The American Psychiatric Association Practice Guideline for the Prevention and Treatment of Delirium

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Table of Contents

Acronyms/Abbreviations

AHRQ Agency for Healthcare Research and Quality

APA American Psychiatric Association

ASA American Society of Anesthesiologists

4AT 4A's Test

CAM Confusion Assessment Method

CAM-ICU Confusion Assessment Method-Intensive Care Unit

CGI Clinical Global Impression

CMS Center for Medicare and Medicaid Services

COVID-19 Coronavirus SARS-CoV-2

CTD Cognitive Test for Delirium

3D-CAM 3-minute Diagnostic Interview-Confusion Assessment Method

DOSS Delirium Observation Screening Scale

DRS Delirium Rating Scale

DRS-R-98 Delirium Rating Scale-Revised-98

DSM-IV Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

DSM-5 Diagnostic and Statistical Manual of Mental Disorders, 5th Edition

DSM-5-TR Diagnostic and Statistical Manual of Mental Disorders, 5th Edition, Text Revision

DTS Delirium Triage Screen

ECG Electrocardiogram

ECT Electroconvulsive therapy

EEG Electroencephalogram

EHR Electronic health record

GAD-7 Generalized Anxiety Disorder 7-Item

GRADE Grading of Recommendations Assessment, Development and Evaluation

GWG Guideline Writing Group

HIE Health information exchange

ICDSC Intensive Care Delirium Screening Checklist

ICU Intensive care unit

MDAS Memorial Delirium Assessment Scale

MMSE Mini-Mental State Examination

MoCA Montreal Cognitive Assessment

NH-CAM Confusion Assessment Method-Nursing Homes

NMS Neuroleptic malignant syndrome

Nu-DESC Nurses Delirium Screening Checklist

PHQ-9 Patient Health Questionnaire-9

PMDP Prescription monitoring data program

PTSD Posttraumatic stress disorder

RASS Richmond Agitation-Sedation Scale

SLUMS Saint Louis University Mental Status

SQEEC Simple Query for Easy Evaluation of Consciousness

SRG Systematic Review Group

RCT Randomized controlled trial

WHODAS 2.0 World Health Organization Disability Assessment Schedule 2.0

WHOQOL-BREF World Health Organization Quality of Life BREF

Introduction

Rationale

The goal of this guideline is to prevent the development of delirium in at-risk individuals and to improve the quality of care and treatment outcomes for patients with delirium.

The prevalence rates of delirium range widely depending on the patient population and treatment setting (e.g., age, hospital vs. outpatient setting, medical vs. cardiac surgical vs. critical care). Most data on the incidence and prevalence of delirium come from hospitalized patients and often older adults (age 65 and older, typically) rather than from the community (Ospina et al. 2018). A meta-analysis of 33 studies of adults (age 18 and older) on medical inpatient units reported an overall delirium occurrence rate of 23% (Gibb et al. 2020). In older adults on medical inpatient units, 11%–25% will have delirium on admission with an additional 29%–31% developing delirium during the hospital stay (Vasilevskis et al. 2012). The pooled prevalence of delirium among adults in intensive care units (ICUs) has been estimated at 31% with a pooled incidence of 4%–11% depending on delirium motor subtype (Krewulak et al. 2018). Delirium appears to be extremely common in mechanically ventilated populations in ICUs and has an estimated prevalence rate of 75% (Mart et al. 2021). With post-operative patients, rates of delirium increase with the severity of the surgery (Vasilevskis et al. 2012). In patients undergoing cardiovascular surgery, the prevalence of post-operative delirium ranges from approximately 7% to 51% depending on the type of surgery and the rating method used (Cai et al. 2022; Wilson et al. 2020). Delirium also occurs in ambulatory settings. For example, among older adult outpatients of a memory clinic in a psychiatric hospital (Quispel-Aggenbach et al. 2021), the rate of probable delirium was 19%. The prevalence of delirium in palliative care populations also varies widely, from a low of 4% to a high of 88% based on care setting and stage of illness (Wilson et al. 2020).

Since 2020, increasing research is exploring the neuropsychiatric side-effects of infection with coronavirus SARS-CoV-2 disease 2019 (COVID-19), including manifestations of delirium. Delirium in the context of COVID-19 may represent a prodromal period before hypoxia, organ failure, acute respiratory failure, or other severe illness occurs, underscoring the importance of rapid identification (Kotfis et al. 2020). A review of 48 observational studies of patients with COVID-19 found delirium was present upon hospital admission in 28% of individuals ages 65 and older and almost 16% of individuals under 65 (Peterson et al. 2021). Delirium incidence while hospitalized with COVID-19 was similarly common, with 25% of those 65 and older and 71% of those younger than 65 afflicted with the condition (Peterson et al. 2021). Among 77 case reports, case series, or observational cohorts, 65%–80% of COVID-19 patients admitted to the ICU exhibited delirium (Hawkins et al. 2021). A myriad of social, epidemiologic, iatrogenic, and psychological factors unique to COVID-19 are hypothesized to play a role in the development and exacerbation of delirium in COVID-19 patients (Kotfis et al. 2020). These include, but are not limited to, social isolation and loneliness related to quarantine procedures; anxiety and fear surrounding the impact of the global pandemic; prolonged mechanical ventilation and immobilization; and delayed extubation due to concerns about aerosol spread of the virus (Kotfis et al. 2020). However, it is unclear whether these findings and contributors to delirium from earlier in the COVID-19 pandemic will continue to hold true in the future.

Delirium exacts a significant economic toll on individuals, their families, and society due to factors such as lengthy hospital stays, ICU admissions, rehospitalizations, and lost wages from work absenteeism (Gou et al. 2021; Kinchin et al. 2021; Vasilevskis et al. 2018). In the United States, direct healthcare costs of hospitalized older adults with delirium are significantly higher than in non-delirious hospitalized patients, even after adjusting for demographic and clinical covariates. Estimates based on data from the late 1990s suggested that total U.S. costs of delirium ranged from $143 billion to $152 billion per year nationally (Leslie et al. 2008). Direct 1-year healthcare costs of post-operative delirium specifically have been estimated at $32.9 billion per year based on data from 2019 (Gou et al. 2021). Patients with hyperactive delirium are estimated to need at least 240 minutes of additional personnel time expended each day of hospitalization (Weinrebe et al. 2016). Additionally, the 30-day incremental cumulative cost of delirium treated in the ICU is approximately $18,000 or roughly an additional $600 per day (Vasilevskis et al. 2018). These costs are almost certainly an underestimate due to the significant mortality rates of patients with delirium in ICU settings (Vasilevskis et al. 2018).

Mortality and morbidity associated with delirium are both substantial. Delirium has been associated with increased mortality during general medical and critical care hospitalization (Hshieh et al. 2020) and more specifically with a 38% increase in the risk of death (Maldonado 2017). Postsurgical delirium has been reported to have a 30-day mortality rate of up to 10% versus 1% in postsurgical patients without delirium (Jin et al. 2020). Delirium was a significant independent predictor of mortality at 30 days, 90 days, 6 months, and 12 months in a population of Medicare beneficiaries discharged from the emergency department (Israni et al. 2018). At 30 days, mortality among patients with delirium was nearly 5 times higher than in patients without delirium, even after adjusting for age, gender, dementia diagnosis, and Charlson Comorbidity Index score (Israni et al. 2018). Delirium also increases risk of death among patients with COVID-19, with a pooled mortality risk (44%) that is triple that of COVID-19 patients without delirium (Peterson et al. 2021).

Delirium has been linked to a host of deleterious outcomes and complications including increased hospital and ICU lengths of stay, greater risk of rehospitalization, more time spent on mechanical ventilation, increased odds of cognitive dysfunction, greater frailty and risk of falls, persistent functional decline, greater likelihood of discharge to long-term care facilities rather than to home, increased risk of respiratory and neurologic sequalae, and higher odds of difficult and extended extubation (Goldberg et al. 2020; Haley et al. 2019; Inouye et al. 2016; Kinchin et al. 2021; Maldonado 2017). Even after remission, patients can continue to experience protracted cognitive impairment, ongoing functional decline, a heightened mortality risk, subsequent rehospitalizations and emergency department visits, and an increased need for long-term care (Fiest et al. 2021; Goldberg et al. 2020; Inouye et al. 2016; Kukreja et al. 2015; Richardson et al. 2021).

Delirium can be a significant strain on patients and caregivers, due in part to subsequent psychosocial distress, such as anxiety and fear; high costs and healthcare utilization; and its association with conditions that are in and of themselves debilitating and burdensome to patients and caregivers, such as Alzheimer's dementia or end-stage diseases (Fong et al. 2019). Delirium-related distress in patients—which can include posttraumatic stress disorder (PTSD)-like symptoms, anxiety, and depression—

appears associated with increased severity of the underlying critical illness, greater cognitive impairment, and longer duration of delirium (Williams et al. 2020). Further, psychosocial consequences of distress during delirium, such as delirium recall or memories, can be upsetting to patients and may persist for months after the condition resolves (Williams et al. 2020). Family members also may report experiencing fear, anxiety, depression, and PTSD-like symptoms from observing their loved one's struggle with cognitive decline, emotional lability, motor disturbances, and disorientation (Rosgen et al. 2021; Williams et al. 2020).

For all of these reasons, this practice guideline focuses on preventing the development of delirium in at-risk individuals and improving the quality of care for patients with delirium, thereby reducing the mortality, morbidity, and significant psychosocial and health consequences of this important psychiatric condition.

Scope of Document

This practice guideline focuses on evidence-based nonpharmacological and pharmacological interventions to prevent or treat delirium in adults. In addition, it includes statements related to assessment and treatment planning, which are an integral part of patient-centered care. The scope of this document is shaped by the diagnostic criteria for delirium with a particular focus on delirium as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition, Text Revision (DSM-5-TR; American Psychiatric Association 2022). Unless otherwise specified, when the term "delirium" is used in this practice guideline, it should be understood in a generic sense. Our comments pertain to delirium due to any cause with the exception of alcohol withdrawal delirium because it is a physiologically discrete condition. As such, alcohol withdrawal delirium has its own clinical assessment and treatment implications, which are often different from the management of delirium due to other causes. Although there are likely to be other physiologically discrete conditions that present with delirium, this practice guideline does not differentiate these conditions as the literature in support of physiological subtypes of delirium remains in its early stages (Bowman et al. 2024). Our comments are also limited by the available evidence, as obtained by a systematic review of the literature through July 9, 2021.

Most studies that were identified in the systematic review for this guideline included patients over age 50 and generally over age 65. Research participants were predominantly male, but in many studies the sample was nearly evenly divided. However, studies of much older adults (age 85 and older) tended to have a predominance of female participants. Studies that specified gender divided the sample into males and females without reporting information on other genders. Most studies also enrolled predominantly White participants or did not specify the racial, ethnic, or cultural characteristics of the sample. Study populations were typically drawn from ICUs or other inpatient hospital settings (e.g., general medical unit, postsurgical unit, cardiac unit), although some studies focused specifically on populations in long-term care facilities, such as nursing homes. These limitations of the evidence emphasize the compelling need for additional research in more representative samples and should be considered in terms of the document scope. In a similar fashion, studies typically did not specify

patients' baseline level of cognitive functioning, which makes it difficult to know whether findings are applicable to all individuals with delirium.

Although delirium can present as hypoactive, hyperactive, or with a mixed level of activity, studies did not typically comment on the motor subtype of delirium that patients exhibited. It is likely that individuals with hypoactive delirium were identified less often and thus, are less likely to be represented in the evidence base. It is also possible that comatose patients may have been viewed as having a hypoactive delirium, influencing the study findings (European Delirium Association and American Delirium Society 2014; Oldham et al. 2017). Furthermore, in contrast to DSM-5 (American Psychiatric Association 2013), DSM-5-TR (American Psychiatric Association 2022) now notes that an inability to respond should be classified as an arousal disorder such as coma or stupor, and not delirium. Because studies rarely assess and report the level of arousal, patients may be misclassified, and study conclusions may be affected. Patient responses to interventions may also differ depending on the specific symptoms of delirium that they exhibit.

It is important to note that the term "delirium" can overlap with related terms that represent clinically distinct entities and concepts. For example, acute encephalopathy describes generalized pathophysiology affecting the brain that can present as subsyndromal delirium or delirium (as well as coma) but may include additional features that are not part of the clinical picture of delirium, such as seizures and extrapyramidal signs (Slooter et al. 2020). As opposed to acute encephalopathy, which lacks a strict clinical definition, delirium describes the clinical syndrome identified during clinical assessment of the patient. Other examples of terms that were outside the scope of this review include "acute confusional state," "acute brain dysfunction," "acute brain failure," and "altered mental status."

Our systematic review did not include studies on alcohol withdrawal delirium because this condition differs in etiology, assessment, and treatment from other types of delirium. Studies on risk factors for delirium were also outside of the scope of our systematic review, although targeted searches on delirium risk factors were conducted and this topic has been reviewed by others (Bramley et al. 2021; Ormseth et al. 2023; Zaal et al. 2015). We also did not examine the impact of potential moderators of interventions for delirium since these were not reported consistently or in relation to primary outcomes. These moderators, including social determinants of health or effects of health disparities (Arias et al. 2022; Boltz et al. 2021; Reppas-Rindlisbacher et al. 2022; Wu et al. 2021), are important areas of further study. Although treatment-related costs are often barriers to receiving treatment, costs of treatment typically differ by country and geographic region and vary widely with the health system and payment model. Consequently, cost-effectiveness and reimbursement considerations are also outside of the scope of this guideline.

Overview of the Development Process

Since the publication of the Institute of Medicine (now known as National Academy of Medicine) report, *Clinical Practice Guidelines We Can Trust* (Institute of Medicine 2011), there has been an increasing focus on using clearly defined, transparent processes for rating the quality of evidence and the strength of the overall body of evidence in systematic reviews of the scientific literature. This guideline was

developed using a process intended to be consistent with the recommendations of the Institute of Medicine (2011) and *the Principles for the Development of Specialty Society Clinical Guidelines* of the Council of Medical Specialty Societies (2017). Parameters used for the guideline's systematic review are included with the full text of the guideline; the development process is fully described in the following document available at the American Psychiatric Association (APA) Web site: https://www.psychiatry.org/psychiatrists/practice/clinical-practice-guidelines/guideline-development-process.

Rating the Strengths of Guideline Statements and Supporting Research Evidence

Development of guideline statements entails weighing the potential benefits and harms of the statement and then identifying the level of confidence in that determination. This concept of balancing benefits and harms to determine guideline recommendations and strength of recommendations is a hallmark of GRADE (Grading of Recommendations Assessment, Development and Evaluation), which is used by multiple professional organizations around the world to develop practice guideline recommendations (Guyatt et al. 2013). With the GRADE approach, recommendations are rated by assessing the confidence that the benefits of the statement outweigh the harms and burdens of the statement, determining the confidence in estimates of effect as reflected by the quality of evidence, estimating patient values and preferences (including whether they are similar across the patient population), and identifying whether resource expenditures are worth the expected net benefit of following the recommendation (Andrews et al. 2013).

In weighing the balance of benefits and harms for each statement in this guideline, our level of confidence is informed by available evidence, which includes evidence from clinical trials as well as expert opinion and patient values and preferences. Evidence for the benefit of a particular intervention within a specific clinical context is identified through systematic review and is then balanced against the evidence for harms. In this regard, harms are broadly defined and may include serious adverse events, less serious adverse events that affect tolerability, minor adverse events, negative effects of the intervention on quality of life, barriers and inconveniences associated with treatment, direct and indirect costs of the intervention (including opportunity costs), and other negative aspects of the treatment that may influence decision making by the patient, the clinician, or both.

Many topics covered in this guideline have relied on forms of evidence such as consensus opinions of experienced clinicians or indirect findings from observational studies rather than research from randomized trials. It is well recognized that there are guideline topics and clinical circumstances for which high-quality evidence from clinical trials is not possible or is unethical to obtain (Council of Medical Specialty Societies 2017). For example, many questions need to be asked as part of an assessment and inquiring about a particular symptom or element of the history cannot be separated out for study as a discrete intervention. It would also be impossible to separate changes in outcomes due to assessment from changes in outcomes due to ensuing treatment. Research on psychiatric assessments and some psychiatric interventions can also be complicated by multiple confounding factors such as the interaction between the clinician and the patient or the patient's unique circumstances and experiences. The GRADE working group and guidelines developed by other professional organizations have noted

that a strong recommendation or "good practice statement" may be appropriate even in the absence of research evidence when sensible alternatives do not exist (Andrews et al. 2013; Brito et al. 2013; Djulbegovic et al. 2009; Hazlehurst et al. 2013). For each guideline statement, we have described the type and strength of the available evidence as well as the factors, including patient preferences, that were used in determining the balance of benefits and harms.

The authors of the guideline determined a final rating for each guideline statement using a process that is endorsed by the APA Board of Trustees (Table 1). The Guideline Writing Group (GWG) determined ratings of strength of the statement (i.e., recommendation or suggestion) by a modified Delphi method using blind, iterative voting and discussion. In order for the GWG members to be able to ask for clarifications about the evidence, the wording of statements, or the process, the vice-chair of the GWG served as a resource and did not vote on statements. The chair and other formally appointed GWG members were eligible to vote. In weighing potential benefits and harms, GWG members considered the strength of supporting research evidence, their own clinical experiences and opinions, and patient preferences. For recommendations, at least 11 out of 12 members must have voted to recommend the intervention or assessment after three rounds of voting, and at most one member was allowed to vote other than "recommend" the intervention or assessment. On the basis of the discussion among the GWG members, adjustments to the wording of guideline statements could be made between the voting rounds. If this level of consensus was not achieved, the GWG could have agreed to make a suggestion rather than a recommendation. No suggestion or statement could have been made if three or more members voted "no statement." Differences of opinion within the GWG about ratings of strength of recommendation, if any, are described for each statement in Appendix F.

A *recommendation* (denoted by the numeral 1 after the guideline statement) indicates confidence that the benefits of the intervention clearly outweigh harms. A *suggestion* (denoted by the numeral 2 after the guideline statement) indicates greater uncertainty. Although the benefits of the statement are still viewed as outweighing the harms, the balance of benefits and harms is more difficult to judge, or either the benefits or the harms may be less clear. With a suggestion, patient values and preferences may be more variable, and this can influence the clinical decision that is ultimately made. When a negative statement is made, ratings of strength of recommendation should be understood as meaning the inverse of the above (e.g., *recommendation* indicates confidence that harms clearly outweigh benefits). In addition, these strengths of recommendation correspond to ratings of *strong* or *weak* (also termed *conditional*) as defined under the GRADE method for rating recommendations in clinical practice guidelines (described in publications such as Guyatt et al. 2008 and others available on the Web site of the GRADE Working Group at http://www.gradeworkinggroup.org/).

Each guideline statement also has an associated rating for the *strength of supporting research evidence*. Three ratings are used: *high*, *moderate*, and *low* (denoted by the letters A, B, and C, respectively) and reflect the level of confidence that the evidence for a guideline statement reflects a true effect based on consistency of findings across studies, directness of the effect on a specific health outcome, precision of the estimate of effect, and risk of bias in available studies (Agency for Healthcare Research and Quality

2014; Balshem et al. 2011; Guyatt et al. 2006). These ratings were determined by the methodologist (L.J.F.) and reviewed by members of the systematic review group (SRG) and GWG.

Table 1. Rating the strengths of guideline statements and evidence for guideline statements

Strength of guideline statement			Strength of evidence		
1	Recommendation	Denotes confidence that the benefits of the intervention clearly outweigh the harms.	A	High confidence	Further research is very unlikely to change the estimate of effect and our confidence in it.
2	Suggestion	Denotes benefits that are viewed as outweighing harms, but the balance is more difficult to judge and patient values and preferences may be more variable.	B	Moderate confidence	Further research may change the estimate of effect and our confidence in it.
			C	Low confidence	Further research is likely to change the estimate of effect and our confidence in it.

Proper Use of Guidelines

The APA Practice Guidelines are assessments of current (as of the date of authorship) scientific and clinical information provided as an educational service. The guidelines 1) do not set a standard of care and are not inclusive of all proper treatments or methods of care; 2) are not continually updated and may not reflect the most recent evidence, as new evidence may emerge between the time information is developed and when the guidelines are published or read; 3) address only the question(s) or issue(s) specifically identified; 4) do not mandate any particular course of medical care; 5) are not intended to substitute for the independent professional judgment of the treating clinician; and 6) do not account for individual variation among patients. As such, it is not possible to draw conclusions about the effects of omitting a particular recommendation, either in general or for a specific patient. Furthermore, adherence to these guidelines will not ensure a successful outcome for every individual, nor should these guidelines be interpreted as including all proper methods of evaluation and care or excluding other acceptable methods of evaluation and care aimed at the same results. The ultimate recommendation regarding a particular assessment, clinical procedure, or treatment plan must be made by the clinician directly involved in the patient's care in light of the psychiatric evaluation, other clinical data, and the diagnostic and treatment options available. Such recommendations should be made in collaboration with the patient, whenever possible, and incorporate the patient's personal and

sociocultural preferences and values in order to enhance the therapeutic alliance, adherence to treatment, and treatment outcomes. For all of these reasons, the APA cautions against the use of guidelines in litigation. Use of these guidelines is voluntary. APA provides the guidelines on an "as is" basis and makes no warranty, expressed or implied, regarding them. APA assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of the guidelines or for any errors or omissions.

Guideline Statement Summary

Assessment and Treatment Planning

1. APA recommends **(1C)** that patients with delirium or who are at risk for delirium undergo regular structured assessments for the presence or persistence of delirium using valid and reliable measures.
2. APA recommends **(1C)** that a patient's baseline neurocognitive status be determined to permit accurate interpretation of delirium assessments.
3. APA recommends **(1C)** that patients with delirium or who are at risk for delirium undergo a detailed review of possible predisposing or contributing factors.
4. APA recommends **(1C)** that a detailed medication review be conducted in patients with delirium or who are at risk for delirium, especially those with pre-existing cognitive impairment.
5. APA recommends **(1C)** that physical restraints not be used in patients with delirium, except in situations where injury to self or others is imminent and only:
    - after review of factors that can contribute to racial/ethnic and other biases in decisions about restraint;
    - with frequent monitoring; and
    - with repeated reassessment of the continued risks and benefits of restraint use as compared to less restrictive interventions.
6. APA recommends **(1C)** that patients with delirium have a documented, comprehensive, and person-centered treatment plan.

Non-Pharmacological Interventions

7. APA recommends **(1B)** that patients with delirium or who are at risk for delirium receive multi-component non-pharmacological interventions to manage and prevent delirium.

Pharmacological Interventions

8. APA recommends **(1C)** that antipsychotic agents and other medications to address neuropsychiatric disturbances of delirium be used only when all the following criteria are met:
    - verbal and non-verbal de-escalation strategies have been ineffective;
    - contributing factors have been assessed and, insofar as possible, addressed; and
    - the disturbances cause the patient significant distress and/or present a risk of physical harm to the patient or others.
9. APA recommends **(1C)** that antipsychotic agents not be used to prevent delirium or hasten its resolution.
10. APA recommends **(1C)** that benzodiazepines not be used in patients with delirium or who are at risk for delirium, including those with pre-existing cognitive impairment, unless there is a specific indication for their use.

11. APA suggests that **(2B)** dexmedetomidine be used rather than other sedating agents to prevent delirium in patients who are undergoing major surgery or receiving mechanical ventilation in a critical care setting.
12. APA suggests **(2C)** that when patients with delirium are sedated for mechanical ventilation in a critical care setting, dexmedetomidine be used rather than other sedating agents.
13. APA suggests **(2C)** that melatonin and ramelteon not be used to prevent or treat delirium.

Transitions of Care

14. APA recommends **(1C)** that, in patients with delirium or who are at risk for delirium, a detailed medication review, medication reconciliation, and reassessment of the indications for medications, including psychotropic medications, be conducted at transitions of care within the hospital.
15. APA recommends **(1C)** that, when patients with delirium are transferred to another setting of care, plans for follow-up include:
    - continued assessments for persistence of delirium;
    - detailed medication review, medication reconciliation, and reassessment of the indications for medications, including psychotropic medications;
    - assessment of consequences of delirium (e.g., post-traumatic symptoms, cognitive impairment); and
    - psychoeducation about delirium for patients and their care partners.

Guideline Statements and Implementation

Assessment and Treatment Planning

Statement 1 – Structured Assessments for Delirium

APA recommends **(1C)** that patients with delirium or who are at risk for delirium undergo regular structured assessments for the presence or persistence of delirium using valid and reliable measures.

Implementation

Despite its high prevalence, delirium is widely known to be under-detected, especially in the acute hospital setting (Bush et al. 2017; Carpenter et al. 2021; Geriatric Medicine Research Collaborative 2019). Research suggests that even highly trained healthcare professionals may be prone to overlooking delirium in the absence of validated screening tools, underscoring the value of routine assessment for ensuring safe and high-quality care (Bush et al. 2017; Devlin et al. 2007; Grossmann et al. 2014; Kotfis et al. 2018; Spronk et al. 2009). Under-recognition is particularly common among patients with hypoactive delirium (Inouye et al. 2001). Consequently, literature supports the use of regular assessments for monitoring patients for presence of delirium or exacerbation of symptoms (Bush et al. 2017; Devlin et al. 2018; Kotfis et al. 2018; Mart et al. 2021). The *2018 Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU* recommend regular assessment of delirium in critical care patients using validated measures (Devlin et al. 2018).

Patients with delirium often experience a longer and more complicated hospital stay, difficulties in participating in their care, challenges in developing a safe discharge plan, and increased morbidity and mortality (Fong and Inouye 2022; Marcantonio 2017; Prendergast et al. 2022). Assessment of delirium may be of particular importance in hospitalized patients with COVID-19 given the increased prevalence and incidence of delirium in this population and the virus' potential long-term impact on cognition (Duggan et al. 2021; Wong et al. 2022). For these reasons, screening, assessment, and early recognition of delirium can hasten evaluation and identification of possible causes, facilitate early intervention, and improve clinical outcomes (Devlin et al. 2018).

Though helpful, results of screening tools should not be accepted uncritically. Rather, if abnormalities are detected on screening tools, it should prompt a more detailed clinical assessment. If screening tests indicate that delirium is present when it is not, unnecessary evaluations could be pursued including laboratory testing, lumbar puncture, or imaging studies. Conversely, screening tests can miss detecting delirium when it is present. In addition, different screening tools focus on different aspects of delirium and may yield different results. Results can also vary depending on the individual administering the screening tool, the extent of their training and experience, and workflow and staffing considerations (Awan et al. 2021).

Patients' ability to cooperate with screening tool administration can also influence results. A patient's awareness and attention may vary due to delirium but also due to other factors such as pain, sedation, or sleep deprivation. The experience of being ill and hospitalized can affect patients' willingness to

cooperate with repeated questioning. Some patients may become overstimulated or irritable or refuse to answer questions. In such instances, screening questions may need to be adjusted or postponed.

Risk factors

Use of structured assessments are recommended for patients at risk for delirium as well as in patients who are exhibiting signs of possible delirium. The list of risk factors for delirium is lengthy and includes both predisposing and precipitating factors (Ormseth et al. 2023). Systematic literature reviews and meta-analyses have helped narrow down the list of known risk factors to those with the strongest relationships with delirium. Commonly identified predisposing factors have included, but are not limited to, advanced age, cognitive impairment including dementia, hearing impairment, functional impairment, multiple comorbidities or frailty, malnutrition, cardiovascular disease, diabetes, central nervous system disorders, depression, and alcohol use disorder (Ormseth et al. 2023; Zaal et al. 2015). Commonly identified precipitating factors have included, but are not limited to, trauma, neurological injury, organ dysfunction (e.g., kidney, liver, respiratory), metabolic abnormalities, hypoalbuminemia, anemia, pain, hypoxemia, fever, infection, medications (e.g., anticholinergics, opioids, benzodiazepines, other sedatives), urinary catheterization, and mechanical ventilation (Bramley et al. 2021; Ormseth et al. 2023; Zaal et al. 2015). Among post-operative patients, additional predisposing features include a high score on the American Society of Anesthesiologists (ASA) physical status classification or Charlson Comorbidity Index (Aldecoa et al. 2017; Bramley et al. 2021), whereas additional precipitating factors include the type of surgery, the duration of surgery, the extent of intraoperative blood loss, the presence of post-operative complications (Aldecoa et al. 2017; Bramley et al. 2021; Ormseth et al. 2023).

The relative contributions of specific risk factors can also vary by treatment setting. For instance, among older adults in the emergency department, delirium was more common in patients who lived in a nursing home (3.4 times more likely), had cognitive impairment (4.4 times more likely), had a hearing impairment (2.5 times more likely), or had a prior stroke (3.2 times more likely) (Silva et al. 2021). In the postsurgical cardiac setting, being over age 65 was associated with 3 times the risk of developing delirium, having diabetes with 1.6 times the risk, cognitive impairment with 5.4 times the risk, and depression with 3.2 times the risk (Chen et al. 2021). By comparison, in an ICU setting, admission risk factors for delirium among individuals 60 years or older were dementia (odds ratio=6.3), receipt of benzodiazepines before ICU admission (odds ratio=3.4), increased creatinine (odds ratio=2.1), and low arterial pH (odds ratio=2.1) (Pisani et al. 2007).

In addition to direct neuropsychiatric effects of COVID-19 infection, a number of other pandemic-related factors may have contributed to the development of delirium. Patients spent extended periods in isolation from family and from healthcare professionals, and communication between staff and patients was hampered because of the need for personal protective equipment (Inouye 2021; Pun et al. 2021). In addition, healthcare facilities were experiencing shortages of staff and higher than usual levels of stress among health care professionals (Inouye 2021; Pun et al. 2021). Increased use of sedative and antipsychotic medication was common as means to help reduce patient anxiety and wandering (Inouye 2021; Pun et al. 2021).

Structured instruments for delirium screening

Several validated tools stand out as being the most psychometrically sound and in widest use to screen for, diagnose, or assess the severity of delirium. In a systematic review of delirium assessment tools for hospitalized adults ages 65 and older, van Velthuijsen and colleagues (2016) found the Delirium Observation Screening Scale (DOSS), Nurses Delirium Screening Checklist (Nu-DESC), Confusion Assessment Method (CAM), Confusion Assessment Method-Intensive Care Unit (CAM-ICU), and Delirium Rating Scale-Revised-98 (DRS-R-98) to be the most appropriate for routine use in detecting delirium. A systematic review of delirium assessments for use outside of ICU settings identified the CAM, DOSS, DRS-R-98, and Memorial Delirium Assessment Scale (MDAS) as having the strongest validation and closest alignment with delirium diagnostic criteria from the DSM-5 (Helfand et al. 2021). For patients in the ICU, a systematic review found the CAM-ICU and the Intensive Care Delirium Screening Checklist (ICDSC) were the most valid and reliable critical care instruments for delirium assessment (Gélinas et al. 2018).

In selecting a structured instrument for delirium screening, other factors to consider in addition to the setting of care include the availability of the scale (e.g., cost, electronic formats, languages), training and time needed to administer the scale, criteria and population used to validate the scale, and sensitivity and specificity of the scale. In interpreting the results of delirium screening, it is important to recognize that results may be influenced by other conditions that affect a patient's mental state, such as dementia, catatonia, or severe psychotic or mood disorders. To assist in scale selection, features of commonly used scales are described in this section and in Table 2.

The CAM is a widely used instrument to screen for and diagnose delirium. It has been adapted to be used in many settings, including in the ICU (CAM-ICU) and in nursing homes (NH-CAM; De and Wand 2015; Wei et al. 2008). The CAM consists of four core features: 1) acute onset and fluctuating course, 2) inattention, 3) disorganized thinking, and 4) altered level of consciousness. Features 1, 2, and either 3 or 4 are required for a diagnosis of delirium (Wei et al. 2008). The CAM was validated against the DSM-III-R. When performed by trained clinicians and scored based on the results of formal cognitive testing, it has been reported to demonstrate sensitivities from 94% to 100%, specificities from 90% to 95%, and interrater reliability ranging from 0.81 to 1.00 (Wei et al. 2008).

The CAM-ICU is a structured assessment for scoring the short version of the CAM that was developed specifically for assessing mechanically ventilated patients in the ICU. Thus, it can be administered to individuals who are nonverbal, unlike the CAM and its nursing home adaptation, the NH-CAM. Training is recommended when the CAM-ICU is used, and a training manual is available (Ely 2016). The CAM-ICU consists of the same four core features as the CAM and uses the same scoring algorithm (Ely et al. 2001). The CAM-ICU has excellent sensitivity and specificity, ranging from 95% to 100% and from 93% to 98%, respectively (Wei et al. 2008). The nonverbal items have a sensitivity of 73% and specificity of 100%. The CAM-ICU-7 uses a different approach to scoring the CAM-ICU and scores have high internal consistency, good correlations with DRS-R-98 scores, and good predictive validity in reflecting delirium severity (Khan et al. 2017).

The 3D-CAM is a 3-minute diagnostic interview for the CAM that was developed for use in verbal patients (Marcantonio et al. 2014; Palihnich et al. 2016). The authors mapped more than 120 items from the CAM to diagnostic features of delirium and then used item-response theory and statistical approaches to identify 20 of the most informative items. The 3D-CAM shows good agreement with the CAM, although the 3D-CAM may overidentify delirium (Oberhaus et al. 2021). In a sample of medical inpatients older than age 75, the 3D-CAM took 2 to 5 minutes to administer with a sensitivity of 95% and specificity of 94% for identification of delirium, including hypoactive delirium (Marcantonio et al. 2014). Although the specificity of the 3D-CAM was reduced in individuals with dementia, the sensitivity remained high (Marcantonio et al. 2014). A subsequent systematic review and meta-analysis obtained estimates for pooled positive and negative likelihood ratios of 18.6 and 0.09, respectively (Ma et al. 2023). When an alternative scoring approach is used, the 3D-CAM can be used to assess the severity of delirium as well as its presence (Vasunilashorn et al. 2016). Administration of the 3D-CAM can be facilitated with the use of apps (Marcantonio et al. 2022) and incorporation of skip logic into the 3D-CAM can further reduce administration times (Marcantonio et al. 2022; Motyl et al. 2020).

The NH-CAM is derived from the Minimum Data Set Resident Assessment Instrument and contains nine items that cover the same four features as the CAM and CAM-ICU (Dosa et al. 2007; Wei et al. 2008). Scoring is also similar to the CAM and CAM-ICU, but the included algorithms can detect two stages of subsyndromal delirium as well. Although inter-rater reliability of individual items ranges from 0.38 to 0.80, predictive validity is good, and the NH-CAM can be used to stratify patients based on risk of future rehospitalization and mortality (Dosa et al. 2007).

Another common tool for assessment of delirium severity is the DRS-R-98. It is a 16-item clinician-rated scale with 13 severity items and 3 diagnostic items, yielding total scores that range from 0 to 46 with higher scores indicative of more severe delirium (Trzepacz et al. 2001). The DRS-R-98 was validated against the Cognitive Test for Delirium (CTD), Clinical Global Impression scale (CGI), and Delirium Rating Scale (DRS). Sensitivities ranged from 91% to 100% and specificities from 85% to 100% for the total score; for severity scores, sensitivities ranged from 86% to 100% and specificities from 77% to 93%, depending on the cutoffs or comparison groups used (Trzepacz et al. 2001).

The MDAS is a 10-item clinician-rated assessment for delirium severity, with scores ranging from 0 to 30 and higher scores indicating greater delirium severity (Breitbart et al. 1997). The MDAS has good inter-rater reliability (e.g., overall Cronbach's α=0.91), and scores correlate significantly with those from other validated delirium measures, including the DRS, Mini-Mental State Examination (MMSE), and clinician's global rating of delirium and delirium severity. Although it was not designed as a diagnostic tool, a cutoff score of 13 on the MDAS has been found to adequately discriminate between patients with and without delirium, with a sensitivity of 70% and specificity of 94% (Breitbart et al. 1997).

The 4 'A's Test (4AT) is named to reflect its four components: Alertness, the Abbreviated Mental Test-4 (AMT4), Attention, and Acute change or fluctuating course (Bellelli et al. 2014). Scores on the 4AT range from 0 to 12, and a value of 4 or greater suggests the possibility of delirium, cognitive impairment, or both (MacLullich 2024). In emergency patients or acute medical patients age 70 or older, the 4AT had a

sensitivity of 76% and a specificity of 94% as compared to values of 40% and 100%, respectively for the CAM relative to a standard assessment using DSM-IV criteria (Shenkin et al. 2019). A pooled analysis of studies of the 4AT yielded a sensitivity of 88% and a specificity of 88% (Tieges et al. 2021). Elevated scores on the 4AT have been associated with greater rates of mortality (Anand et al. 2022; Evensen et al. 2021).

The Nu-DESC is a 5-item scale that can be quickly administered (generally <2 minutes) to detect delirium (Gaudreau et al. 2005). Items are scored on a scale of 0 to 2, for a total maximum score of 10. A cutoff score of 2 suggests the presence of delirium and has a diagnostic accuracy of 86%. In validation studies, the Nu-DESC demonstrated a sensitivity of 86% and specificity of 87% (Gaudreau et al. 2005). Scores on the Nu-DESC correlated significantly with DSM-IV criteria and with scores from the MDAS.

The ICDSC assesses 8 areas based on DSM-IV criteria and common features of delirium (Bergeron et al. 2001). A cutoff score of 4 has been shown to identify delirium in 99% of patients who have the diagnosis but also 36% of patients who do not (Bergeron et al. 2001). Its inter-rater reliability is high, at 94%, with an intraclass correlation coefficient of 0.86 (Gélinas et al 2018). Sensitivity of the ICDSC ranges from 64% to 99% and specificity ranges from 61% to 88% (Gélinas et al. 2018).

The DOSS is available in English but has only been validated in Dutch and does not include all of the criteria needed to establish a diagnosis of delirium (Schuurmans et al. 2003). Other instruments that are sometimes used include the Simple Query for Easy Evaluation of Consciousness (SQEEC), the 4AT, and the Delirium Triage Screen (DTS) (De and Wand 2015). Although the Richmond Agitation-Sedation Scale (RASS) has been used in some studies, it is not a scale for assessment of delirium. Rather, it is intended for assessing the degree of sedation in critical care patients. In addition, RASS ratings are centered around 0 and include negative as well as positive integers. This can yield summary statistics such as mean values, that are potentially misleading.

546 Table 2. Summary of validated assessment tools for delirium

Assessment Tool	Reference	Number of Items	Approximate Completion Time	Advantages	Disadvantages	Access
4AT	MacLullich 2024	4	2 minutes	Validated in multiple settings; can be used in nonverbal patients and those who are unable to cooperate with testing; available in 20 languages; can be easily integrated into electronic medical records; apps are available; no specific training required	Insufficient to establish a diagnosis of delirium	Freely available through the 4AT website (https://www.the4at.com)
CAM	Inouye et al. 1990	9	10–15 minutes (long form); 3–5 minutes (short form)	Largely aligns with DSM-5-TR diagnostic criteria; offers 2 forms (short and long) that incorporate specific cognitive tests as detailed on scoring sheets; can be easily integrated into electronic medical records; can be used for screening, diagnosis, and severity ratings; has been translated to 7 languages	The short form does not cover as many domains as some other delirium assessments; thus, the short form may be more reliable as a screening instrument than as a diagnostic one; if used without training, validity and reliability are reduced	The CAM is copyrighted and owned by the American Geriatrics Society. Nonprofit and clinical use are allowed free of charge only after permission is granted from the American Geriatrics Society. Information about obtaining permission can be found at the American Geriatrics Society website.
CAM-ICU	Ely et al. 2001	9	<5 minutes	Requires minimal training to administer;	Certain items may be difficult to assess in patients with	The CAM-ICU and its related materials (e.g., training materials, pocket guide,

				can be used with ventilated and nonverbal patients; can be used for diagnosis; has been translated to 32 languages and validated in 4 languages	brain injury, cognitive impairment, and moderate to deep sedation	worksheets) are freely available for unrestricted use by Vanderbilt University's Critical Illness, Brain Dysfunction, and Survivorship Center. Materials are available in English and in 31 other languages.
3D-CAM	Marcantonio et al. 2014	20	2–5 minutes	Requires minimal training to administer; can be used for diagnosis; can be scored to reflect delirium severity	May over-identify delirium; requires that patients be able to respond to questions verbally	The 3D-CAM is available in English and 15 other languages.
DRS-R-98	Trzepacz et al. 2001	16	20–30 minutes (scoring), preceded by gathering information from nurses, the family, and the patient chart	Aligned with DSM-5-TR diagnostic criteria; can be used for screening, diagnosis, and severity ratings; has been translated to and validated in 3 languages	Time consuming to administer; administration is more labor intensive than some other delirium assessments; designed to be administered by a healthcare professional with psychiatric training (e.g., psychiatrist, psychologist)	Permission to use the DRS-R-98 must be obtained from the author (pttrzepacz@outlook.com).
ICDSC	Bergeron et al. 2001	8	7–10 minutes	Can be used for screening; can be administered by non-specialist ICU staff; has been translated to and validated in 6 languages	May be prone to Type I error (false positive results); not intended to be used for diagnosis or severity ratings	The ICDSC is freely available for clinical or research use; however, the following citation of the original paper is required: Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist:

						evaluation of a new screening tool. Intensive care medicine 27(5):859-864, 2001
MDAS	Breitbart et al. 1997	10	10–15 minutes (scoring), preceded by interviews and gathering information from nurses, the family, and the patient chart	Can be used for severity ratings; well suited for use in delirium treatment research	Not originally designed for use as a screener or diagnostic tool, although data suggest it can be used as a diagnostic tool as well; does not cover DSM-5 items of acute onset and fluctuating course	The MDAS is freely available from the MDAS publisher's website.
Nu-DESC	Gaudreau et al. 2005	5	<2 minutes	Can be used for screening; takes much less time to administer compared with many other validated delirium assessment tools; has been translated to and validated in 4 languages	Not based on DSM diagnostic criteria and therefore cannot be used for diagnosis; may not be as effective in detecting delirium in hypoactive patients; requires training for administration	The Nu-DESC is freely available from the Nu-DESC publisher's website.
NH-CAM	Dosa et al. 2007	9	5 minutes	Uses existing items from the National Repository of the Minimum Data Set Resident Assessment Instrument	Requires training for administration	Uses items B5f, E3, B5a, B5b, B5c, B6, B5d, B5e, and E5 of the National Repository of the Minimum Data Set Resident Assessment Instrument, the full version of which is available at: https://www.cms.gov/Medicare/Quality-Initiatives-Patient-Assessment-

						Instruments/NursingHomeQualityInits /MDS30RAIManual

Abbreviations. CAM=Confusion Assessment Method; CAM-ICU=Confusion Assessment Method–Intensive Care Unit; 3D-CAM=3-minute Diagnostic Interview-Confusion Assessment Method; DRS-R-98=Delirium Rating Scale-Revised-98; DSM=*Diagnostic and Statistical Manual of Mental Disorders*; DSM-5=*Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition; DSM-5-TR=*Diagnostic and Statistical Manual of Mental Disorders*, 5th Edition, Text Revision; ICDSC=Intensive Care Delirium Screening Checklist; ICU=intensive care unit; MDAS=Memorial Delirium Assessment Scale; NH-CAM=Nursing Home-Confusion Assessment Method; Nu-DESC=Nursing Delirium Screening Scale.

Source. Bergeron et al. 2001; Gaudreau et al. 2005; Gélinas et al. 2018; Grover and Kate 2012; Helfand et al. 2021; van Velthuijsen et al. 2016.

Statement 2 – Determination of Baseline Neurocognitive Status

APA recommends **(1C)** that a patient's baseline neurocognitive status be determined to permit accurate interpretation of delirium assessments.

Implementation

To permit accurate interpretation of clinical or structured assessments for delirium, a patient's baseline neurocognitive status should be determined (Duggan et al. 2021; Fong and Inouye 2022; Grover and Kate 2012; Kotfis et al 2018; Maldonado 2017; Meagher and Leonard, 2008; Oh et al. 2017; Ospina et al. 2018). In DSM-5-TR, the criteria for delirium require that "the disturbance …. represents a change from baseline attention and awareness" (American Psychiatric Association 2022). Accordingly, many screening tools for delirium also incorporate a requirement that the patient's clinical findings must represent a change from their baseline cognitive functioning.

Baseline neurocognitive status is also essential to determining when delirium has resolved. The longitudinal course of delirium varies, but delirium may still be present when a patient leaves the hospital and for some time thereafter (Pereira et al. 2021; Wilcox et al. 2021). Obtaining and documenting the patient's baseline neurocognitive status at the time of index hospitalization will reduce the confounding effects of retrospective recall and will aid in identifying persistent delirium.

Baseline neurocognitive status can be determined in a number of ways. For patients who are being admitted for an elective surgical procedure (e.g., major orthopedic or cardiac surgery) that is associated with a significant risk of delirium, it may be helpful to administer a cognitive screening test such as the Montreal Cognitive Assessment (MoCA; Nasreddine et al. 2005) in advance of the procedure. In other circumstances, information can be obtained by speaking with family members or others who are part of the patient's support network. Review of prior medical records and input from the patient's primary care clinician can also provide details on the patient's baseline cognitive status.

Determining baseline neurocognitive status can be a particular challenge in individuals with pre-existing cognitive impairment related to conditions such as intellectual developmental disorder, stroke, traumatic brain injury, dementia, or other degenerative nervous system disease (Fong and Inouye 2022). Rates of pre-existing cognitive impairment are increased in hospitalized patients. In ICU settings, the prevalence of pre-existing cognitive impairment has been reported to be 37% among patients 65 years and older (Pisani et al. 2003). Individuals with pre-existing cognitive impairment may be more likely to develop delirium during a hospital stay, and knowledge of baseline cognitive status may help in determining relative risk (Tsui et al. 2022). In addition, cognitive changes that do occur may be erroneously disregarded by clinicians if they are viewed as a manifestation of the patient's baseline cognitive impairment (Bergl 2019; Oh et al. 2017). Interventions that are aimed at reducing or preventing delirium, such as orienting the patient or providing education, may also require adjustment if a patient has a pre-existing cognitive impairment.

Statement 3 – Review for Predisposing or Contributing Factors

APA recommends **(1C)** that patients with delirium or who are at risk for delirium undergo a detailed review of possible predisposing or contributing factors.

Implementation

As discussed in Statement 1, there are multiple factors that can predispose to or contribute to the development of delirium although risk factors (as shown in Table 3) may differ with the patient population, treatment setting, or subtype of delirium (Aldecoa et al. 2017; Bramley et al. 2021; Ghezzi et al. 2022; Krewulak et al. 2020; Ormseth et al. 2023; Zaal et al. 2015; Wilson et al. 2020). Individuals may also have several of these factors that together contribute to the development of delirium, although each factor alone may not have precipitated a delirious state. Because delirium is not a unitary entity with a single cause, it is only through addressing these manifold precipitating and predisposing factors, insofar as possible, that we can fully treat delirium in individual patients.

An increase in delirium risk has also been noted in the literature with factors that likely act in a complex or indirect fashion (e.g., recent fall; hip fracture; trauma; hospitalization; ICU admission; specific surgical procedures; hospital-acquired conditions; use of interventions that restrict movement such as cardiac monitoring, intravenous lines, traction device, or pneumatic leg compression devices). Other factors may worsen the apparent symptoms of delirium. For example, an individual who is restrained, in pain, or withdrawing from nicotine may become more agitated if they are delirious whereas an individual whose primary language differs from that of the staff may be less likely to receive interventions such as frequent re-orientation. These factors are also important to recognize in providing quality care to patients with delirium.

Table 3. Some common predisposing and contributing factors for delirium

- Demographic factors
  - Advancing age commonly defined as ≥65 years
  - Residing in structured setting (e.g., residential, long-term care)
- Aspects of history
  - Prior delirium
- Co-occurring conditions
  - Psychiatric disorders
    - Cognitive impairment, including dementia
    - Alcohol or other substance use disorders
    - Depressive disorders
  - Other central nervous system abnormalities
    - Cerebrovascular disease, including prior stroke
    - Alzheimer's disease
    - Parkinson's disease
    - Traumatic brain injury
    - Meningitis or encephalitis
    - Vasculitis

        - Seizure disorder
        - Other central nervous system disorders
    - Other medical illnesses
        - Infection (e.g., pneumonia, urinary tract infection, HIV, COVID-19)
        - Sepsis
        - Cardiovascular disease (e.g., heart failure)
        - Pulmonary disease (e.g., chronic obstructive pulmonary disease)
        - Kidney disease
        - Hepatic failure
        - Diabetes mellitus
        - Other endocrine abnormalities (e.g., thyroid, adrenal)
        - Metastatic disease
        - Paraneoplastic syndromes
        - Obstructive sleep apnea
        - Multiple chronic conditions, including as measured by Charlson Comorbidity Index
- Commonly implicated medications and other substances
    - Specific medications and medication classes
        - Benzodiazepine or other sedatives
        - Medications with anticholinergic properties
        - Opioid analgesics, including meperidine
        - Corticosteroids
        - Immunosuppressive agents
        - Sympathomimetics
    - Herbal medications or nutraceuticals
    - Use of multiple medications, including adding 3 or more medications during admission
    - Medication related toxicities
        - Neuroleptic malignant syndrome
        - Serotonin syndrome
        - Toxicity with elevated serum levels (e.g., lithium, valproic acid, carbamazepine, amiodarone, digoxin, phenytoin, salicylate)
        - Medication related metabolic disturbances (e.g., hyponatremia related to antidepressants or carbamazepine, hyperammonemia related to valproic acid)
    - Toxins (e.g., heavy metals, pesticides, solvents, carbon monoxide)
- Physiological abnormalities
    - Hypotension
    - Anemia or significant blood loss, including situations requiring blood transfusions
    - Metabolic disturbances (e.g., sodium, calcium, magnesium, phosphate abnormalities)
    - Acid-base abnormalities
    - Hyperammonemia
    - Hypoglycemia
    - Elevated BUN/Creatinine
    - Hypoxemia
    - Malnutrition or hypoalbuminemia
    - Vitamin deficiency (e.g., thiamine, vitamin B6, vitamin B12)
- Sensory or functional impairments

673 - Visual impairment
674 - Hearing impairment
675 - Immobility
676 - Frailty[1]
677 - Other functional impairments
678 • Factors related to urgent/emergent procedures
679 - High ASA status
680 - Recent surgical complications including cardiopulmonary complications
681 - Operative times
682 - Anesthesia type and depth
683 - Prolonged time on cardiac bypass
684 • Factors related to hospitalization
685 - High illness severity (e.g., as reflected by an elevated APACHE score or SOFA score)
686 - Use of indwelling bladder catheter
687 - Use of mechanical ventilation
688 • Other factors
689 - Fever
690 - Dehydration
691 - Constipation including fecal impaction
692 - Urinary retention
693 - New pressure ulcers
694 - Hyper- or hypothermia
695 - Sleep deprivation or sleep-wake cycle disturbance
696 - Social isolation
697 - Lack of a familiar environment
698 - Environmental overstimulation

699 *Abbreviations*. APACHE= Acute Physiology and Chronic Health Evaluation; ASA=American Society of
700 Anesthesiologists; HIV=Human Immunodeficiency Virus; SOFA=Sequential Organ Failure Assessment.
701 *Source*. Ali et al. 2021; Béland et al. 2021; Bramley et al. 2021; Bush and Bruera 2009 ; Chaiwat et al. 2019; Chen et
702 al. 2021; Duceppe et al. 2019; Featherstone et al. 2022; Fong et al. 2015; Geriatric Medicine Research Collaborative
703 2019; Girard et al. 2018; Greaves et al. 2020; Hshieh et al. 2020; Iamaroon et al. 2020; Kang et al. 2019; Maldonado
704 2017; Marquetand et al. 2021, 2022; Mattison 2020; Mauri et al. 2021; Mevorach et al. 2023; Nagari and Babu
705 2019; Ormseth et al. 2023; Pisani et al. 2007; Pun et al. 2021; Saljuqi et al. 2020; Silva et al. 2021; Spiropoulou et al.
706 2022; Vacas et al. 2022; Visser et al. 2021; Wilke et al. 2022; Wilson et al. 2020; Zaal et al. 2015; Zhang et al. 2021;
707 Zipser et al. 2019a, 2019b.

708 The presence of neurocognitive impairment, including dementia, is a frequent predisposing factor in
709 individuals who develop delirium and may change interpretation of cognitive findings (Fong and Inouye
710 2022; Fong et al. 2015). In hospitalized patients, it has been estimated that up to half of individuals with
711 dementia will also have superimposed delirium (Han et al. 2022). As described in Statement 2, this
712 makes it important to determine the patient's baseline neurocognitive status, to identify whether

[1] Examples of scales that have been used to assess frailty include, but are not limited to, the Cardiovascular Health Study Index, also referred to as Fried's frailty phenotype; the Clinical Frailty Scale; the Edmonton Frailty Scale; the Fatigue, Resistance, Ambulation, Illness, and Loss of Weight Index [FRAIL]; and the Frailty Index of Accumulated Deficits of Rockwood and Mitnitski).

cognitive impairment is present prior to hospitalization, and to determine whether patients have delirium alone or delirium superimposed on pre-existing cognitive impairment. When patients are frail, there is a high rate of developing delirium, but paradoxically, delirium is less likely to be identified when patients are frail (Geriatric Medicine Research Collaborative 2019). Although biases in the diagnosis of delirium are not well studied, incorrect assumptions about cognitive decline or fluctuations in cognition in older individuals may play a role. Racial or ethnic biases may also influence identification of delirium or associated risk factors for delirium. For example, one study showed that Black individuals were more likely than other patients to be identified as cognitively impaired, independent of actual results on a cognitive screening test (Campbell et al. 2014). For these reasons, it is crucial to consider the impact of possible biases in diagnosing delirium or identifying predisposing or contributing factors to delirium.

Although a significant number of risk factors appear to be associated with an increase in the likelihood of delirium, many individuals who have these factors will not exhibit delirium. Possible precipitants or contributors to delirium also need to be considered in the context of other clinical findings. For example, a female may have evidence of bacteriuria due to urinary colonization without having it precipitate or contribute to delirium (Krinitski et al. 2021; Nicolle 2016; Nicolle et al. 2019). Thus, it would be important to determine whether other urinary symptoms are present or whether there are signs of systemic infection such as fever or an elevated white blood cell count (Krinitski et al. 2021; Nicolle 2016; Nicolle et al. 2019). Other sources of infection would also need to be ruled out before attributing delirium to a urinary tract infection. Without a detailed consideration of the meaning of a finding such as bacteriuria, antibiotics may contribute to delirium (Bhattacharyya et al. 2016), be instituted inappropriately contributing to antibiotic resistance, or target the wrong organism and be ineffective (Nicolle 2016; Nicolle et al. 2019).

Information about possible predisposing or contributing factors may be able to be obtained from the patient, if they are able to respond to questions, or from family members or others involved in the patient's care. Other physicians or health care professionals who are treating the patient can be contacted for information and details of past medical history, prior cognitive or functional status, current problems, and medications may be available through medical records, prescription monitoring data programs (PMDPs), external prescribing histories, health information exchanges (HIEs), and other electronic sources of information. Patients or families may also be able to bring in current prescription bottles to determine current medication regimens.

Additional health-related information will become available in the course of evaluation through physical examination, laboratory studies, or other tests (e.g., imaging, electrocardiography, cultures). There is no routine battery of tests or other investigations that should be done in all patients with delirium or who are at risk for delirium. Rather, the evaluation will depend on common contributors to delirium as well as factors of relevance to the individual patient's condition (see Table 4).

Table 4. Suggested laboratory tests and other studies in the assessment of patients with delirium

Commonly done laboratory tests and other studies

- Vital signs (pulse, blood pressure, respiratory rate, temperature; orthostatic pulse and blood pressure if indicated)
- Pulse oximetry
- Complete blood count with differential
- Glucose measurement
- Comprehensive metabolic panel
- Urinalysis

Laboratory tests and studies that are sometimes done, depending on history, clinical findings, and results of other evaluations

- Magnesium
- Phosphate
- Creatine phosphokinase (CPK)[2]
- Ammonia
- Thyroid stimulating hormone (TSH)
- Vitamin B12; methylmalonic acid, as indicated
- Thiamine
- Serum levels of medications (e.g., lithium, valproic acid, carbamazepine, amiodarone, digoxin, phenytoin, salicylate)
- C-reactive protein and/or erythrocyte sedimentation rate (ESR)
- Antinuclear antibody (ANA)
- Severe acute respiratory syndrome coronavirus 2 (COVID-19) test
- HIV test
- Syphilis test[3]
- Blood gases
- Cultures (e.g., urine, blood, sputum, wound, cerebrospinal fluid)
- Blood alcohol level
- Urinary toxicology screen, with confirmation if appropriate
- Bladder scan[4]
- Abdominal X-ray/KUB
- Chest X-ray

[2] Significant elevations of CPK can be seen in neuroloeptic malignant syndrome or serotonin syndrome.
[3] Under most circumstances, it is recommended to screen with an initial nontreponemal test (e.g., Venereal Disease Research Laboratory [VDRL] or rapid plasma reagin [RPR] test) with confirmation of a positive result using a treponemal antibody detection test (e.g., T pallidum particle agglutination [TP-PA] test) (U.S. Preventive Services Task Force 2022).
[4] To identify urinary retention

- Neuroimaging (e.g., brain magnetic resonance imaging [MRI], head computed tomography [CT])
- Electroencephalogram (EEG)
- Lumbar puncture[5]

[5] Consultation with neurology is suggested prior to lumbar puncture to determine the most appropriate tests to obtain on the cerebrospinal fluid.

Statement 4 – Review of Medications

APA recommends **(1C)** that a detailed medication review be conducted in patients with delirium or who are at risk for delirium, especially those with pre-existing cognitive impairment.

Implementation

As discussed in Statement 3 and delineated in Table 4, a number of medications and medication classes can contribute to delirium. Individuals with pre-existing cognitive impairment are often especially sensitive to the effects of such medications. Consequently, in patients who have delirium or who are at risk for delirium (as described in Statements 1 and 3), a detailed review of medications is helpful. The goals of a detailed medication review include obtaining an accurate list of the patient's medications. In addition to identifying medications that have a significant likelihood of contributing to delirium, other goals of medication review include identifying agents that may be able to be reduced in dose, that may no longer be needed, or that may be contributing to drug-drug or drug-disease interactions.

Much has been written on approaches to obtaining a medication history and clarifying discrepancies in the medication list, a process known as medication reconciliation (Greenwald et al. 2010; Institute for Healthcare Improvement 2023; Schnipper et al. 2022). For patients who are admitted from another facility, a current medication list will typically be provided. In other circumstances, information sources that can be used in constructing the medication list include interviewing the patient, the patient's family, and other involved caregivers; asking to see the patient's medication bottles; accessing recent records through an electronic health record (EHR) or HIE; accessing recent pharmacy dispensing records through external pharmacy prescribing databases; or checking PMDPs for histories of controlled substance prescriptions (Centers for Disease Control and Prevention 2021). The complete medication list should include prescribed medications as well as over-the-counter medications, herbal products, supplements, or nutraceuticals whether taken on a routine or "as needed" (i.e., prn) basis. The dose, route, frequency, and indication for the medication should be listed, when known. Documenting the date and time of the last medication dose is also helpful when scheduling and informing patients about the timing of next doses at transitions of care.

Although medication reconciliation has been recommended for use at transitions of care and in ambulatory settings for over a decade, there are still challenges in its application and limitations in the evidence supporting its use (Ceschi et al. 2021; Killin et al. 2021; Mekonnen et al. 2016a; Redmond et al. 2018; Rungvivatjarus et al. 2020; Tamblyn et al. 2019). Patients, family members, or other involved caregivers may not have access to current medications in the context of an emergency visit or hospital admission. Follow-up is often needed to complete the initial medication history. Prescribed medications may have changed since the patient's last visit to a facility, or they may not have been taking a medication even though it was dispensed by a pharmacy or recorded in a PMDP. When patients are taking long-acting medications (e.g., long-acting injectable formulations of antipsychotic medications, naltrexone, or contraceptives; implantable formulations of buprenorphine or contraceptives), EHRs may not list them as active medications, and patients or other informants may not recall that they are taking them unless specifically asked. For medications that are prescribed on an "as needed" (i.e., prn) basis, the frequency of actual use may be quite variable. It can be difficult to obtain a full list of over-the-

counter medications, herbal products, supplements, and nutraceuticals, and these may include contaminants and may vary in their active ingredients or drug interactions, even when they are documented.

As a result of the complexities of medication reconciliation, errors of omission may occur in taking the medication history. It is also possible for medications that have been previously discontinued to be erroneously resumed as part of the medication reconciliation process. With medications that require gradual dose adjustment on initiation (e.g., clozapine, lamotrigine), an abrupt resumption of a therapeutic dose of medication can lead to adverse effects.

Evidence suggests that the medication reconciliation process can be more efficient and more effective when done by a pharmacist, pharmacy technician, or other designated staff member who has knowledge of medications (Marshall et al. 2022; Mekonnen et al. 2016b; Schnipper et al. 2023). Such an approach is now required in acute care settings in some jurisdictions (California Senate Bill No. 1254 2018). Without a designated individual to be responsible for medication reconciliation, accountability is unclear and, in a busy clinical environment, obtaining the medication history may be delayed or bypassed entirely.

Once the medication list has been documented as accurately as possible, review of the medication list can assess whether specific medications may be able to be reduced in dose or discontinued, a process that has been termed deprescribing (Bloomfield et al. 2020; Curtin et al. 2020; Lee et al. 2021; McDonald et al. 2022; Reeve 2020). As discussed in Statement 3, medications that may be more likely to contribute to delirium include benzodiazepine or other sedatives, narcotic analgesics, corticosteroids, immunosuppressive agents, sympathomimetic agents, and medications with anticholinergic properties (Maldonado 2017; Mattison 2020; Ryan and Kimchi 2021). Delirium may also occur in the context of medication related toxicity syndromes (e.g., neuroleptic malignant syndrome, serotonin syndrome) or with elevated serum levels of medications (e.g., lithium, valproic acid, carbamazepine, amiodarone, digoxin, phenytoin, salicylate). Medication-specific effects, such as hyperammonemia due to valproic acid or hyponatremia due to antidepressive agents, should also be considered. Many tools exist that can help identify other medications that may need to be tapered or discontinued (Reeve 2020), but the Beers criteria (American Geriatrics Society Beers Criteria® Update Expert Panel 2023) and the STOPP/START criteria (O'Mahony et al. 2015) are commonly referenced.

Pharmacokinetic and pharmacodynamic considerations are also relevant when reviewing medications (Derendorf and Schmidt 2020; Levenson and Ferrando 2024), identifying those that may be contributing to delirium, or determining when tapering or discontinuation of a medication may be indicated. When a patient is prescribed multiple medications, it is always helpful to use a drug interaction database to determine whether drug-drug interactions may be occurring. Such interactions can be mediated by metabolic enzymes (e.g., cytochrome P450 enzyme system), drug transporters (e.g., P-glycoprotein), displacement from protein binding sites, or other mechanisms (Akamine et al. 2012; Armstrong et al. 2003; Darwich and von Moltke 2019; Derendorf and Schmidt 2020; Flockhart et al. 2021; Gessner et al. 2019; Kiang et al. 2005; Levenson and Ferrando 2024; Linnet and Ejsing 2008; Sandson et al. 2005;

Tornio et al. 2019). In other circumstances, medication side effects, such as sedation or hypotension, may be additive or synergistic when associated with two or more medications. Medication absorption and first-pass metabolism of medications may be altered by disease (e.g., bowel disease; Megna and Vaughn 2022) or prior surgical procedures (e.g., bariatric surgery, gastric or intestinal resection; Brill et al. 2015; Roerig and Steffen 2015). Other pharmacokinetic factors that can influence medication levels include age, body size, relative body fat, genetic subtypes of metabolic enzymes (e.g., rapid vs. slow metabolizer status), and renal and hepatic status (Derendorf and Schmidt 2020; Gouju and Legeay 2023; Keller and Hann 2018; Levenson and Ferrando 2024; Mangoni and Jackson 2004; Trifirò and Spina 2011). Drugs that are lipophilic will be distributed in greater levels to body fat and to brain. As a result, when levels of lipophilic medications have been high, delirium and other central nervous system findings may dissipate gradually after medication tapering or discontinuation. Pharmacodynamic considerations that may affect drug responses or side effects in the aging brain include neurotransmitter and receptor changes (e.g., cholinergic, dopaminergic) (Mangoni and Jackson 2004; Trifirò and Spina 2011).

As with any decisions related to medications, it is important for the members of the health care team to consider the potential benefits, side effects, and other disadvantages of a medication prior to adjusting a medication dose. When a medication is effective and well tolerated, it will generally be continued although, in some circumstances, pharmacokinetic considerations or other factors may make it preferable to change to another medication in the same class. In other circumstances, an effort may be made to reduce the dose of a medication, particularly when it is known to contribute to delirium or to other potential adverse effects such as falls. When a medication is not usually effective in a specific condition or is otherwise not needed (e.g., some over-the-counter products, herbal preparations, supplements), tapering and discontinuation may be most appropriate.

Even when tapering or discontinuing of a medication seems indicated, it is important to make such decisions in the context of patient-centered decision making, when the patient is able to participate, or in discussion with the patient's health care designee. Individuals, their family members, or other caregivers may be fearful or ambivalent about tapering specific medications based on prior negative experiences with deprescribing or severe symptoms that seemed to be controlled by the current regimen (Sawan et al. 2020; Scott et al. 2022). Individuals may also view deprescribing as an indication that their care is being reduced due to costs, biases, or clinician disengagement (Sawan et al. 2020; Scott et al. 2022). Thus, it is important to obtain patient, family member, and caregiver perspectives and provide information on the reasons for deprescribing whenever possible.

When a patient has been on a stable dose of medication for some time, abrupt tapering or discontinuation could destabilize an underlying condition or result in a withdrawal syndrome (e.g., with sedatives, opioids, some antidepressants). Patients who are receiving a high dose of medication or have had a lengthy period of treatment will typically need a slower speed of medication tapering than individuals on lower medication doses for a shorter period of time (Pottie et al. 2018). In assessing the effects of medication reduction or discontinuation, it may also be preferable to make changes gradually, if possible, so that emergent symptoms or other effects of dose adjustment can be interpreted. Factors

such as medication half-life or the presence of long half-life active metabolites are also relevant to interpreting effects of medication tapering or discontinuation (Hendset et al. 2006).

Statement 5 – Use of Restraints

APA recommends **(1C)** that physical restraints not be used in patients with delirium, except in situations where injury to self or others is imminent and only:

- after review of factors that can contribute to racial/ethnic and other biases in decisions about restraint;
- with frequent monitoring; and
- with repeated reassessment of the continued risks and benefits of restraint use as compared to less restrictive interventions.

Implementation

Use of physical restraints should be minimized and limited to situations where injury to self or others is imminent. Physical restraint use can be associated with a number of potential harms including pressure ulcers, fractures, cardiac arrythmias, musculoskeletal injuries, deep vein thrombosis, aspiration pneumonia, worsening of agitation, and, in rare instances, asphyxiation with potential death from strangulation (Berzlanovich et al. 2012; Ertuğrul and Özden 2020; Funayama and Takata 2020; Sharifi et al. 2021; Teece et al. 2020). These risks may be greater in individuals with impaired consciousness, as occurs in patients with delirium. Psychologically, use of physical restraints is often distressing to patients and families (American Psychiatric Association 2022; Perez et al. 2022; Sharifi et al. 2021; Smithard and Randhawa 2022; Wong et al. 2020). PTSD can also occur in individuals who have been physically restrained although it is unclear if the risk is due to restraints, per se, or related to other aspects of receiving care for critical illness (Franks et al. 2021; Hatchett et al. 2010; Jones et al. 2007; Zghidi et al. 2019). Consequently, before deciding to use physical restraints, it is essential to weigh these risks against the intended benefits of restraint use as compared to other possible interventions.

Often, physical restraints are considered in an effort to enhance patient safety, prevent self-extubation or tube dislodgment, reduce the risk of falls, or protect staff from patient combativeness (Devlin et al. 2018). However, the few studies that have examined these outcomes have not shown a reduction in these risks with use of physical restraints (Perez et al. 2019; Rose et al. 2016). Thus, except in an urgent or emergent situation, other interventions should typically be attempted before initiating physical restraints (American Psychiatric Association 2022; Knox and Holloman 2012; Roppolo et al. 2020). In addition, efforts should be made to treat underlying contributors to delirium (see Statement 3) or other factors that may be affecting agitation such as pain or co-occurring psychiatric conditions.

Attention to the safety of the patient and others should always be a top priority. This may involve repositioning equipment or moving objects from the bedside that could be used to harm self or others. Environmental modifications can be attempted to promote a more calming environment (e.g., turning off television, providing a single room). In an effort to reduce agitation, issues of comfort should also be addressed, such as pain, environmental temperature, urinary retention, constipation, hunger, thirst, positioning in bed, and constraints of monitoring leads or catheters. It may also be possible to reduce

restraint use through non-pharmacological approaches such as educating family members and involving them in the care plan or having a staff member sit with the patient to provide redirection and reassurance (Cui et al. 2022). Verbal de-escalation techniques are often suggested as a way to help the patient calm themselves (American Psychiatric Association 2022; Knox and Holloman 2012; Richmond et al. 2012; Roppolo et al. 2020); however, this approach may not be as effective with patients who are delirious and unable to attend to or process verbal communication. If verbal de-escalation is used, it is important to be respectful, listen to what the patient is saying, use a soft voice, be concise, and set appropriate limits without being provocative (Roppolo et al. 2020). Medication, if used judiciously, can also be helpful in calming the patient (see Statements 8, 9, and 10) and may help in avoiding use of restraint or reducing its duration. In addition, receiving medication is less distressing to most patients than being physically restrained.

If physical restraint is being considered to address the safety of the patient or others, it is important to be aware of biases that can influence decision-making. For example, implicit biases about race, ethnicity, or other factors may be accentuated when clinicians are stressed, fatigued, or under pressure to make a rapid decision (Agboola et al. 2021; Johnson et al. 2016). There is minimal information on biases that affect restraint-related decision-making in patients with delirium. However, a U.S. sample of all acute care hospital discharges found that 7.4% of patients with a diagnosis of “encephalitis” were restrained and that Black patients were more likely to be physically restrained than White patients (Luccarelli et al. 2023). A subset of the sample that had dementia with a behavioral disturbance also had a disproportionately higher percentage of Black patients among individuals who were physically restrained during the admission (Singh et al. 2023). Similarly, in emergency department encounters, including those for emergency psychiatric evaluations, most (Carreras Tartak et al. 2021; Schnitzer et al. 2020; Smith et al. 2022; Walia et al. 2023; Wong et al. 2021) but not all (Conteh et al. 2023) studies have shown a significantly greater likelihood of being physically restrained in Black patients as compared to White patients. Some (Khatri et al. 2022; Robinson et al. 2022) but not all (Conteh et al. 2023; Wong et al. 2021) studies have also shown that Black patients were more likely to be treated with sedating medications (e.g., antipsychotics, benzodiazepines, ketamine) to address agitation in emergency settings. Information on relative likelihood of physical restraint among Asian patients or Hispanic patients has been mixed with some studies showing greater restraint rates and other studies showing lower or comparable restraint rates than White patients (Carreras Tartak et al. 2021; Conteh et al. 2023; Schnitzer et al. 2020; Walia et al. 2023; Wong et al. 2021). In a Canadian study of patients with delirium, there was also a significantly greater rate of physical restraint use among patients who did not prefer English as their dominant language compared with patients who did prefer English (Reppas-Rindlisbacher et al. 2022). Furthermore, men consistently had greater restraint rates than women, but no data were reported for individuals of other genders (Schnitzer et al. 2020; Walia et al. 2023; Wong et al. 2021).

It is important to note that some approaches that have been developed to assist staff in addressing behavioral issues may also exhibit racial biases. These could, in turn, influence and interject systematic biases into decisions about restraint. For example, one approach to managing behavioral issues in hospital inpatients on non-psychiatric services has been to deploy behavioral response teams. Although

the efficacy of such teams has not been well studied, one report suggests that a behavioral response team at one hospital was contacted more often about Black patients than White patients (Moore et al. 2019). Another study of a behavioral response team found that Black and Asian patients were more likely to receive parenteral medications and a numerically greater percentage of Black patients were placed in four-point restraints as compared to other racial or ethnic groups (Caravella et al. 2023). In terms of emergency security responses, rates were significantly higher in Black as compared to White patients whereas rates for Hispanic and non-Hispanic patients did not differ (Valtis et al. 2023). Electronic behavioral alerts are an additional method that has been used to alert staff to patients who had safety-related concerns on a prior visit, typically verbal or physical incidents involving other patients or staff members. Here too, non-Hispanic Black patients were substantially more likely to have an electronic behavioral alert on their chart than non-Hispanic White patients and men were more likely to have such an alert than women (Haimovich et al. 2023). Thus, if electronic behavioral alerts are used, it is important to institute processes for reviewing them for possible bias and linking them to patient-specific plans of care for addressing behavioral issues.

If physical restraint is still felt to be indicated after considering the risks and benefits of restraint, use of other interventions, and sources of potential bias in decision making, the type of restraint that is chosen should be targeted to the patient's circumstances and be as minimally restrictive as possible. For example, use of mittens may prevent a patient from pulling at tubes without being as restrictive to patient movement as soft limb restraints. The duration of restraint should be as brief as possible and repeated reassessments of patients' status are essential, particularly given the waxing and waning nature of delirium.

It is also critical to monitor the patient closely while physical restraints are in place. The specific monitoring requirements will be determined by requirements of the Center for Medicare and Medicaid Services (CMS) Conditions of Participation (Code of Federal Regulations 2023), Joint Commission or other accrediting bodies, state regulations, and hospital policy. However, monitoring should include physiological monitoring (e.g., vital signs, evidence of circulatory or neuronal impairments in extremities with limb restraints), assessment of psychological symptoms in response to restraints, and attention to nutrition, hydration, or elimination needs while restrained. Respect for the patient's privacy while in restraints is also crucial. Once the period of restraint has been completed, it is helpful to discuss the experience with the patient, if they are able, and with family members or others who are part of the patient's care team to address any questions or concerns related to the restraint episode.

Statement 6 – Person-Centered Treatment Planning

APA recommends **(1C)** that patients with delirium have a documented, comprehensive, and person-centered treatment plan.

Implementation

No single medication or intervention exists that serves as a universal treatment for all patients with delirium. Rather, treatment is individualized based on the patient's clinical picture. Delirium has multiple etiologies, heterogenous phenotypes, and a large number of potential risk factors (see Statement 3);

because of this, treatment planning can be challenging, and changes in the treatment plan are often needed (Devlin et al. 2018; Mart et al. 2021; Ormseth et al. 2023). Individuals who are older, frail, or have significant multi-system disease may have limited reserves and less resilience in the face of physiologic disruptions, a situation that has been termed homeostenosis (Fried et al. 2021). Consequently, factors, combinations of factors, or degrees of abnormality may be overlooked or de-emphasized as being unlikely to cause delirium in individuals with greater reserves. It is also possible for decision making to be influenced by biases related to apparent functioning at baseline (Bergl 2019) or related to race, ethnicity, gender, or age (see Statement 5). Thorough documentation of a comprehensive, person-centered treatment plan reduces the possibility for biases and helps ensure that interventions are appropriately selected to address the full range of each patient's medical and psychosocial needs (see Table 5).

Table 5. Factors to consider in developing a person-centered treatment plan

Medical interventions, including medication review

- Instituting specific interventions to address likely contributors to the patient's delirium (see Statement 3), recognizing that multiple contributors may co-exist
- Reviewing and, if indicated, making adjustments to medications, including long-acting medications (e.g., injected, implanted), over-the-counter medications, herbal products, or nutraceuticals (see Statements 3 and 4)
- Obtaining laboratory, imaging, or other evaluations to identify unrecognized contributors to the patient's delirium (e.g., infection, cardiorespiratory disease, thromboembolism, abdominal processes, head injury, medication-related toxicity; see Statement 3)
- Assessing for hypoxia and providing supplemental oxygen, continuous positive airway pressure (CPAP), or ventilatory support, as needed
- Ensuring pulmonary care (e.g., to avoid atelectasis)
- Correcting abnormalities in blood pressure, severe anemia, electrolytes, glucose, fluid, and acid-base status, insofar as possible
- Assessing for medical contributors to pain or distressing somatic symptoms, including post-operative pain, decubitus ulcers, degenerative joint disease, dyspnea, nausea, constipation, urinary retention, dehydration, dry mouth, or fever
- Conducting regular assessments for potential complications of delirium, including injury due to falls, pressure sores, dehydration, malnourishment, infection, venous thromboembolism, and, if applicable, post-operative or immobility related complications
- Identifying and addressing side effects of medications, such as akathisia related to antipsychotic medications
- Identifying and addressing withdrawal symptoms related to recent use of substances (e.g., nicotine, marijuana, alcohol, sedative-hypnotics, opioids)
- Identifying and, insofar as possible, addressing co-occurring psychiatric disorders

Psychosocial support and engagement

- Assessing mental status on an ongoing basis for persistence or resolution of delirium, including a plan for follow-up assessment if delirium persists at discharge
- Providing aids to orientation and reorientation (e.g., clock, whiteboard with date)
- Ensuring availability and adequacy of dentures, glasses, hearing aids, or assistive devices
- Optimizing communication through use of communication technologies, if indicated, and ensuring availability and use of translation services for patients whose primary language is other than English
- Providing appropriate levels of social interaction, including increasing family engagement
- Identifying and addressing distressing somatic symptoms, including pain, and psychological contributors to distress (e.g., fear, boredom, over- or under-stimulation, co-occurring psychiatric conditions, responses to caregiver dynamics, frustration with hospital requirements and constraints)
- Providing education about delirium to patients, insofar as possible, and to family members and others in the patient's support network

Personal care and environmental interventions

- Ensuring early mobility
- Scheduling and providing assistance with toileting, if necessary
- Providing adequate hydration and assistance with meals, if necessary
- Reviewing lines, tubes, monitoring cables, restraints, and other "tethers" and removing those that are not needed
- Minimizing devices with audible alarms that can produce "alarm fatigue" in patients and in staff
- Minimizing disruptions to the sleep-wake cycle (e.g., adequate daytime lighting, provide ear plugs or eye masks, insofar as possible minimizing night-time medication doses, blood draws, vital signs, and numbers of continuous infusions with associated IV pump alarms)
- Providing an increased level of supervision and support, if necessary
- Preventing potential complications such as falls, pressure sores, dehydration, malnourishment, infection, venous thromboembolism, and, if applicable, post-operative or immobility related complications
- Considering personal and environmental factors that could be contributing to patient discomfort or distress (e.g., hunger/thirst, feeling hot/cold, uneven mattress or bedclothes, foreign objects left in bed, need for repositioning)

Multi-component nonpharmacologic treatments (as discussed in Statement 7) are the primary approaches used for preventing delirium (Ely 2017; Inouye 2021; Inouye et al. 2000; Marra et al. 2017; Mart et al. 2021; Oh and Park 2019; Society of Critical Care Medicine 2023). Selection of other treatment plan elements will depend in large part on whether delirium is present and on the patient's presenting symptoms, predisposing and precipitating risk factors, and co-occurring disorders (Maldonado 2017; Marcantonio 2017; Mattison 2020; Wilson et al. 2020). For instance, delirium that is medication-induced suggests a need for medication titration or discontinuation. Patients with vision or auditory deficits may experience improvement in delirium symptoms from use of eyeglasses or hearing aids. Patients who are

in physical restraints or who have been immobile will likely need a mobility protocol or physical rehabilitation included in their treatment plan. Patients with a history of substance use will need monitoring for signs of withdrawal and any indicated treatment. Patients with a co-occurring psychotic disorder will need standing treatment with an antipsychotic whereas those exhibiting catatonic signs will generally be treated with benzodiazepines or electroconvulsive therapy (ECT) with avoidance of antipsychotic medication. Patients with pain may not always be able to ask for "as needed" (i.e., prn) medications but may also experience side effects from frequent standing doses of pain medication such as opioids.

Person-centered treatment planning should include consideration of how family and caregivers can be incorporated into care, as appropriate (Kukreja et al. 2015). For many patients with delirium, family and caregivers play a valuable role in providing patients with support, functional assistance, and reassurance (McKenzie and Joy 2020; Pandhal and Van Der Wardt 2022). In addition, because of their proximity to and knowledge of the patient, family and caregivers may have an awareness of the patient's baseline level of cognition and functioning and may notice subtle changes in thinking and behavior that could inform treatment selection.

Non-Pharmacological Interventions

Statement 7 – Multi-Component Non-Pharmacological Interventions

APA recommends **(1B)** that patients with delirium or who are at risk for delirium receive multi-component non-pharmacological interventions to manage and prevent delirium.

Implementation

Non-pharmacological interventions are an essential element in prevention of delirium and are typically delivered as a bundle of multiple components (see Appendix C, Statement 7). Evidence is less compelling for effects of non-pharmacological interventions on the management of delirium, but they are typically considered to be good clinical practice and unlikely to be harmful. Due to their common use and the challenges of doing blinded studies with many of these interventions, it is difficult to distinguish unique effects of individual components of non-pharmacological bundles. Bundles of non-pharmacological interventions that have been studied most widely include the ABCDEF Bundle and the Hospital Elder Life Program; however, individual studies and guidelines have emphasized different combinations of non-pharmacological interventions (see Table 6). Furthermore, some interventions may be implemented in different ways in different organizations. Given this, it is worth noting that studies tend to show greater benefits, particularly in preventing delirium, when a greater number of non-pharmacological interventions are used consistently (Balas et al. 2022; Barnes-Daly et al. 2017; Hshieh et al. 2018; Inouye et al. 2003; Mion et al. 2023; Pun et al. 2019).

Table 6. Examples of multi-component interventions

Core Component	Hospital Elder Life Program	ABCDEF Bundle	U.K. NICE guideline	Scottish Intercollegiate Guidelines Network
Assessment, prevention, and management of delirium		X	X	X
Assessment, prevention, and management of pain		X	X	X
Early mobilization	X	X	X	X
Daily removal of sedation and ventilation daily in ICU		X		
Review medications and optimize medication choice		X	X	X
Vision protocol	X			X
Hearing protocol	X		X	X
Oral volume repletion/feeding assistance	X		X	X
Sleep enhancement	X		X	X
Daily visitor/orientation	X		X	X
Therapeutic activities	X		X	
Family engagement		X	X	X

Abbreviation. NICE=National Institute for Health and Care Excellence.

The ABCDEF bundle includes six specific elements (Marra et al. 2017; Society of Critical Care Medicine 2023): (A) Assess, prevent, and manage pain; (B) Both spontaneous awakening trials and spontaneous breathing trials; (C) Choice of analgesia and sedation; (D) Delirium: assess, prevent, and manage; (E) Early mobility and exercise; and (F) Family engagement and empowerment. Pain assessment includes obtaining information from patient self-reports but also can incorporate observed signs of pain (e.g., facial expressions, muscle tension, restlessness, vocalizations). In addition to treating pain when it is present, it is important to address pain proactively before painful procedures. Although details of the pharmacological management of pain is beyond the scope of this guideline, the advantages and disadvantages of specific medications, including their potential to worsen delirium, should be kept in mind. Non-pharmacological approaches to pain or discomfort (e.g., repositioning, application of heat or cold) can also be helpful and are often overlooked. Spontaneous awakening trials include stopping

sedatives and, if possible, opioids, and are accompanied by trials of spontaneous breathing in ventilated patients. In choosing sedative and analgesic medications, dexmedetomidine may be preferable to other agents (see Statements 11 and 12), and benzodiazepines should be avoided where possible (see Statement 10). Another key element of the ABCDEF bundle is assessment of delirium using a standardized approach (see Statement 1) and interventions to address delirium if it is identified, as discussed throughout this guideline. Early mobility is important as an element of the ABCDEF bundle but also in reducing complications of prolonged immobilization such as muscle weakness and reductions in functional status. If ambulation is not possible, active range of motion activities three times daily can be done instead. Minimizing catheters, monitoring leads, restraints, and other "tethers" can also help foster greater mobility. Family engagement and empowerment are also integral to the ABCDEF bundle and can incorporate family presence on rounds, shared decision-making, and education about delirium and aspects of medical events and procedures.

The Hospital Elder Life Program interventions include a geriatric nursing assessment and interventions to address cognitive and functional impairment, dehydration, nutrition, psychoactive medication use, and discharge planning (Hshieh et al. 2018; Inouye 2021; Inouye et al. 2000). These components can include early mobilization, use of an orientation board (with date, activities, names of team members), cognitively stimulating activities (e.g., discussion of current events, structured reminiscence, word games), interventions to enhance sleep (e.g., quiet hallways, calming music, relaxation apps, reduction in alarms, rescheduling of medications and procedures to minimize sleep disruptions), vision and hearing protocols (e.g., earwax disimpaction as needed), and appropriate use of visual and hearing aids and other adaptive equipment (e.g., magnifying lenses, large illuminated telephone key-pads, large print books, fluorescent tape on call bell). Other program elements include twice-weekly interdisciplinary rounds to discuss each patient, set goals, review issues, and track interventions, with additional interdisciplinary consultation as needed. Geriatric consultation can also occur on referral by attending physicians with input from program staff. A healthcare professional education program is provided as part of the Hospital Elder Life Program that includes formal didactic sessions, one-on-one interactions, and resource materials to educate nursing and physician staff about the program elements (Hshieh et al. 2018). Linkages and communication with community agencies are used to optimize patients' transition to home. A telephone follow-up within seven days after discharge is also provided for all patients (Hshieh et al. 2018).

Importantly, the implementation of multi-component non-pharmacological interventions, such as the ABCDEF Bundle or Hospital Elder Life Program, is often spotty without concerted and consistent efforts on a unit or organizational level to ensure that each intervention is completed with fidelity for each patient (Hshieh et al. 2018; Inouye et al. 2003; Pun et al. 2019). Nursing staff deliver or assure delivery of most of these interventions, and adequate nursing staffing is crucial to robust implementation. Other key features for successful implementation of multi-component non-pharmacological interventions include gaining support of staff and organizational leadership (including nursing and physician leaders), assuring intervention fidelity within organizational workflows, integrating components with existing programs (e.g., geriatric care), identifying approaches to help assure delivery of interventions (e.g., rounding checklists, training sessions or web-based materials to educate staff or family, community

volunteers to assist with some tasks, quality improvement collaboratives), using data to assess program outcomes and demonstrate benefits (e.g., decreases in delirium, fall reduction, enhanced patient and family satisfaction), changing organizational culture related to delirium assessment and interventions, and addressing program sustainability (Balas et al. 2022; Bradley et al. 2004, 2006; Brockman et al. 2023; Inouye et al. 2003; Hshieh et al. 2018; King et al. 2023; Mion et al. 2023; SteelFisher et al. 2011, 2013).

Pharmacological Interventions

Statement 8 – Principles of Medication Use

APA recommends **(1C)** that antipsychotic agents and other medications to address neuropsychiatric disturbances of delirium be used only when all the following criteria are met:

- verbal and non-verbal de-escalation strategies have been ineffective;
- contributing factors have been assessed and, insofar as possible, addressed; and
- the disturbances cause the patient significant distress and/or present a risk of physical harm to the patient or others.

Implementation

As with any decisions related to medication use, initiating a new medication in a patient with delirium requires consideration of the potential benefits of the medication as compared to the potential risks of use. Under some circumstances, neuropsychiatric disturbances of delirium may be able to be addressed by correcting underlying contributors to delirium (see Statement 3) or through non-pharmacological approaches such as redirection, reassurance, verbal de-escalation techniques, or family education and engagement. In other circumstances, however, non-pharmacological approaches may not be effective. Furthermore, it may not be possible to identify or resolve underlying contributors to delirium, either in a timely fashion or at all.

Delirium can be associated with a wide range of neuropsychiatric disturbances ranging from apathy to agitation and including psychosis, catatonia, and other neuropsychiatric manifestations. When an individual with delirium is experiencing severe and distressing neuropsychiatric disturbances, such as hallucinations, delusions, or agitation, these can require rapid intervention. This is particularly true when neuropsychiatric disturbances are serious enough to present a risk of physical harm to the patient or others. Evidence from randomized controlled trials (RCTs) does not support benefits of medications such as antipsychotics or benzodiazepines in the treatment of delirium (see Appendix C, Statements 9 and 10); however, there are also situations in which neuropsychiatric disturbances of delirium require a rapid resolution because of significant distress or risk to the patient or others. Although data from clinical trials is limited, expert consensus based on substantial clinical experience suggests that medication can be appropriate and helpful in calming a patient under such circumstances if used judiciously (Jaworska et al. 2022; see Statement 5). In addition, it may help in avoiding use of physical restraint or reducing the duration of time in restraint. Nevertheless, if medication is being considered, it is important to be aware of biases, including racial/ethnic biases, that can influence decision-making regarding neuropsychiatric disturbances of delirium (see Statement 5).

Any possible benefit of medications in reducing distress or agitation must be weighed against potential harms of medication. In individuals with neuropsychiatric disturbances of dementia, treatment with antipsychotic medications for 6 to 12 weeks in clinical trials has been associated with dose-dependent increases in the relative risks for mortality and other adverse effects (Maust et al. 2015; Schneider-Thoma et al. 2018; U.S. Food and Drug Administration 2005, 2008; Yunusa et al. 2019). In addition, one retrospective study showed an associated between antipsychotic use and death or nonfatal cardiopulmonary arrest during hospitalization (Basciotta et al. 2020). This association was present for any type of antipsychotic medication in patients ages 65 and older as well as for first-generation antipsychotic use in the full cohort of hospitalized patients and in patients with delirium (Basciotta et al. 2020). However, in RCTs of antipsychotic treatment in individuals with delirium, brief treatment with an antipsychotic such as haloperidol has not been associated with significant increases in mortality or other adverse effects (Andersen-Ranberg et al. 2022, 2023a, 2023b). In addition, it does not appear to increase the risk of delirium (Reisinger et al. 2023).

Other possible side effects of antipsychotic medications vary with the specific agent and are typically dose-dependent (American Psychiatric Association 2021). With short-term use of an antipsychotic to address neuropsychiatric disturbances of delirium, specific side effects include sedation, anticholinergic effects, and orthostatic hypotension. Other side effects of antipsychotic medications include akathisia, which can be mistaken for agitation; dystonic reactions, which can rarely be associated with laryngospasm; and parkinsonism, with associated tremor, akinesia, and motor rigidity. Dyskinesia is typically considered to result from long-term treatment with an antipsychotic (i.e., tardive dyskinesia), but some patients develop dyskinesias with relatively short periods of treatment. In addition, patients may inadvertently be continued on an antipsychotic medication for longer periods of time (e.g., after discharge from the hospital) resulting in a risk for tardive dyskinesia or other tardive motor syndromes. Oropharyngeal dysphagia has also been reported with antipsychotic medication use (Miarons and Rofes 2019) as has an increase in the risk of aspiration pneumonia (Herzig et al. 2017).

Neuroleptic malignant syndrome (NMS) occurs rarely but can be life-threatening due to the combination of rigidity (with elevations in serum creatine kinase), hyperthermia (>100.4°F/38.0°C on at least two occasions, measured orally), and sympathetic nervous system lability, including hypertension and tachycardia. Other diagnoses that may have a similar clinical presentation include malignant catatonia, malignant hyperthermia (in association with anesthetic administration), heat stroke, serotonin syndrome (in patients also taking serotonergic drugs such as selective serotonin reuptake inhibitors), alcohol or sedative withdrawal, anticholinergic syndrome, hyperthermia associated with use of stimulants and hallucinogens, central nervous system infections, limbic encephalitis, and inflammatory or autoimmune conditions (American Psychiatric Association 2022; Caroff et al. 2021; Strawn et al. 2007). If signs of apparent NMS develop, antipsychotic medications should be discontinued, and supportive treatment should be provided to maintain hydration, treat fever, and address cardiovascular, renal, or other abnormalities (Caroff et al. 2021; Guinart et al. 2021; Strawn et al. 2007). Assistance with emergency management of NMS is recommended and can be obtained through NMSContact (www.mhaus.org/nmsis/nmscontact).

Treatment with an antipsychotic medication can be associated with QTc interval prolongation and, if significant, an increased risk for torsades de pointes, which can lead to life-threatening consequences (e.g., ventricular fibrillation, sudden death) (Funk et al. 2018). A QTc interval > 500 msec is sometimes viewed as a threshold for concern; however, "there is no absolute QTc interval at which a psychotropic should not be used" (Funk et al. 2018, p. 2). In addition, with marked tachycardia or bradycardia (i.e., significantly greater than or less than 60 beats/minute), alternative formulas may need to be used because the QTc interval will, respectively, be overestimated or underestimated by the formula used to calculate QTc intervals in automated electrocardiogram (ECG) reports. Among antipsychotic medications that are available in parenteral formulations, chlorpromazine, droperidol, and ziprasidone appear to be associated with the greatest risk of QTc prolongation (Funk et al. 2018). Concern has also been raised about QTc interval prolongation with haloperidol, although the risk of significant QTc interval changes appears to be relatively small (Beach et al. 2020). For example, in a large RCT of haloperidol (N=192) as compared to ziprasidone (N=190) or placebo (N=184), QTc prolongation that resulted in holding of medication was more common in the ziprasidone group (2% of doses) than in the haloperidol group or placebo group (1% of doses in each group). In another large multicenter placebo-controlled randomized trial of intravenous haloperidol (N=987, 2.5 mg 3 times daily plus 2.5 mg as needed up to a total maximum daily dose of 20 mg) in adult ICU patients, QTc prolongation was associated with medication discontinuation in 2.4% of the haloperidol group as compared to 1.4% of the placebo group (Andersen-Ranberg et al. 2022). However, because of potential risk, particularly at high doses, the FDA recommends cardiac monitoring of patients when intravenous haloperidol is used (Meyer-Massetti et al. 2010). Many other antipsychotic agents also have FDA warnings or possible risks for QTc interval prolongation (Funk et al. 2018). Additional factors that influence the risk of QTc interval prolongation include whether the patient is taking other medications that are known to prolong QTc intervals; whether the patient has factors that would influence drug metabolism, leading to higher blood levels of a drug (e.g., poor metabolizer status, pharmacokinetic drug-drug interactions, hepatic or renal disease, drug toxicity); whether the patient is known to have a significant cardiac risk factor (e.g., congenital long QT syndrome, structural or functional cardiac disease, bradycardia, family history of sudden cardiac death); or other factors associated with an increased risk of torsades de pointes (e.g., female sex; advanced age; personal history of drug-induced QTc prolongation; severe acute illness; starvation; risk or presence of hypokalemia, hypomagnesemia, or hypocalcemia) (Funk et al. 2018).

If a decision is made to begin an antipsychotic to reduce neuropsychiatric disturbances of delirium, antipsychotic medications are usually begun on an "as needed" (i.e., prn) basis and should be started at a low dose, typically half or less than that of a usual adult dose. Although medications are often given in combination when treating agitation (e.g., haloperidol plus lorazepam, haloperidol plus diphenhydramine), using an antipsychotic medication alone is preferred in a patient with delirium and in older individuals because of a potential increase in sedation and worsening of delirium (Korczak et al. 2016; Yap et al. 2019). Before administering additional doses of antipsychotic or other sedating medications, a sufficient period of time should occur for the initial medication to take effect. This is dependent on the route of administration and the pharmacological properties of the medication but can require 5–15 minutes for intravenous doses and 30–45 minutes for intramuscular or oral doses. If an

additional dose of a medication appears to be needed after waiting an appropriate time for it to take effect, a second dose should be the same or less than the initial dose due to the cumulative nature of a repeat dose. Alternatively, a different medication could be tried instead of repeating the dose of the initial medication. Inclusion of a maximal daily dose as part of the medication order can help avoid excess sedation or other side effects of treatment. In addition, orders for antipsychotic medication should be limited in duration (e.g., 3–5 days), and there should be a review of potential benefits and risks of use before continuing treatment.

Table 7. Antipsychotic medications that may be used in the treatment of patients with severe neuropsychiatric disturbances of delirium

Medication[1,2,3]	Aripiprazole	Haloperidol	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Pharmacological Properties[4]						
Route	Oral (tablet, disintegrating tablet, solution)[5]	Oral (tablet, concentrate), parenteral (short acting lactate injection IM or IV)[6]	Oral (tablet, disintegrating tablet),[4] parenteral (short acting solution for IM injection)[7]	Oral (immediate-release tablet, extended-release tablet)	Oral (tablet, disintegrating tablet,[4] solution)	Oral (capsule), parenteral (short acting solution for IM injection)
Starting dose in delirium[8]	2 mg	0.5–2 mg	2.5 mg	25 mg immediate release[9]	0.25–0.5 mg	20 mg oral; 10–20 mg IM

[1] Droperidol is a first-generation antipsychotic medication that is available in a parenteral form. It been used for the prevention and treatment of post-operative nausea and vomiting and also has efficacy in treating agitation. Droperidol has an FDA boxed warning recommending that it be used only when there has not been an acceptable response to other adequate treatments. The boxed warning also recommends that a 12-lead ECG be done prior to administration to assess for QTc prolongation, and that ECG monitoring be done during treatment and for 2–3 hours after completing treatment to monitor for QT prolongation and serious arrhythmias (e.g., torsades de pointes). For these reasons, droperidol rarely used in patients with delirium.

[2] Brexpiprazole is a second-generation antipsychotic medication, available as an oral tablet, that is infrequently used in patients with delirium. It has a long half-life and can require dose adjustment in patients with renal impairment, moderate or severe hepatic impairment, poor metabolism through CYP2D6, or with concomitant use of moderate/strong CYP2D6 or CYP3A4 inhibitors.

[3] For patients with Parkinson's disease or dementia with Lewy bodies, there is an increased sensitivity to drug-induced parkinsonism and a second-generation antipsychotic medication, such as quetiapine, is preferable to medications such as haloperidol or risperidone.

[4] Pharmacological properties may differ with patient age (particularly in older individuals), body size and composition, and organ system impairment, among other factors.

[5] The oral disintegrating tablet formulation is absorbed enterally and not sublingually. Thus, its absorption and other pharmacokinetic properties are similar to those of other oral formulations.

[6] Haloperidol is available in a long-acting IM decanoate formulation as well as a short-acting parenteral formulation. Only the short-acting parenteral formulation is appropriate for use in patients with delirium unless a patient is already being treated with the long-acting injectable decanoate formulation for a pre-existing psychotic disorder.

[7] The parenteral formulation of olanzapine has also been used IV (typically in a dose of 2.5– 5 mg) and most often in emergency and critical care settings for the treatment of agitation.

[8] Suggested starting doses are based on expert consensus. Typically, the starting dose in a patient with delirium is one half, or less, than the recommended starting doses for the same medication in adults with other psychiatric conditions.

[9] Although an extended-release formulation of quetiapine is available, the immediate release formulation is suggested for use in individuals with delirium.

Medication[1,2,3]	Aripiprazole	Haloperidol	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Typical maximum daily dose in delirium	5–10 mg	2.5–20 mg	5–10 mg oral; 5 mg IM	100–200 mg immediate release	1–2 mg	40–80 mg oral; 20–40 mg IM
Oral bioavailability	87%	60–70%	57%	100%	70%	60% (with food)
Time to peak level[10]	3–5 hours oral	2–6 hours oral; 20 minutes IM; 2–10 minutes IV	6 hours oral; 15–45 minutes IM	Immediate release 1.5 hours oral; extended release 6 hours oral	1 hour oral	6–8 hours oral; 15–60 minutes IM
Protein binding	>99%	89%–93%	93%	83%	90%	>99%
Metabolic enzymes/transporters	CYP2D6 (major), CYP3A4 (major) substrate	CYP2D6 (major), CYP3A4 (major), CYP 1A2 (minor) substrate; 50%–60% glucuronidation	CYP 1A2 (major), CYP2D6 (minor) substrate; metabolized via direct glucuronidation	CYP3A4 (major), CYP2D6 (minor) substrate	CYP2D6 (major), CYP3A4 (minor) substrate; CYP 2D6 weak inhibitor; ABCB1 substrate/N-dealkylation (minor)	CYP 1A2 (minor), CYP3A4 (minor) substrate; 50-glutathione, aldehyde oxidase
Elimination half-life	75 hours, 94 hours for active metabolite, 146 hours in poor CYP2D6 metabolizers	14–37 hours	30 hours	6–7 hours, 12 hours for active metabolite	3–20 hours, 21–30 hours for active metabolite	7 hours oral, 2–5 hours IM
Excretion	55% fecal, 25% renal	15% fecal, 30% renal (1% as unchanged drug)	30% fecal, 57% renal	20% fecal, 73% renal	14% fecal, 70% renal	66% fecal, 20% renal

[10] The initial onset of action of a medication may precede the time at which the peak drug level is reached.

Medication[1,2,3]	Aripiprazole	Haloperidol	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Renal dosing adjustments	No dosing adjustments needed	No dosing adjustments needed	Not removed by dialysis	No dosing adjustments needed	Use lower initial dose and slower titration rate if CrCl is <30 ml/minute	IM formulation should be used with caution as it includes a cyclodextrin excipient, which is cleared by the kidney.
Hepatic dosing adjustments	No dosing adjustments needed	No dosing adjustments needed	Use with caution	Use initial dose of 25 mg and increase by no more than 25–50 mg daily in the presence of hepatic impairment	Use lower initial dose with mild to severe hepatic impairment (Child-Pugh Class A, B, or C) and slower titration rate with severe hepatic impairment (Child-Pugh Class C; not more than 0.5 mg twice a day and not more than 1.5 mg twice a day dose by one week)	Use with caution
Relative Frequency of Side Effects[11]						
Akathisia	++	+++	++	+	++	++

[11] The relative frequency of side effects is designated by + = seldom; ++ = sometimes; +++ = often.

Medication[1,2,3]	Aripiprazole	Haloperidol	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Parkinsonism	+	+++	++	+	++	+
Dystonia	+	+++	+	+	++	+
Tardive dyskinesia	+	+++	+	+	++	+
Hyperprolactinemia	+	+++	++	+	+++	++
Anticholinergic	+	+	++	++	+	+
Sedation	+	+	+++	+++	++	++
Seizures	+	+	++	++	+	+
Orthostasis	+	+	++	++	++	++
QT prolongation	+	++	++	++	++	+++
Weight gain	+	++	+++	++	++	+
Hyperlipidemia	+	+	+++	+++	+	+
Glucose abnormalities	+	+	+++	++	++	+

Medication[1,2,3]	Aripiprazole	Haloperidol	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Comments[12,13,14,15]	Reduce dose in poor CYP2D6 metabolizers or with concomitant CYP3A4 or CYP2D6 inhibitor. FDA safety alert for impulse control disorders (e.g., gambling, binge eating)		Administer IM slowly, deep into muscle; do not give subcutaneously. Concomitant use of IM olanzapine and IM or IV benzodiazepine (e.g., within 1 hour) is not recommended due to potential for excessive sedation or cardiorespiratory depression. Women may need a lower dose. 40% of oral doses are removed via first-pass metabolism. Oral formulations may be given with or without food.	Reduce dose with concomitant CYP3A4 inhibitor.	Reduce dose with concomitant CYP2D6 inhibitor. Inform patients with phenylketonuria that oral disintegrating tablets include phenylalanine. Oral disintegrating tablets should not be split or crushed. Check labeling for compatibility of oral solution with other liquids. Intraoperative floppy iris syndrome reported.	Give capsules with > 500 calories of food. See labeling for reconstitution and storage of IM solution.

Abbreviations. CrCl=creatinine clearance; FDA=U.S. Food and Drug Administration; IM=intramuscular; IV=intravenous.

[12] Patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared with placebo, and an FDA boxed warning applies to all antipsychotic medications. Antipsychotic agents with an indication for augmentation treatment in major depressive disorder or bipolar depression (e.g., aripiprazole, olanzapine, quetiapine) have an additional black box warning related to increased risk of suicidal thinking/behaviors in children, adolescents, and young adults taking antidepressants.

[13] May be taken without regard to food or other medications unless specifically noted.

[14] Tablets can be crushed or split unless specifically noted.

[15] As described by Pugh et al. (1973), Child-Pugh class A corresponds to a Child-Pugh score of 5–6, class B corresponds to a Child-Pugh score of 7–9, and class C corresponds to a Child-Pugh score of 10–15.

Source. American Psychiatric Association 2021; Curry et al. 2023; Hospira 2021; Hunt et al. 2021; Lexicomp 2023; Martel et al. 2016; Micromedex 2023; Procyshyn et al. 2023; Roppolo et al. 2020; Thom et al. 2019; Tsai et al. 2021; Wang et al. 2022; Wilson et al. 2012.

Package insert references. Abilify 2022; Aripiprazole orally disintegrating tablets 2018; Aripiprazole solution 2016; Geodon 2022; Haloperidol 2008, 2019; Haloperidol lactate 2008; Haldol lactate injection 2020; Haloperidol lactate injection 2011; Haloperidol lactate oral solution 2016; Haloperidol lactate oral solution USP 2020; Haloperidol tablets 2015, 2019; Risperdal 2020, 2022; Risperidone orally disintegrating tablets 2019; Seroquel 2022; Seroquel XR 2022; Zyprexa 2021.

Statement 9 – Antipsychotic Agents

APA recommends **(1C)** that antipsychotic agents not be used to prevent delirium or hasten its resolution.

Implementation

Evidence from RCTs does not support benefits of antipsychotic medications in preventing or treating delirium (see Appendix C, Statement 9). Because of the potential risks associated with antipsychotic medication treatment and the lack of apparent benefits in preventing or treating delirium, use of an antipsychotic for these purposes is not recommended.

An antipsychotic medication may sometimes be appropriate when an individual with delirium is experiencing severe neuropsychiatric disturbances that cause the patient significant distress and/or present a risk of physical harm to the patient or others (see Statement 8). However, such use of antipsychotic medication should be time-limited (e.g., at most 3–5 days per order), with frequent review of the need for further use. An antipsychotic medication can also be initiated or continued in a patient with delirium superimposed on a co-occurring psychotic disorder (American Psychiatric Association 2021). If patient has been receiving treatment with an antipsychotic medication to address severe neuropsychiatric disturbances related to dementia, the rationale and history of use should be reviewed to determine whether the patient would potentially benefit from an attempt to taper the antipsychotic medication (American Psychiatric Association 2016).

Statement 10 – Benzodiazepines

APA recommends that benzodiazepines not be used in patients with delirium or who are at risk for delirium, including those with pre-existing cognitive impairment, unless there is a specific indication for their use.

Implementation

In patients with delirium or who are at risk for delirium, use of benzodiazepines is not typically recommended (Curry et al. 2023; Shenvi et al. 2020). Randomized studies of midazolam or lorazepam in treatment or prevention of delirium are limited in number but have not shown benefits of benzodiazepine treatment as compared to other treatment options (see Appendix C, Statement 10). Although perioperative use of a benzodiazepine does not appear to increase the likelihood of delirium overall (Wang et al. 2023), the incidence and duration of delirium appear to be greater with use of midazolam as compared to dexmedetomidine (Hassan et al. 2021; He et al. 2018; Maldonado et al. 2009; Yu et al. 2017). Furthermore, in ICU patients, the duration of mechanical ventilation is somewhat greater with midazolam than with dexmedetomidine (Jakob et al. 2012) whereas no differences have been noted on most other outcomes. In observational and database studies in other settings, some research suggests that delirium may be increased by use of a benzodiazepine, but evidence is mixed and its reliability is low (Reisinger et al. 2023; see also Appendix C, Statement 10).

Side effects of benzodiazepines can also add to potential risks of treatment, particularly in older individuals and those with pre-existing cognitive impairment (American Geriatrics Society Beers Criteria® Update Expert Panel 2023; Shenvi et al. 2020). Such effects can include an increased risk of falls,

oversedation, or respiratory depression (American Geriatrics Society Beers Criteria® Update Expert Panel 2023; Engstrom et al. 2023; Korczak et al. 2016; Roppolo et al. 2020; Shenvi et al. 2020; Yap et al. 2019; Wilson et al. 2012). Paradoxical increases in agitation have also been reported with benzodiazepines but appear to be uncommon (Champion et al. 2021; Mancuso et al. 2004).

With these caveats, it is important to note there are a number of circumstances in which treatment with a benzodiazepine may still be indicated in a patient with delirium or at risk for delirium (see Table 8).

Table 8. Factors suggesting that a benzodiazepine may be indicated in a patient with delirium

- High likelihood of alcohol or sedative hypnotic withdrawal by clinical history and symptoms
- Acute intoxication from anticholinergic agents, stimulant use, psychedelic drugs, or multiple unknown substances
- Prominent signs of catatonia
- Neuroleptic malignant syndrome
- Serotonin syndrome
- Autoimmune encephalitis
- Longstanding use of a benzodiazepine prior to hospitalization for which discontinuation may prompt withdrawal symptoms or symptom rebound
- Seizure disorder that requires use of a benzodiazepine for adequate seizure control

In individuals whose clinical history and symptoms suggest apparent alcohol or sedative hypnotic withdrawal, treatment with a fixed dose of a benzodiazepine (i.e., diazepam, chlordiazepoxide, lorazepam) is effective in reducing the likelihood of alcohol withdrawal seizures (Bahji et al. 2022) and is more effective than use of anticonvulsant medication (Lai et al. 2022). The available studies also suggest that diazepam can reduce the incidence of delirium tremens (Bahji et al. 2022). Of the benzodiazepines, lorazepam is shorter acting, does not have active metabolites, and can be given intravenously and intramuscularly as well as orally (Procyshyn et al. 2023); thus, it may be preferable to diazepam or chlordiazepoxide in older individuals in an acute care setting.

In a patient who appears to be intoxicated and is experiencing agitation in an acute care setting, a benzodiazepine is generally preferable to an antipsychotic medication when the cause of intoxication is unclear or appears related to anticholinergic agents, stimulants, or psychedelic drugs (Engstrom et al. 2023; Roppolo et al. 2020; Shenvi et al. 2020; Wilson et al. 2012). In contrast, administration of a benzodiazepine to treat agitation is not recommended in a patient who is intoxicated with alcohol or a sedative hypnotic because of potential additive effects (Curry et al. 2023; Engstrom et al. 2023; Roppolo et al. 2020; Shenvi et al. 2020; Wilson et al. 2012).

Other acute conditions in which use of a benzodiazepine may be indicated include catatonia, NMS, serotonin syndrome, autoimmune encephalitis, or status epilepticus (Connell et al. 2023; Denysenko et al. 2018; Huang et al. 2020; Jaimes-Albornoz et al. 2022; Moss et al. 2019; Rogers et al. 2023; van Rensburg and Decloedt 2019; Zaman et al. 2019).

On a longer-term basis, benzodiazepines may be an appropriate treatment for a number of conditions such as seizure disorders, severe anxiety, or panic attacks. In some instances, benzodiazepine treatment for these conditions may be initiated while a patient is also experiencing delirium. More often, a patient will be treated with a benzodiazepine prior to the development of delirium and questions may arise as to whether the benzodiazepine should be continued. For a patient whose condition has been stable during long-term treatment with a benzodiazepine, no immediate change will be needed. In addition, whatever the indication for longstanding benzodiazepine treatment, withdrawal symptoms or symptom rebound can occur with discontinuation. If a decision is made to reduce or stop a benzodiazepine, the time needed to do so will depend on the duration of treatment and the total daily dose (Markota et al. 2016). Furthermore, dose reduction may need to occur even more slowly towards the end of the tapering process (Markota et al. 2016).

Statement 11 – Dexmedetomidine to Prevent Delirium

APA suggests **(2B)** that dexmedetomidine be used rather than other sedating agents to prevent delirium in patients who are undergoing major surgery or receiving mechanical ventilation in a critical care setting.

Implementation

Dexmedetomidine has a number of benefits in patients at risk for delirium as well as a number of potential risks. Consequently, the decision to use dexmedetomidine vary with the individual patient's physical status and co-occurring conditions. Nevertheless, in patients at risk for delirium who are undergoing major surgery or receiving mechanical ventilation in a critical care setting, the possibility of using dexmedetomidine can be raised with the patient's critical care intensivist, surgeon, anesthesiologist, or other health professionals on the treatment team.

In patients undergoing major surgery and in those who are receiving mechanical ventilation in a critical care setting, evidence consistently shows a significant reduction in the incidence of delirium when dexmedetomidine is used (see Appendix C, Statement 11). The superiority of dexmedetomidine in terms of delirium incidence is also seen when dexmedetomidine is compared in a head-to-head fashion with other sedating medications (e.g., haloperidol, propofol, midazolam, clonidine, opioids). In terms of other outcomes, the benefits of dexmedetomidine are less robust, but a shorter period of mechanical ventilation and a shorter length of stay in the ICU and the hospital has been observed in many studies of dexmedetomidine as compared to placebo or other sedating medications (Lewis et al. 2022; see Appendix C, Statement 11). Benefits of dexmedetomidine (administered as a sublingual film) have also been found in treatment of agitation in patients with schizophrenia, schizoaffective disorder, and bipolar disorder (Citrome et al. 2022; Karlin et al. 2023).

Dexmedetomidine binds to both presynaptic and postsynaptic α_2-adrenergic receptors and is more selective for α_2-adrenergic receptors than clonidine (Weerink et al. 2017). Central effects in the locus coeruleus are thought to account for the ability of dexmedetomidine to produce sedation without respiratory depression (Weerink et al. 2017). It may also act on α_2-adrenergic receptors in the spinal cord to modify pain sensation (Weerink et al. 2017). Other physiological effects of dexmedetomidine

include bradycardia and hypotension, which are estimated to occur in 13% and 25% of patients, respectively, with a serious impact in 0.9% and 1.7% of patients, respectively (Keating 2015). Because of these effects, greater caution may be needed in patients with heart block, bradycardia, severe ventricular dysfunction, chronic hypertension, or hypovolemia (Lexicomp 2023). Some patients also exhibit an increase rather than a decrease in blood pressure with dexmedetomidine (Keating 2015). These effects on blood pressure and heart rate appear to be mediated by peripheral effects on vascular smooth muscles and vascular endothelial cells (Weerink et al. 2017).

Dexmedetomidine provides light sedation, which is advantageous in terms of early patient mobilization, but it would need to be used in combination with other agents or substituted with an alternative agent if deep sedation is required (Lexicomp 2023). In addition, if amnesia is crucial, another agent will need to be used instead of or in addition to dexmedetomidine because dexmedetomidine does not have reliable amnestic effects (Lexicomp 2023). High fever has been associated with dexmedetomidine use in a number of case reports and may need to be distinguished from other causes of fever such as infection, malignant hyperthermia, or NMS (Krüger et al. 2017).

Dexmedetomidine is administered as a continuous intravenous infusion with typical starting doses as shown in Table 9. Although the manufacturer's labelling in the United States recommends a treatment duration of up to 24 hours (Lexicomp 2023), dexmedetomidine infusions lasting up to 14 days have shown ongoing safety and efficacy (Ber et al. 2020). In terms of pharmacokinetics, dexmedetomidine is highly bound to plasma proteins and metabolized by cytochrome P450 (CYP) enzymes and uridine 5-diphospho-glucuronosyltransferase (UGT) (Ber et al. 2020; Keating 2015). Because there is substantial interindividual variability in estimates of pharmacokinetic parameters (e.g., volume of distribution) and organ system function in critical illness (Tse et al. 2018), empiric dose titration is needed (Ber et al. 2020; Keating 2015; Weerink et al. 2017). Typically, the dose of dexmedetomidine is titrated by 0.2 mcg/kg/hour every 30 minutes to achieve the desired clinical effect (Lexicomp 2023). Because clearance of the drug occurs almost entirely through the liver, lower doses of dexmedetomidine are needed in individuals with hepatic function impairment (Weerink et al. 2017). In addition, sedative effects of dexmedetomidine may be somewhat longer in patients over age 65 and in those with significant reductions in renal function (Keating 2015).

When patients receive doses at the upper end of the dose range or longer-term infusions, abrupt cessation of dexmedetomidine may be associated with withdrawal symptoms including hypertension, tachycardia, or agitation. Withdrawal symptoms may also be more likely in patients who are simultaneously discontinued from opiates or benzodiazepines (Pathan et al. 2021). In addition, patients with pre-existing hypertension may be more likely to have an increase in blood pressure with abrupt dexmedetomidine discontinuation. These withdrawal symptoms may be reduced by gradual discontinuation of dexmedetomidine (Lexicomp 2023). A transition to clonidine (0.1–0.3 mg orally or enterally every 6–8 hours or transdermal clonidine 100 pg/24 hour patch) may also be helpful in reducing the likelihood or magnitude of withdrawal symptoms (Glaess et al. 2020). Guanfacine (0.5–1 mg two to three times daily) has been suggested as an alternative to clonidine because of its lesser effects on the vascular system as compared to the central nervous system (Fetters et al. 2022).

Table 9. Typical doses of dexmedetomidine

Clinical circumstances	Dose (mcg/kg/hour)[1,2]
Adjunctive use with general anesthesia	0.1 to 0.8 mcg/kg/hour
Mechanically ventilated patients in critical care	0.2 to 1.5 mcg/kg/hour[3]

Statement 12 – Dexmedetomidine in Patients with Delirium

APA suggests **(2C)** that when patients with delirium are sedated for mechanical ventilation in a critical care setting, dexmedetomidine be used rather than other sedating agents.

Implementation

In patients who have delirium and are sedated for mechanical ventilation in a critical care setting, use of dexmedetomidine appears to be associated with faster resolution of delirium and fewer days with delirium than comparison treatments (see Appendix C, Statement 12). Potential risks of dexmedetomidine also exist as described in Statement 11. Consequently, the decision to use dexmedetomidine varies with the individual patient's physical status and co-occurring conditions and can be raised with the patient's critical care intensivist or other health professionals on the treatment team.

Statement 13 – Melatonin and Ramelteon

APA suggests **(2C)** that melatonin and ramelteon not be used to prevent or treat delirium.

Implementation

Melatonin is an endogenous hormone that affects sleep through regulation of circadian rhythm (Moon et al. 2022a, 2022b). Sleep is a problem for most hospitalized patients due to noise, ambient light, monitoring devices, tubes and intravenous lines, and interruptions of sleep for medications, vital signs, and other interventions (Showler et al. 2023). Circadian rhythms are often disrupted, and medications can affect sleep patterns and REM sleep (Showler et al. 2023). Sleep changes are common with aging, and hospitalized patients may have had sleep difficulties prior to admission (Showler et al. 2023). Furthermore, disruption of the sleep-wake cycle is common in individuals with delirium (American Psychiatric Association 2022).

When studied in patients with delirium or at risk for delirium, some studies have shown small benefits of exogenous melatonin and melatonin agonists, such as ramelteon; however, as described in Appendix C, Statement 13, the bulk of the evidence, when taken together, shows small or no effects of these agents on preventing or treating delirium (e.g., decreasing delirium incidence, severity, or duration; reducing

[1] Caution is needed when writing dexmedetomidine orders and preparing intravenous solutions because it is dosed in units of mcg/kg/hour in contrast to many intravenous solutions, which are dosed based on mcg/kg/minute.
[2] For individuals with a BMI ≥ 30 kg/m^2, adjusted body weight should be used to calculate an initial dose (Lexicomp 2023).
[3] Doses greater than 1.5 mcg/kg/hour do not appear to have additional clinical efficacy although doses up to 2.5 mcg/kg/hour have been used (Lexicomp 2023).

mortality in patients with delirium). For these reasons, we suggest that melatonin and ramelteon not be used to prevent or treat delirium.

Although this guideline statement is specific to delirium, melatonin and ramelteon have also been used clinically with variable benefits in patients with delayed sleep phase syndrome, as well as in shift-workers, long distance travelers with jet lag, and individuals with insomnia (Moon et al. 2022a, 2022b). When used in these contexts, it is important to recognize that, to achieve a physiological effect, these medications require timing of their administration to the patient's circadian phase (Moon et al. 2022a, 2022b), which is not often done in hospitalized patients. For acute and chronic insomnia, evidence suggests few side effects but the benefits of melatonin and ramelteon are also limited (De Crescenzo et al. 2022; Maruani et al. 2023; Sateia et al. 2017). With melatonin, an additional concern is the lack of standardization of doses and preparations of natural products (Erland and Saxena 2017).

Transitions of Care

Statement 14 – Medication Review at Transitions of Care

APA recommends **(1C)** that, in patients with delirium or who are at risk for delirium, a detailed medication review, medication reconciliation, and reassessment of the indications for medications, including psychotropic medications, be conducted at transitions of care within the hospital.

Implementation

Several studies have found benefits of medication review in decreasing the incidence, severity, or duration of delirium (Burton et al. 2021; Drewas et al. 2022; van Velthuijsen et al. 2018). In addition, medication review is often a component of multi-component nonpharmacologic interventions for patients at risk for delirium (Burton et al. 2021; see Statement 7).

For hospitalized patients, transitions of care are frequent and may involve changing levels of care (e.g., critical care to step down unit or general unit), changing services (e.g., medicine to surgery), changing units (e.g., in relation to bed availability), or changing care teams. Often, several such changes may occur at once. Consequently, transitions of care can contribute to gaps in communication, particularly with respect to medications. In patients with delirium or who are at risk for delirium, a detailed medication review, medication reconciliation, and reassessment of the indications for medications at transitions of care can assure that medication related plans are communicated correctly. Such a review also provides an opportunity to identify medications that may be contributing to delirium or constitute a risk for delirium, as discussed in Statements 3 and 4. Table 10 provides a list of key questions related to medication review and reconciliation at transitions of care.

Table 10. Medication related considerations at transitions of care

- Is the patient's current list of medications accurate?
    - Has medication reconciliation been completed?
    - Are there any medications included in clinical notes, orders, and/or medication administration records that differ from those on the list of reconciled medications?
    - Were any medications that the patient is supposed to be taking inadvertently discontinued?

    - Did the patient receive any long-acting injectable or implanted medications prior to hospitalization or during the hospitalization that are not listed with the other medications (e.g., antipsychotic medications, naltrexone, buprenorphine, contraceptives, glucagon-like peptide-1 receptor agonists)?
- Are any adjustments to the patient's medications needed?
    - Do any medications need to be added, or prior medications resumed?
    - Are any of the patient's current medications likely to increase the risk or duration of delirium? If so, is adjustment of medication dose or discontinuation of the medication warranted?
    - Are any medication related side effects present that would warrant adjustment of medication dose or discontinuation of the medication?
    - Do any of the patient's current medications interact with other medications that they are taking? If so, are adjustments in medication doses needed or should the medication be discontinued? Should there be additional monitoring instituted for side effects or to assure that medications are producing their intended benefits?
    - Are any of the patient's current medications potentially problematic in terms of their current diagnoses? (e.g., renally excreted medications with acute kidney injury)
    - Are there any medications, including "as needed" (i.e., prn) medications (e.g., for reasons such as pain, nausea, agitation, sleep, gastrointestinal reflux, or constipation), that may be able to be discontinued?
- Does the documentation at the transition of care include all necessary communications about the patient's medications that will be relevant to future care and decision-making?
    - Were any of the patient's medications initiated during the hospitalization? If so, is there a clear description of the reason that the medication was begun?
    - Is the patient taking psychotropic medication either as a standing dose or "as needed" (i.e., prn) medication? If so, is there a clear description of the reason that the medication has been prescribed?
    - Was the patient taking medications prior to admission that have been stopped? If so, is the reason for stopping those medications clear (e.g., non-formulary, oral formulation in a patient who was not able to take medications orally, adverse effects of medication, lack of therapeutic benefit)?
    - Was the patient taking over-the-counter medications, herbal products, supplements, or nutraceuticals at home for which they may need instructions (i.e., to continue or stop) at discharge?
    - Are any of the patient's medications time-limited, with a defined stop date (e.g., antibiotics)? If so, is this information noted, including a discontinuation date?
    - Are there specific plans to increase or decrease the dose of specific medications or discontinue a medication prior to discharge? If so, are these described clearly?

Documentation at transitions of care should note whether home medications have been substituted with another medication due to formulary considerations or whether home medications are on hold for another reason (e.g., lack of a parenteral formulation to use while a patient is not taking oral medications). If a home medication has been discontinued with no intention to resume it, this should be communicated along with the reason for discontinuation. The rationale for changes in medication doses

or addition of new medications during the hospitalization are also important to document so that this will be clear to subsequent clinicians (Jaworska et al. 2022). Planned increases or decreases in medication doses should also be noted. If a medication is being given for a specified number of days (e.g., course of antibiotics, post-operative pain medication), those treatment durations should be specified. Documentation should list a specific date on which the course of treatment is expected to end to avoid confusion due to copying and pasting of electronic record information from earlier days.

Information should also be noted on any long-acting medications (e.g., long-acting injectable formulations of antipsychotic medications, naltrexone, contraceptives, glucagon-like peptide-1 receptor agonists; implantable formulations of buprenorphine or contraceptives), "as needed" (i.e., prn) medications, and over-the-counter medications, herbal products, supplements, or nutraceuticals that may have been taken at home or during the hospital stay. Medication review, reconciliation, and reassessment are also critical to identify medications, such as antipsychotics, that are started during the hospital stay but are no longer needed. Once prescribed, these medications are often continued at transfers of care and hospital discharge (Boncyk et al. 2021; Dixit et al. 2021; Flurie et al. 2015; Johnson et al. 2017; Lambert et al. 2021; see also Statements 15 increasing the risk of adverse effects (D'Angelo et al. 2019; Johnson et al. 2017; Lambert et al. 2021; Markota et al. 2016). Other goals of medication review include identifying agents that may be producing side effects or contributing drug-drug or drug-disease interactions through pharmacokinetic or pharmacodynamic effects (see Statement 4).

Statement 15 – Follow-up Planning at Transitions of Care

APA recommends **(1C)** that, when patients with delirium are transferred to another setting of care, plans for follow-up include:

- continued assessments for persistence of delirium;
- detailed medication review, medication reconciliation, and reassessment of the indications for medications, including psychotropic medications;
- assessment of consequences of delirium (e.g., post-traumatic symptoms, cognitive impairment); and
- psychoeducation about delirium for patients and their care partners.

Implementation

As with transitions of care within the hospital, a detailed review and reconciliation of medications is important when a patient is transferred to another setting (see Statement 14 and Table 10). This process should include reassessment of the indications for medications, including psychotropic medications. Multiple retrospective studies suggest that a significant fraction of hospitalized individuals with delirium have been started on an antipsychotic or sedative medication during the inpatient stay and continue on it after discharge (Boncyk et al. 2021; Burry et al. 2023; Dixit et al. 2021; Flurie et al. 2015; Johnson et al. 2017; Lambert et al. 2021; Welk et al. 2021). Medication review at the time of transfer or discharge can identify medications that can be discontinued or that need to be tapered and then stopped (Adeola et al. 2018; American Geriatrics Society Beers Criteria® Update Expert Panel 2023; D'Angelo et al. 2019; Kram et al 2019; McDonald et al. 2022; Redmond et al. 2018; Stuart et al. 2020; Tamblyn et al. 2019; see Appendix C, Statement 14).

Follow-up care is critical for patients who have had delirium because symptom resolution can vary widely, from hours to days to weeks, or even months in some patients (Oldham et al. 2017). Despite this, persistent delirium is often unrecognized and may reflect ongoing physical health issues that need further evaluation or treatment. Persistent delirium is also a risk factor for cognitive impairment, emergency visits, hospitalization, or death (Cole et al. 2017; Pereira et al. 2021). As described in Statement 1, there are a number of structured assessments that can be used to identify delirium and its persistence after discharge.

Even when delirium has resolved, discharge from the hospital is a transition that is associated with significant risk of readmission, nursing facility placement, and mortality (Rahman and Byatt 2021). Ongoing assessments of cognitive and physical functioning are recommended after hospital discharge (Guthrie et al. 2018; Mikkelsen et al. 2020). Risks of persistent cognitive impairment are increased in patients who have been delirious (Cole and McCusker 2016; Goldberg et al. 2020; Pandharipande et al. 2013; Pereira et al. 2021; van den Boogaard et al. 2012) as is functional decline and disability (Wilson et al. 2020) as compared to hospitalized patients without delirium. Bedside assessments of cognitive function such as the MoCA (Nasreddine et al. 2005), the MMSE (Folstein et al. 1975, 2010), and the Saint Louis University Mental Status (SLUMS; Cummings-Vaughn et al. 2014; Tariq et al. 2006) are often used for assessing cognitive domains. For rating of functioning, the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0) is available in a 36-item version that requires about 20 minutes to complete, as well as a 12-item version, which requires about 5 minutes to complete (American Psychiatric Association 2022; World Health Organization 2010). In addition to providing scores for cognition, mobility, self-care, getting along, life activities (household and work), the WHODAS 2.0 is available in multiple languages and can be completed by the patient, a proxy, or an interviewer either in person or by phone (World Health Organization 2010).

In addition to a need for post-discharge assessment of cognition, other long-term consequences of delirium that warrant assessment during follow-up can include anxiety, depression, PTSD, and lower quality of life (Bolton et al. 2021; Guthrie et al. 2018; Mikkelsen et al. 2020; Ramnarain et al. 2023; Weidman et al. 2022; Wilson et al. 2020; Wolters et al. 2016). Rates of PTSD have been best studied in ICU patients but appear to be increased in patients with delirium (Battle et al. 2017; Bolton et al. 2021; Bulic et al. 2020; Friberg et al. 2023; Griffin et al. 2023; Rengel et al. 2021). Examples of scales that can be used to assess for post-traumatic stress symptoms or PTSD, include the Impact of Event Scale-Revised (Creamer et al. 2003) and the PTSD Checklist for DSM-5 (PCL-5; Blevins et al. 2015), respectively. Rates of anxiety and depression also appear to be increased after critical care hospitalization but have been less well studied in patients with delirium (Bolton et al. 2021; Ramnarain et al. 2023; Rengel et al. 2021; Wilson et al. 2020). Screening for depression and anxiety can be done with scales such as the Patient Health Questionnaire-9 (PHQ-9; Kroenke et al. 2001), the Generalized Anxiety Disorder Scale (GAD-7; Spitzer et al. 2006), or the Hospital Anxiety and Depression Scale (Zigmond and Snaith 1983). For individuals who are able to complete a self-report measure, quality of life can be assessed using the World Health Organization Quality of Life BREF (WHOQOL-BREF; The WHOQOL Group 1998a) and has strong psychometric properties (Grassi et al. 2020; The WHOQOL Group 1998a, 1998b). Other measures are also available for assessing cognition, functioning, and quality of life (Giedzinska and Wilson 2023;

Rush et al. 2008), although interventions during follow-up to improved outcomes have been limited (Schofield-Robinson et al. 2018).

It is imperative that patients, caregivers, and family members receive education about delirium following discharge to home; however, provision of such information is often lacking (Chuen et al. 2021). Patients often report feeling distressed while delirious and, in some, delusional ideas about their experiences and persistent fears are present after hospital discharge (Gaete Ortega et al. 2020). Family members and other caregivers also are interested in receiving information about delirium including information on symptoms and causes of delirium as well as ways to help in managing it (Shrestha and Fick 2020). The fluctuating presentation of delirium as well as symptoms such as hallucinations, delusions, and agitation can be concerning to have seen, and family members and caregivers can benefit from transparent discussion of these emotions.

After discharge, formal or informal caregivers may be needed to help patients adhere to post-discharge medical plans (e.g., assist with remembering to take medication), including physical rehabilitation, and in some instances assist with activities of daily living (O'Rourke et al. 2021; Rengel et al. 2021). Consequently, they are in a good position to recognize changes in symptoms and functioning and ensuring patients receive quick access to health care if they experience physical symptoms or reductions in functioning (Carbone and Gugliucci 2015). Studies suggest that, when properly educated, family members and other caregivers can be reliable informants and can accurately identify and describe in detail the patient's delirium symptoms (Shrestha and Fick 2020), which can be useful in identifying persistence or recurrence of delirium. For these reasons, providing patients, families, and other caregivers with information about delirium can help diminish residual emotional effects of the delirium experience and can enhance their ability to partner in care after discharge.

Areas for Further Research

As with any psychiatric disorder, there are multiple issues related to delirium that would benefit from further research. These include research topics such as the following:

Screening and Assessment

- Determine whether patient characteristics and factors that confer risk for delirium can be used to identify patients at a high likelihood of developing delirium who could benefit from early intervention
- Determine whether patterns of subsyndromal symptoms, either alone or in combination with patient characteristics and delirium risk factors, can be used to identify patients at a high likelihood of developing delirium who could benefit from early intervention
- Determine whether additional rating scales need to be developed for delirium identification, diagnosis, or rating of severity that are brief to administer, require limited training, and are valid and reliable among a broad range of settings (e.g., critical care, other hospital units, ambulatory practice, skilled nursing facilities), ages, genders, cultures, languages, social determinants of health, symptom patterns (e.g., hyperactive vs. hypoactive), and underlying pathophysiologies
- Identify methods that will allow refinement of clinical assessment and delirium “phenotyping" using physiological monitoring (e.g., EEG, ECG), wearable technology, and large-scale data analytics

Treatment

- Identify physiological subtypes of delirium that would require distinct treatment approaches to achieve optimal patient outcomes
- Identify significant symptoms (e.g., agitation, hallucinations), co-occurring conditions (e.g., COVID-19, substance-related disorders, other psychiatric disorders), biomarkers, and other factors that can help in individualizing treatment selection, frequency, and duration to achieve optimal patient outcomes
- Identify approaches to individualizing treatment selection and delivery to optimize outcomes among a broad range of settings (e.g., critical care, other hospital units, ambulatory practice, skilled nursing facilities), ages, genders, cultures, languages, social determinants of health, symptom patterns (e.g., hyperactive vs. hypoactive), and underlying pathophysiologies
- Obtain additional evidence on novel or existing pharmacotherapies (e.g., cholinesterase inhibitors; α-adrenergic agents) in the treatment of delirium
- Obtain additional evidence on novel or existing pharmacotherapies (e.g., dexmedetomidine, antipsychotic agents) in the treatment of specific symptoms of delirium (e.g., agitation, aggression, psychosis)
- Identify the specific elements of multi-component interventions that have highest impact on specific delirium outcomes as well as the intervention “dose” (e.g., time spent, frequency, consistency of use) and implementation features (e.g., workflows, staffing) that are needed for benefits to occur

- Identify the treatment elements and approaches that are viewed as most and least helpful by individuals who have recovered from delirium and by their family members or other caregivers
- Identify optimal approaches to providing patient and family/caregiver education and support when delirium is present and after it has resolved

Systems of care

- Identify approaches to adapting workflows and models of care delivery to improve the use of best practices and reduce inequities in the care of individuals with delirium
- Identify approaches to adapting workflows and models of care delivery to reduce biases (including race/ethnicity and preferred language) in delirium identification (e.g., hypo- vs. hyperactive subtype, pre-existing cognitive impairment or frailty) and use of interventions (e.g., physical restraints, psychotropic medication)
- Identify optimal approaches to longitudinal monitoring and follow-up care of patients with delirium after transitioning from an acute care setting

Study design considerations

In addition to these specific topics that would benefit from additional research, our ability to draw clinically meaningful conclusions from research would be augmented by improvements in the design of studies. Current evidence on delirium has been limited by a number of factors:

- Studies are not always registered (e.g., in ClinicalTrials.gov) with pre-specification of outcomes of interest
- Study designs do not typically fulfill all elements to achieve a low risk of study bias or do not provide sufficient information to determine the degree of study bias with accuracy (e.g., randomization and blinding procedures, statistical approaches for missing data)
- Procedures for the screening and assessment of delirium have not always been well described in terms of scale administration, training of raters, and inter- and intra-rater reliability
- Sample sizes are often small, limiting the ability to stratify analyses or achieve statistical power to detect differences due to intervention effects.
- Sample characteristics have been limited in their breadth (e.g., older individuals, critical care or medical inpatients) and ascertainment approaches (e.g., particular units, post-operative patients with cardiac or orthopedic procedures)
- Sample characteristics are not well described (e.g., age; gender; race/ethnicity; preferred language; hypo- vs. hyperactive delirium; levels of consciousness and arousal; underlying pathophysiology; presence or absence of specific risk factors, diagnostic criteria exclusions, or pre-existing cognitive impairment)
- Samples have not always excluded comatose patients or patients with pre-existing delirium
- Interventions for prevention and treatment of delirium have varied in the study design and treatment implementation (e.g., variable use of non-pharmacological approaches; differences in dose, timing, frequency, and route of medication administration)

- Outcomes of medication studies have not distinguished between effects on delirium, per se, as compared to reductions in hyperactivity due to sedation.
- Information on harms, including in non-pharmacological studies, has typically not been collected in a systematic fashion.
- Follow-up duration is, often, brief and outcomes have focused on delirium incidence, delirium duration, length of stay (ICU or hospital), or readmission rates with minimal attention to specific symptoms (e.g., agitation, aggression, hallucinations) or short- and long-term functional outcomes.

Guideline Development Process

This guideline was developed using a process intended to meet standards of the Institute of Medicine (2011) (now known as the National Academy of Medicine). The process is fully described in a document available on the APA Web site at: www.psychiatry.org/psychiatrists/practice/clinicalpractice-guidelines/guideline-development-process. Key aspects of the process for developing the guideline statements are also described in the introduction (see Rating the Strengths of Guideline Statements and Supporting Research Evidence).

Management of Potential Conflicts of Interest

Members of the GWG are required to disclose all potential conflicts of interest before appointment, before and during guideline development, and on publication. If any potential conflicts are found or disclosed during the guideline development process, the member must recuse himself or herself from any related discussion and voting on a related recommendation. The members of both the GWG and the SRG reported no conflicts of interest. The Disclosures section includes more detailed disclosure information for each GWG and SRG member involved in the guideline's development.

Guideline Writing Group Composition

In addition to the chair of the GWG (C.C.), the GWG was initially composed of five psychiatrists with general research and clinical expertise (I.A., R.B., J.E., M.J.-T., A.S.) and one psychiatrist with general research and clinical expertise who is also board certified in family medicine (T.H.). This non-topic-specific group was intended to provide diverse and balanced views on the guideline topic to minimize potential bias. Two psychiatrists (J.L.L., M.O.), , one internist (M.M.), and one critical care nursing researcher (M.C.B.) were added to provide subject matter expertise in delirium. One fellow (J.M.T.) was involved in the guideline development process. The vice-chair of the GWG (L.J.F.) provided methodological expertise on such topics as appraising the strength of research evidence. The GWG was also diverse and balanced with respect to other characteristics, such as geographical location and demographic background. <<Insert names of relevant groups>> reviewed the draft and provided perspective from patients, families, and other care partners.

Systematic Review Methodology

This guideline is based on a systematic search of available research evidence conducted by the Pacific Northwest Evidence Based Practice Center. The methods for this systematic review followed the Agency

for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (available at https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview).

Searches were conducted in Ovid® MEDLINE®, PsycINFO®, Embase®, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews from database inception through October 2020 (as described in Appendix B, Tables B-1 through B-6) to identify studies eligible for this review, according to pre-established criteria listed in Appendix B, Table B-7 and summarized in Table 11. An updated search using the same criteria spanned the period from October 2020 through July 9, 2021. Studies were restricted to adults (18 years and older) who were at risk for delirium, had a clinical diagnosis of delirium, or met DSM criteria for delirium. Included studies were restricted to English-language articles and interventions that were available in the United States. Observational studies with at least 50 participants were included only if inadequate evidence was found in RCTs for primary outcomes on any Key Questions (see Appendix A).

Table 11. Criteria for population, intervention, comparison, and outcomes of eligible studies

	Include	Exclude
Populations	Adults (≥ 18 years old) at risk for delirium or with delirium, including those on palliative care and at end of life	Children and adolescents (<18 years old)
Interventions	Drug interventions (e.g., antipsychotics, cholinesterase inhibitors, sedatives, hypnotics, analgesics, melatonin, over-the-counter medications, complementary and alternative medicine) and non-drug interventions (e.g., environmental, light therapy, pain management, psychosocial interventions, reduction of unnecessary medications)	No intervention
Comparisons	Placebo, no intervention (usual care), other drug interventions, other non-drug interventions, different doses, frequencies, or intensities of interventions	No comparison
Outcomes	Incidence and severity of delirium, frequency of delirium episodes, duration of delirium, agitation, re-admission or admission to hospital, quality of life (including PTSD, cognitive decline, etc.), caregiver burden, rescue medication use, length of stay in hospital or ICU, mortality, adverse events	None
Duration	Any duration	None
Settings	Any setting, including inpatient, hospice, and nursing homes	None
Study designs	RCTs, observational studies with N ≥ 50, non-randomized clinical studies with a comparator; best evidence approach	Uncontrolled, observational study with no comparator

Abbreviations. ICU=intensive care unit; N=number; PTSD=posttraumatic stress disorder; RCT=randomized controlled trial.

As shown in Appendix B, Figure B-1, the systematic review retrieved 12,102 articles of which 10,903 were excluded based on screening of titles and abstracts. The full text of the remaining 1,199 articles was reviewed and 277 articles met the inclusion criteria, of which 204 articles related to prevention of delirium, 51 articles related to treatment, and 12 articles related to both prevention and treatment. The updated search yielded an additional 912 articles of which 805 were excluded based on title and abstract screening. Of the remaining 107 articles that were reviewed in full text, 37 articles met inclusion criteria, with 31 articles related to prevention of delirium, 4 articles related to treatment, and 2 articles related to both prevention and treatment. For both the initial and updated searches, title and abstract were screened by an initial reviewer with excluded articles screened by a second reviewer. Full text review was conducted in duplicate. Any discrepant determinations in title/abstract or full text review were resolved by consensus with input included from a third individual if consensus could not be reached. Available guidelines from other organizations were also reviewed (Aldecoa et al. 2017; American College of Emergency Physicians 2014; American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults 2015; American Psychiatric Association 1999; BC Center for Palliative Care 2017a, 2017b; Bush et al. 2018; Cancer Care Ontario 2010; Chow et al. 2012; Danish Health Authority 2021; Devlin et al. 2018; Gage and Hogan 2014; Martin et al. 2010; Mohanty et al. 2016; National Institute for Health and Care Excellence 2023; Potter et al. 2006; Registered Nurses' Association of Ontario 2016; Scottish Intercollegiate Guidelines Network 2019; Tropea et al. 2008; see Appendix F).

Data were abstracted from included studies into evidence tables (Appendix D), including study and patient characteristics and study results, with data verified for accuracy and completeness by a second team member. Predefined criteria were used to assess the risk of bias of included trials. RCTs were assessed based on criteria established in the Cochrane Handbook for Systematic Reviews of Interventions (Furlan et al. 2015; Higgins et al. 2023) with observational studies assessed using criteria developed by the U.S. Preventive Services Task Force (Harris et al. 2001). Two team members independently assessed risk of bias and assigned an overall rating of low, moderate, or high risk of bias, with disagreements were resolved by consensus. Risk of bias ratings are included in evidence tables (see Appendix D) with specific factors contributing to the risk of bias for each study shown in Appendix E.

Evidence was analyzed according to Key Question, using both qualitative (narrative) and where possible quantitative (meta-analysis) methods. In both approaches, drug studies were grouped by setting (e.g., surgical, ICU, general inpatient), and non-drug studies by intervention type (single component vs. multi-component). For drug studies, within each setting, drugs of the same general class were assessed together. For outcomes of delirium incidence, severity, and duration, ICU and hospital length of stay, and mortality, meta-analyses were conducted when there were at least two studies reporting the same outcome. Study quality and heterogeneity among studies (in design, patient population, interventions, and outcomes) were also considered in choosing to conduct meta-analysis. A detailed description of meta-analytic methods is provided in Appendix B. In addition, the Pacific Northwest Evidence Based Practice Center graded primary outcome-intervention pairs for delirium incidence, severity, and duration, and adverse events. Using AHRQ methods (Berkman et al. 2015), the body of research evidence was categorized as having high, moderate, or low strength, reflecting the confidence or

certainty in the findings (see Appendix B, Table B-8). Bodies of research evidence with inadequate evidence were judged to be insufficient to draw conclusions. In addition, the magnitudes of effects were summarized according to thresholds of little to no difference, small, moderate or large effects, regardless of the statistical significance of the differences (see Appendix B, Table B-9).

External Review

This guideline was made available for review in <<MONTH, YEAR>> by the APA membership, scientific and clinical experts, allied organizations, and the public. In addition, a number of patient advocacy organizations were invited for input. <<NUMBER>> individuals and <<NUMBER>> organizations submitted comments on the guideline (see the section "Individuals and Organizations That Submitted Comments" for a list of the names). The Chair and Co-chair of the GWG reviewed and addressed all comments received; substantive issues were reviewed by the GWG.

Funding and Approval

This guideline development project was funded and supported by the APA without any involvement of industry or external funding. The guideline was submitted to the APA Assembly and APA Board of Trustees and approved on <<MONTH DATE, YEAR>> and <<MONTH DATE, YEAR>>, respectively.

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Disclosures

The Guideline Writing Group and Systematic Review Group reported the following disclosures during development and approval of this guideline:

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Individuals and Organizations That Submitted Comments

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