (i.e., sedative-associated delirium) are important to consider when selecting a suitable population for future trials. Overall, despite many drug therapy studies that have successfully sought to prevent delirium in various patient cohorts, the 2018 PADIS guidelines do not recommend the use of any pharmacological agent to prevent delirium.[21]

However, after the release of these guidelines, Burry et al.[74] published a systematic review and network meta-analysis of the *Pharmacological and Non-Pharmacological Interventions to Prevent Delirium in Critically Ill Patients* in 2021. Eleven pharmacological interventions across 38 trials connected to the evidence network for delirium occurrence in this review. Only dexmedetomidine (21/22 alpha-2 agonist studies utilized dexmedetomidine at similar dose ranges) decreases the occurrence of delirium in critically ill adults compared with placebo (OR 0.43, 95% CI: 0.21–0.85; moderate certainty).

10 | DISCUSSION

We have described a broad overview of delirium in critical illness, as well as a complex picture of predisposing and precipitating risk factors that result in alteration in brain network connectivity (functional connectivity) and transition to delirium. The evidence base for precision in delirium subtypes and clinical phenotypes has depended, to date, on a secondary analysis of clinical trials. Krewulak et al.[2] reported that hypoactive delirium is the most prevalent phenotype in ICU. This matters because we know that hypoactive delirium, the predominant psychomotor subtype in large RCTs, does not respond to antipsychotic prevention or treatment despite widespread prescribing. Girard et al.[12] in their retrospective analysis of MENDS-2 and BRAIN-ICU shared that sedation-associated, sepsis, and hypoxic delirium differ from metabolic delirium, although there is considerable overlap and sedation-associated, septic, and hypoxic delirium are associated with cognitive decline.

While psychomotor subtype categorization based on RASS assessment is helpful, the confounder, as Bowman elegantly shared, is that hypoactive delirium could merely be sedation-associated delirium in disguise and plausibly explain the reduction in cognitive decline in both the sedation-associated clinical phenotype and hypoactive psychomotor classifications.[11] Therein, it could be hypothesized that hypoactive and sedative-associated delirium may be one and the same phenotype, and the sedation itself may be what induces cognitive decline perhaps, in part, by an altered anticholinergic pathway (either exogenously or endogenously induced).

Regarding biomarker measurements and delirium, a reasonable term to describe the current landscape is “messy” notwithstanding two distinct features: (1) The presence of inflammatory biomarkers endorses the neuroinflammatory hypothesis for delirium-altered functional connectivity; and (2) EEG and altered functional connectivity holds much promise in broadening our understanding of delirium vulnerability, incidence, and severity, as well as recovery.[49]

Finally, we consider evidence-based pharmacotherapy in critical care delirium. There is a lack of overall efficacy in the current evidence base for delirium treatment. The overall goal in medication optimization for delirium management is to personalize care for the critically ill patient at the bedside, either with or at high risk of delirium, with attention to sedation choice and depth, anticholinergic or CNS burden, medication reconciliation, and targeted therapies that have evidence of benefit (i.e., dexmedetomidine).[21] Broad recommendations that can be made after undertaking this review include: precision in reducing delirium burden in critical illness requires an in-depth understanding of this complex syndrome before assessing individual patient risk, appropriate assessment and consideration of phenotypes, a focus on modifiable factors (specifically medication optimization), utilization of altered functional connectivity as a diagnostic or interventional tool, and finally, therapeutic agents that have a high certainty of evidence in delirium prevention and treatment (i.e., alpha-2 agonists, notably dexmedetomidine).[1,21]

Looking forward, would pharmacotherapy combinations with mechanistic plausibility for additionally proposed inducers of delirium hold a greater chance of success? Perhaps a combination of low-dose dexmedetomidine and IV thiamine supplementation with the aim of modifying glucose metabolism and neurotransmitter pathways could be effective in preventing delirium occurrence? Assessing cumulative risk of the anticholinergic burden in health

care may help to reduce delirium in any setting. The future of delirium therapies could legitimately be assessed by the ability to modify functional connectivity, as assessed by EEG, which evidence suggests is our most precise delirium biomarker.

There are limitations of this review based upon our focus on evidence-based pathophysiology and pharmacotherapy of delirium. We have not included non-pharmacological or environmental therapies which may have benefits yet can be difficult to objectively and reproducibly quantify. In addition, we have not considered pharmacogenomics and its place in delirium, either as an individual risk for delirium or a predictor of response to pharmacotherapy.

In conclusion, the authors purport that delirium is highly likely to occur in critical illness and that the critical care community focus should lie on modifiable interventions and precision in treatment to reduce the overall delirium burden (in both duration and severity). This could hopefully reduce cognitive decline and loss of independent living, which is devastating to our patient's lives.

CONFLICT OF INTEREST STATEMENT

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