REVIEW ARTICLE

Delirium in older adults

Delirium em idosos

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ABSTRACT

INTRODUTION: This narrative review provides a broad examination of the most current concepts on the etiopathogenesis, diagnosis, prevention, and treatment of delirium, an acute neuropsychiatric syndrome characterized by fluctuating changes in cognition and consciousness. With the interaction of underlying vulnerability and severity of acute insults, delirium can occur at any age but is particularly frequent in hospitalized older adults. Delirium is also associated with numerous adverse outcomes, including functional impairment, cognitive decline, increased healthcare costs, and death. Its diagnosis is based on clinical and cognitive assessments, preferably following systematized detection instruments, such as the Confusion Assessment Method (CAM). Delirium and its consequences are most effectively fought using multicomponent preventive interventions, like those proposed by the Hospital Elder Life Program (HELP). When prevention fails, delirium management is primarily based on the identification and reversal of precipitating factors and the non-pharmacological control of delirium symptoms. Pharmacological interventions in delirium should be restricted to cases of dangerous agitation or severe psychotic symptoms.
KEYWORDS: delirium; aged; diagnosis.

RESUMO

INTRODUÇÃO: Esta revisão narrativa examina de maneira abrangente os conceitos mais atuais sobre etiopatogenia, diagnóstico, prevenção e tratamento do delirium, uma síndrome neuropsiquiátrica aguda caracterizada por mudanças flutuantes na cognição e na consciência. Com a interação entre a vulnerabilidade subjacente e a gravidade dos insultos agudos, delirium pode ocorrer em qualquer idade, mas afeta com notória frequência idosos hospitalizados. Delirium também está associado a diversos desfechos adversos, incluindo prejuízo funcional, declínio cognitivo, aumento dos custos de saúde e morte. O diagnóstico é baseado em avaliações clínicas e cognitivas, com preferência para o uso de instrumentos de detecção sistematizados, como o Confusion Assessment Method (CAM). Delirium e suas consequências são combatidos de forma mais eficaz por meio de intervenções preventivas com múltiplos componentes, como as propostas pelo Hospital Elder Life Program (HELP). Quando há falha na prevenção, o manejo do delirium se baseia principalmente na identificação e na reversão dos fatores precipitantes e no controle não farmacológico dos sintomas do delirium. As intervenções farmacológicas no delirium devem ser restritas aos casos de agitação perigosa ou sintomas psicóticos graves.
PALAVRAS-CHAVE: delirium; idoso; diagnóstico.

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INTRODUCTION

Since the late 19th century, physicians have described an acute-onset neurocognitive syndrome appearing after systemic insults, which we now recognize as delirium.[1] Delirium occurs in the context of acute encephalopathy and can result from various noxious events (e.g., infection, surgical procedures, medications). Changes in attention and cognition characterize it, usually evolving in a few hours or days.[2] Although severe acute insults can trigger delirium in younger and robust individuals, it is much more common in patients with underlying physical and cognitive vulnerabilities. In fact, up to 50% of hospitalized older adults and 80 to 90% of those in the intensive care unit (ICU) may be affected.[2,3]

Delirium has been associated with higher complexity of care and a cascade of unfavorable events in various settings, often leading to functional and cognitive decline, prolonged length of hospital stay, increased healthcare costs, and higher mortality.[4-6] Given that delirium is a preventable condition, its occurrence is also considered a measure of quality of care. The estimated cost savings of delirium prevention strategies in hospital settings are as high as $1.1 million annually or approximately $1,000 per hospitalized patient with delirium.[7,8] Delirium also has notable effects on families, caregivers, and society as a whole, with functional and cognitive consequences that frequently outlast the hospital stay and contribute to the burden of disability for older adults living both in the community and in long-term care facilities.[9-11] Despite the elevated prevalence and burden associated with delirium, underdiagnosis remains a critical concern in clinical settings, with up to 72% of cases being missed in general wards.[12]

The clinical impact of delirium is undeniable, and healthcare professionals across all disciplines should be educated regarding its central aspects. To this end, our review will focus on the epidemiology, etiopathogenesis, diagnosis, prevention, and management of delirium in older adults. Specific features of delirium in younger populations, such as critically ill children, can be examined elsewhere.[13,14]

EPIDEMIOLOGY

The frequency of delirium varies across populations (e.g., dementia vs. no dementia), clinical settings (e.g., medical vs. surgical), and assessment methods (e.g., diagnostic vs. screening tools).[15] The highest prevalence rates are usually observed in palliative care (59%) and ICUs (82%).[2,16] In the emergency department, delirium affects 10 to 13% of older adults,[17] and is associated with a three-fold increase in mortality, leading to a mortality rate that is similar to that reported for myocardial infarction or sepsis.[17] In medical and geriatric wards, the overall prevalence of delirium ranges from 29 to 49% and 45 to 54%, respectively.[2]

The incidence of adverse outcomes associated with delirium is also noteworthy. For instance, patients with delirium—particularly those with dementia—are more likely to die during an admission or be discharged to nursing homes when they survive the hospitalization.[2] Delirium can also accelerate the effects of Alzheimer's disease and contribute to the associated long-term cognitive decline.[18,19] However, even individuals with normal baseline cognition have a higher risk of cognitive decline after experiencing delirium. In a cohort of adults aged 60 years or older without preexisting cognitive impairment, delirium was associated with a two-fold increase in the risk of post-discharge dementia.[20] The incidence of new cognitive decline after delirium has also been demonstrated in the postoperative and intensive care settings.[21,22]

Most epidemiological data related to delirium derive from studies in North America and Europe. In contrast, other regions (e.g., Latin America and Africa) are underrepresented in the literature, with little data available on incidence/prevalence and outcomes. Even so, the existing literature suggests a similar overall incidence of delirium in Latin America, with most cases detected in ICUs (Brazil 93%; Uruguay 80%).[23,24] Medical patients in these regions frequently experience delirium as well, as observed in a large cohort of Latin American older adults from São Paulo, Brazil, in which delirium was diagnosed in 47% of hospital admissions.[25] Finally, delirium rates in sub-Saharan Africa are probably underestimated.[26]

ETIOPATHOGENESIS

System integration failure hypothesis

The neuropathogenesis of delirium has been evaluated in several studies. Many mechanistic pathways have been proposed, but none is sufficient to explain the development of delirium.[27] The most recent models attempt to encompass the complex interaction between neurological, endocrinological, and inflammatory mechanisms in a construct known as the *system integration failure hypothesis* (Figure 1).[28] According to this theoretical framework, delirium is the intersecting result of the activation of five systemic components by acute organic insults.

A central concept of the hypothesis is that aging facilitates delirium by decreasing physiological reserves and increasing brain vulnerability to organ damage. Moreover, aging is associated with neuronal loss, neurotransmitter dysregulation, alterations in blood circulation, and impairment in compensatory mechanisms that also increase the risk of delirium.[2] In other words, delirium results from the synergy

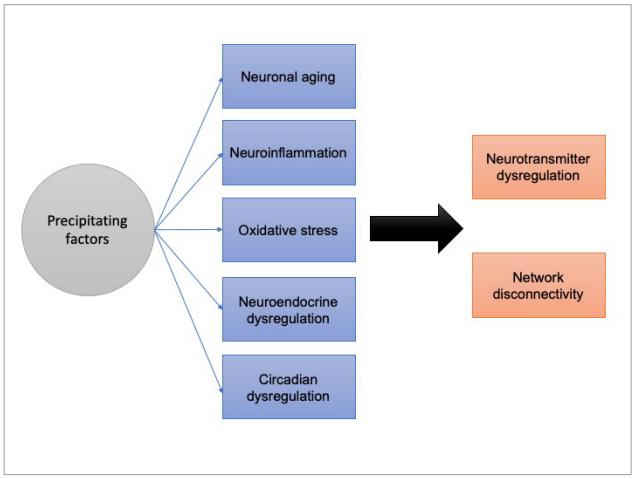


Figure 1. Overview of the system integration failure hypothesis for delirium etiopathogenesis.

among various neurobiological mechanisms (Figure 1), which, in the context of physiological stress, leads to acute dysfunction of brain networks and dysregulation of neurotransmission—represented mainly by reduced cholinergic activity and increased dopamine, norepinephrine, and glutamate activity.[28]

Biomarkers

Akin to other disease contexts, in delirium the study of biomarkers aims at understanding the underlying pathophysiology and ultimately generating knowledge to guide prevention and treatment approaches.[29] Ideally, biomarkers should be cost-effective, specific, and reflect a fundamental pathophysiological aspect of the underlying disease. The associated measures should also be reliable and reproducible, and easily obtained from non-invasive, preferably bedside tests. Given these requirements, numerous challenges arise when investigating biomarkers in delirium research. First, delirium is a clinical syndrome without a prevailing pathological substrate. Second, precise onset times and endpoints can be difficult to determine due to its fluctuating nature, which complicates the identification of an ideal testing timeline. Finally, delirium predominantly affects hospitalized older adults with acute conditions, a scenario often characterized by additional age-related alterations, comorbidities, and medications, which interfere with biomarker analysis and interpretation.[30]

Potential delirium biomarkers have been studied in both serum and cerebrospinal fluid (CSF) samples. Serum biomarkers are thought to be less reliable, considering that delirium is a central nervous system (CNS) disease, and thus measurable repercussions may be dampened by the blood-brain barrier. Still, the inflammatory process that occurs during delirium may breach the blood-brain barrier protection, allowing some central biomarkers to reach the systemic circulation.[30,31] CSF biomarkers have the advantage of directly reflecting alterations in the CNS. Furthermore, the CSF is sensitive to biochemical changes in the brain, and its low protease activity guarantees a higher molecular stability in the subarachnoid space. Unfortunately, extraction of CSF biomarkers depends on lumbar puncture, an invasive procedure with sufficient patient discomfort to discourage routine clinical use, and with obvious ethical and practical obstacles for research purposes.[32]

Despite these challenges, many serum and CSF biomarkers have been investigated in recent years. So far, most studies have examined whether biomarkers might improve baseline risk stratification, early detection, or prognostic assessment of delirium. Serum biomarkers have also helped elucidate potential pathophysiological pathways.[33] An inclusive list of investigated biomarkers is reported in Table 1.[33,34]

More recently, Khan et al. demonstrated that in critically-ill patients, biomarkers of systemic inflammation and astrocyte and glial activation (S100β) were associated with longer duration, greater severity, and higher hospital mortality from delirium.[35]

Table 1. Biomarkers in delirium research.

Investigational biomarkers	Association with delirium*
Adiponectin	+
Acetylcholinesterase (ACHE)	-
Brain-derived neurotrophic factor (BDNF)	+
Cortisol	+
C-reactive protein (CRP)	+
Galectin-3	+
Glial fibrillary acidic protein (GFAP)	-
Interferon-gamma (IFN-γ)	+ / -
IL-2, IL-6, IL-8, IL-10, IL-β	+
IL-1, IL-5, IL-11, IL-17	Inconclusive
Insulin-like growth factor-1 (IGF-1)	-
Leptin	+
Matrix metalloproteinase-9 (MMP-9)	+
Methyl-accepting chemotaxis protein-1 (MCP-1)	Inconclusive
Neopterin	+
Neuron-specific enolase (NSE)	+ / -
Plasminogen activating inhibitor-1 (PAI-1)	+
Procalcitonin	+
Protein C	+
S100β	+
Tumor necrosis factor (TNF)	+/-
Soluble tumor necrosis factor receptor (STNFR)	+
Zinc alpha-2 glycoprotein (AZGP1)	+

*The association with delirium is represented as present (+), absent (-) or both present and absent (+/-) according to different investigational studies.

In hospitalized older adults, serum interleukin (IL)-6, IL-8, and plasminogen-activating inhibitor-1 (PAI-1) measured in the emergency department were significantly associated with prolonged delirium in patients without baseline dementia.[36] Other biomarkers have been studied in the context of delirium, with negative or inconclusive results (Table 1).

Further research on delirium biomarkers is still needed before any possible applications in clinical practice. There are no data to support the reliability, validity, or cut-off points of existing biomarkers for delirium screening, diagnosis, monitoring, prognostication, or treatment.[33,37] It is reasonable to assume that different precipitating factors and clinical settings (e.g., medical, postoperative, intensive care) will distinctly affect delirium biomarkers. Therefore, we also need to understand whether simultaneously testing several biomarkers might more accurately reflect the multifactorial nature of delirium.[34] In this regard, a recent investigation using a multi-protein signature for delirium identified two distinct pools of biomarkers for the preoperative and postoperative periods. The finding indicates the need for better discrimination between risk and disease markers in future research and the potential for improved efficacy when using a panel of biomarkers.[38]

Predisposing and precipitating factors

From a clinical perspective, delirium is inherently multifactorial and arises from the interaction between predisposing (determinants of underlying vulnerability) and precipitating (acute stressors) factors. The combination of baseline predisposition and severity of noxious insults creates the milieu for the occurrence of delirium. The foremost predisposing factors in hospitalized older adults include cognitive impairment, older age, functional dependency, illness severity, and visual impairment (Table 2).[39] Baseline dementia is the most decisive predisposing factor in most cohorts, with a pooled 6.6-fold increase in delirium risk.[40] As for precipitating factors in the same setting, the most relevant are the use of physical restraints, polypharmacy, malnutrition, urinary catheterization, length of hospital stay, blood urea, and electrolyte imbalance.[3,40] Iatrogenic events play a crucial role as precipitating factors; for example, the risk of developing delirium is 4 times higher in patients with physical restraints vs. those without restraints.[3]

Table 2. Main predisposing and precipitating factors for delirium occurrence.

Predisposing factors	Precipitating factors
• Age (≥75 years) • Dementia or baseline cognitive impairment • Male sex • Depression • Functional dependence • Comorbidities or illness severity • Malnutrition • Visual and hearing impairment • Alcohol abuse	• Infections • Medications: polypharmacy, psychoactive drugs, sedatives • Iatrogenic events (e.g., physical restraint) • Bladder catheter • Urea and electrolyte imbalance • Hospitalization • Low albumin level • Surgical procedures (cardiac surgery, neurosurgery)

DIAGNOSIS AND ASSESSMENT

Clinical characteristics

Delirium is characterized by an acute change in mental status associated with disturbances in one or more neurocognitive components, such as attention, memory, orientation, or language. Disorganized thinking is a common finding, represented by incoherent or illogical speech. Inattention is considered a core feature of delirium, and is consistently observed in association with other components.[41] Acute onset (hours to a few days) and the fluctuation of symptoms (alteration between presence vs. absence or severe vs. mild) are also key features.[2,4] Some non-cognitive findings are also commonly observed, including perceptual (hallucinations or illusions, predominantly visual) and psychomotor disturbances (agitation or retardation), inappropriate behavior, and alterations of the sleep-wake cycle.

Delirium is typically categorized according to psychomotor activity as either hyperactive, hypoactive, mixed, or without psychomotor features.[42,43] Hyperactive delirium is characterized by agitation and frequently coexists with hypervigilance; hypoactive delirium is defined by a reduction in psychomotor activity an lethargy; and patients who alternate between hypoactive and hyperactive features are defined as having mixed delirium. Despite being more common,[42,44] hypoactive delirium often goes unnoticed. The delay in diagnosis can at least partially explain why hypoactive delirium is generally associated with worse outcomes, as it opens a window for the occurrence of other clinical complications (i.e., immobility, aspiration pneumonia, pressure ulcers).[25,42,45]

In some cases, the clinical features of delirium can persist for many days or weeks, even after discharge, in what is defined as persistent or prolonged delirium. Prolonged delirium usually affects older adults living with dementia or multimorbidity and has also been associated with adverse outcomes.[46,47]

Delirium should be differentiated from other common neuropsychiatric conditions, such as dementia, depression, and psychotic disorders (schizophrenia). Patients with Alzheimer's disease usually experience slow progression of cognitive symptoms, with preserved attention until later stages of the disease. Differentiating vascular dementia, which can lead to acute cognitive decline, may be more challenging. Likewise, patients

with Lewy body disease commonly have visual hallucinations and fluctuations in cognition that must be considered in the differential diagnosis of delirium. Although psychomotor disturbances are present in patients with dementia, significant alterations in attention or level of consciousness as observed in delirium are not expected.[4,48] Conversely, attention problems may be observed in patients with depression, but without disturbances in content or awareness. Perceptual disturbances and disorganized thought are possible clinical findings of both schizophrenia and bipolar disorder. A detailed clinical history may distinguish these findings from the perceptual disturbances occurring in delirium, which are often related to more immediate circumstances or sensory misperceptions in the hospital environment. Also, hallucinations in delirium are more frequently visual than auditory.[41] Even after detailed evaluation and physical examination, the distinction between delirium and other neuropsychiatric conditions can be challenging, particularly in the absence of a reliable informant or if patients are uncooperative.

Diagnostic criteria

The diagnosis of delirium relies on a thorough clinical assessment, including detailed medical history, identification of possible predisposing and precipitating factors, and complete physical examination. Another vital step when delirium is suspected is the investigation of previous cognitive and behavioral status, which will help determine if the symptoms are acute or part of a preexisting condition. The presence of a reliable informant with appropriate knowledge of the patient's clinical history is critical for this diagnostic step.[4]

The diagnostic standard for delirium is set by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), but similar criteria can be found in the International Statistical Classification of Diseases and Related Health Problems, 11th Revision (ICD-11).[49,50] According to the DSM-5, delirium is present when the following criteria are met:

a. disturbance of attention and awareness;
b. development over a short period of time, representing a change from the baseline mental status, with a propensity to fluctuate during the day;
c. additional disturbance in other cognitive domains (e.g., memory, orientation, language);
d. conditions in "a" and "c" not explained by a preexisting neurocognitive disorder and occurring outside the context of severely reduced arousal (e.g., coma);
e. disturbance as a direct consequence of another medical condition, substance use, or withdrawal, or is multifactorial, based on medical history, physical examination, or laboratory findings.

An expert evaluation is required for a DSM-5 diagnosis of delirium.

Additional workup is also usually recommended, following a targeted approach to identify possible precipitating factors (Figure 2). Laboratory tests, chest radiography, electrocardiography (EKG), neuroimaging, and electroencephalography (EEG) are complementary to clinical history and physical examination and should be tailored accordingly.

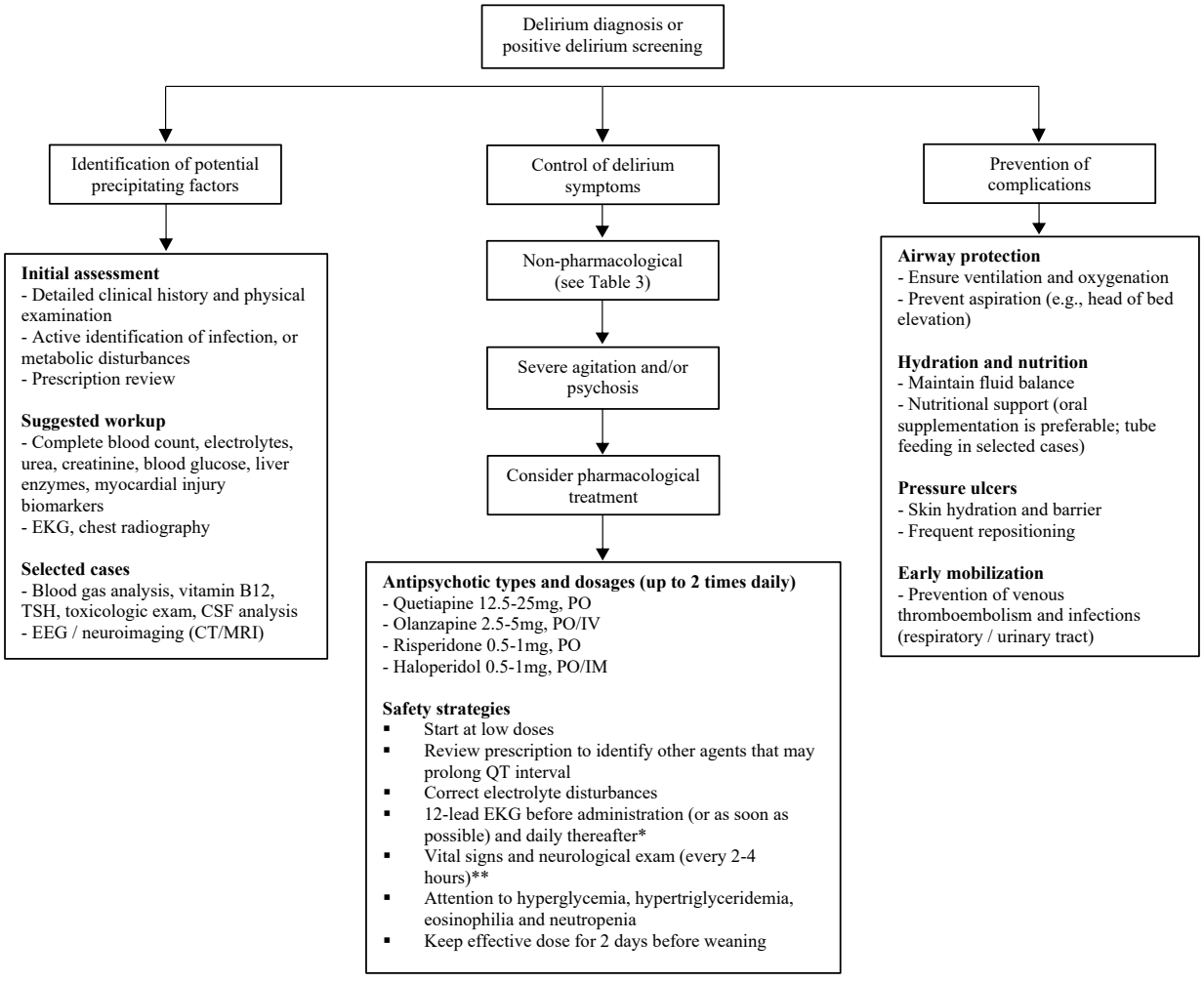
Instruments for delirium detection

It is difficult to systematically diagnose delirium using DSM-5 criteria in clinical practice, given the scarcity of trained personnel and real-life time constraints. Therefore, the development of more straightforward detection tools was an essential step towards improving bedside delirium screening. The Confusion Assessment Method (CAM) is chief among such tools. The CAM was developed in 1990 to operationalize the DSM diagnostic process and has since been extensively used in various clinical settings.[15,51] The original extended version of the CAM included the assessment of nine delirium features, while its final diagnostic algorithm is limited to four items:

1. acute change or fluctuating course (in any component of mental status)
2. inattention
3. disorganized thinking
4. altered level of consciousness.

Delirium is confirmed in the presence of both items 1 and 2, along with either item 3 or 4. The CAM has excellent psychometric properties, with high interrater reliability (kappa = 0.85–0.92), and overall sensitivity and specificity of 94 and 89%.[52,53] Some of its limitations include the need for appropriate rater training and the complementary application of a brief cognitive test, such as the Mini-Cog or the 10-Point Cognitive Screener.[54,55] Patients with severely impaired consciousness should be rated as having stupor or coma rather than delirium. In cases such as these, or when patients are unable to communicate (e.g., endotracheal intubation, aphasia, severe dementia), the CAM-ICU is a top choice for delirium diagnosis.[56]

Implementing a two-step protocol is a straightforward approach to overcoming time barriers and improving delirium detection efficiency.[57,58] The protocol would combine an ultra-brief screener (UB-2) with a more comprehensive detection tool for positive patients. A pilot study by Fick et al. demonstrated that a protocol including an ultra-brief screener based on two questions (state months of the year backwards, and the day of the week) with maximized sensitivity of 93%, followed by a sensitive and specific instrument



EKG: electrocardiogram; TSH: thyroid-stimulating hormone; CSF: cerebrospinal fluid; EEG: electroencephalogram; CT: computed tomography; MRI: magnetic resonance imaging; PO: oral administration; IV: intravenous; IM: intramuscular; *antipsychotics should be halted if EKG shows significant prolongation of the QT interval (increases > 25% from baseline, or larger than 500 ms), abnormalities of the T wave, or Brugada pattern. These effects have been more frequently reported with the use of intravenous haloperidol; **vital signs should be monitored for hyperthermia, hypotension, or tachycardia, and neurological examination should assess the presence of seizures, agitation, irritability, insomnia, and dystonia, or extrapyramidal symptoms.

Figure 2. Flowchart for delirium workup and management.

(3D-CAM), was feasible and effective for delirium identification in older adults.[57] More recently, the UB-2 has been combined with the 3D-CAM with skip pattern to create a new instrument, the Ultra-Brief CAM (UB-CAM). The UB-CAM, which has sensitivity and specificity of 93 and 95% respectively, can be completed in 1 minute or less, with minimum training.[59] The complete UB-CAM instrument can be found at https://deliriumnetwork.org/ub-cam/.

Another instrument with growing use in hospitalized older adults is the 4AT (4 "As" Test), which covers four components:

- alertness or level of arousal;
- abbreviated mental test of four items, or AMT4 (age, date of birth, place, current year);
- attention (months of the year backward);
- acute change or fluctuating course.[60]

A 4AT score higher than three has a 95% specificity and a 76% sensitivity to detect delirium.[61] The 4AT does not require formal training or additional cognitive testing, and is typically completed in 2 to 3 minutes. It does not

require additional cognitive testing and has not been as widely validated as the CAM.[15,62] Moreover, the 4AT can be scored in patients unable to communicate (unarousable or with severe psychomotor agitation). Unlike the CAM, the 4AT does not yield a delirium diagnosis that aligns with DSM-5 and the cut-off can be reached by a variety of other cognitive impairments.

Relevance of individual delirium components

Subsyndromal delirium is defined as an acute change in mental status in the presence of only one or two delirium features, i.e., not all diagnostic criteria are met. Subsyndromal delirium is also associated with adverse outcomes, including functional decline and death, underscoring the relevance of individual delirium components.[46,63] For example, impaired consciousness or arousal has been described as an independent risk factor for death in acutely ill older adults—regardless of delirium or baseline dementia.[64-66] Occasionally, providers are unable to complete the mental status examination, either for lack of patient cooperation (e.g., severe agitation), or limited time in fast-paced clinical settings. In these circumstances, level of consciousness assessments (e.g., Richmond Agitation or Sedation Scale [RASS] or the Observation Scale of Level of Arousal [OSLA]) can help identify patients at greater risk of unfavorable events.[67-69]

PREVENTION AND TREATMENT

Nonpharmacological measures

The most effective strategy to avoid complications and reduce the overall impact of delirium is prevention, and the first step for implementing preventive measures is risk stratification.[2,70,71] The prompt recognition of individuals at a higher risk of delirium and the mitigation of potential precipitating factors are crucial for a successful prevention plan.[72] Several interventions based on single or multiple components have been studied for delirium prevention.[71,73-75] Since single interventions seem less effective in improving outcomes, and delirium is typically multifactorial, simultaneously acting on multiple key issues has become the preferred approach to prevent delirium.[3]

A foremost example of the multicomponent approach against delirium was proposed by Inouye et al. in 1999. The authors tested the first non-pharmacological intervention with a considerable impact on delirium prevention.[76] In a non-randomized controlled study, 852 hospitalized older adults at high risk for delirium were included in a protocol of non-pharmacological measures targeting its main predisposing and precipitating factors (Table 3). Participants in the intervention group had a 40% reduction in delirium incidence compared to the control group.[76] The results laid the

Table 3. Multicomponent intervention for delirium prevention and treatment in older adults.

Components	Interventions*
1. Reorientation strategies	- Communication to promote temporal and spatial orientation - Use of calendars - Orientation board with names of care team members and daily schedule - Family engagement
2. Therapeutic activities	- Cognitive stimulation activities: discussion of current events; word games; reminiscence therapy
3. Sleep enhancement	- At bedtime: hot beverage (milk or tea); relaxing music or sounds; massage - Strategies for noise reduction (e.g., quiet hallways, vibrating beepers) - Adjustment of medication and procedure schedules
4. Early and safe mobilization	- Ambulation or active range-of-motion exercises - Minimizing physical restraints, bladder catheters, or other immobilizing equipment
5. Correction of sensorial deficits	- Vision protocol: glasses or magnifying lenses; large print books; fluorescent tape on call bell - Hearing protocol: portable amplifying devices; cerumen impaction removal; special communication techniques
6. Treatment of acute insults	- Treatment of acute conditions detected during clinical assessment - Maintenance of hydration and nutritional status
7. Management of medications	- Reduce or suspend psychoactive drugs - Avoid rescue doses, particularly of sedatives and antipsychotics - Prioritize non-pharmacological measures for sleep and anxiety

*Adapted with permission of Dr. Sharon Inouye from the Hospital Elder Life Program©. The implementation of these components should consider individual characteristics and screening of the main risk factors (cognitive deficit; sleep deprivation; immobility; visual or impairment; and dehydration). The management of acute insults and medications should be widely implemented in patients with delirium.

groundwork for the Hospital Elder Life Program (HELP), a cost-effective multidisciplinary model of care for delirium prevention that has been implemented in more than 200 hospitals worldwide. Besides reducing the incidence of delirium, HELP has also been shown to prevent falls and functional decline in hospitalized older adults.[71,77]

Non-pharmacological measures for delirium treatment are similar to those recommended for prevention, and should prioritize multicomponent interventions that can effectively reduce the intensity of delirium and the duration of symptoms.[74] The treatment plan should both target the cause of hospitalization and also manage any potential delirium precipitating factors (Figure 2). Moreover, delirium management should not be limited to disease-specific interventions, but instead include rehabilitation measures to prevent physical and cognitive decline.

Pharmacological measures

Although multicomponent non-pharmacological interventions are preferable for delirium management and prevention, they may not be consistently available across clinical settings. Therefore, when resources are limited or psychomotor agitation is severe enough to threaten the patient's or healthcare team's safety, the short-term use of pharmacological measures might be necessary until symptom resolution (Figure 2).[78] Pharmacological control of delirium symptoms is also justified in patients experiencing extreme distress from psychotic symptoms (e.g., anxiety, fear).[79] Nevertheless, evidence does not exist to support the use of any specific pharmacological intervention to prevent delirium or minimize its symptoms. In fact, some studies have reported poorer outcomes in delirium patients who received pharmacological interventions.[80-82]

In a previous systematic review, Serafim et al. concluded that pharmacological interventions may reduce delirium occurrence in ICUs. Their results were mostly based on the use of antipsychotics (i.e., haloperidol and risperidone) and dexmedetomidine in surgical patients.[83] Even so, their overall results suggest that single pharmacological treatments do not reduce delirium duration, length of hospital stay, or mortality—findings that are supported by a recent overview of published metanalyses.[84] The authors go on to conclude that cohort studies are still needed to assess whether delirium treatment has any impact on long-term cognitive and functional impairment.[83]

Antipsychotics

Typical and atypical antipsychotics are routinely prescribed for delirium management in clinical practice. Delirium guidelines have traditionally recommended haloperidol (typical) as a first-line agent when a pharmacological approach is inevitable.[78] Despite the predominance of haloperidol in previous studies, atypical antipsychotics seem to have a safer pharmacological profile, with a faster onset and lower incidence of adverse effects. These characteristics favor their use as preferred options for the symptomatic control of delirium.[85] Risperidone and quetiapine are common choices, although other atypical antipsychotics, such as ziprasidone and aripiprazole, have also been investigated.[85-89] Still, present-day evidence does not support the routine use of antipsychotics to prevent or treat delirium and their administration should be limited to the circumstances mentioned above (i.e., severe agitation or distress).[78,88,90] The recommendation is based not only on the low efficacy of antipsychotics but especially on the considerable risk of adverse events, which varies according to antipsychotic type and dosage, and the patient's susceptibility to alcohol.

Extrapyramidal symptoms (e.g., dystonia, akathisia, parkinsonism) are common adverse effects of typical antipsychotics but less frequent in atypical antipsychotics. Conversely, quetiapine is associated with constipation and urinary retention in older adults due to its anticholinergic properties and may cause orthostatic hypotension.[85] Most importantly, all antipsychotics increase the risk for QT interval prolongation and close monitoring is required. Even in palliative care settings, antipsychotics have been associated with a worse prognosis and their use should be monitored using safety checklists (Figure 2).[90-92]

Alpha-2 adrenergic agonists

A promising agent that has been investigated for delirium prevention and treatment is dexmedetomidine, an alpha-2 adrenergic receptor agonist. Dexmedetomidine is a popular sedative for critically ill patients, given its anxiolytic and analgesic properties that do not induce significant respiratory depression. Moderate to high-quality evidence shows that dexmedetomidine is effective in both delirium prevention and treatment, and that its prescription minimizes the use of benzodiazepines in ICUs.[93-95] Interestingly, a recent study explored the long-term effects of dexmedetomidine in patients with delirium and observed improvements in cognitive function after 3 years of follow-up.[96] Dexmedetomidine should be restricted to ICUs and used in mechanically ventilated patients with severe agitation.[78] Other medications, such as clonidine, an alpha-2 adrenergic agonist administered orally, did not improve delirium outcomes in hospitalized older adults.[97]

Melatonin and melatonin agonists

Abnormalities in melatonin levels have been linked to the occurrence of delirium.[98] Early investigations of melatonin and melatonin agonists (ramelteon) for delirium prevention have yielded conflicting results. However, a recent systematic review has suggested that melatonergic agents are effective in reducing delirium incidence.[99,100] This conclusion was further supported by three randomized controlled trials: two using melatonin and one using ramelteon.[101-103] Although some of the results from these trials have been positive, the findings were not sufficiently robust (e.g., lack of validated tools to detect delirium) to recommend melatonergic drugs for the management of delirium.[101,104,105]

Other pharmacological treatments

There is insufficient evidence to recommend the following medications for delirium prevention and treatment: ketamine, cholinesterase inhibitors, statins, Z-hypnotics (e.g., zolpidem, zopiclone), NMDA receptor blocking agents (amantadine and memantine), methylphenidate, and gabapentin, based on efficacy.[106-111] Additionally, some of these medications are associated with a substantial risk of adverse events, including hallucinations (ketamine) and seizures (Z-drugs), which further discourages their prescription in patients with delirium.

CONCLUSION

Delirium is a common neuropsychiatric condition associated with various adverse outcomes. Acutely ill or hospitalized older adults should be assessed for delirium risk on admission, and routine delirium screening should be implemented accordingly. Any alteration in mental status should be promptly managed with non-pharmacological measures and, in cases of severe agitation or psychosis, with short-term pharmacological interventions. Implementing measures to reduce individual and environmental triggers of delirium occurrence or prolongation is of utmost importance for any provider caring for older adults.

Multicomponent non-pharmacological interventions are currently the best strategy for delirium prevention and treatment, having more significant benefits than single pharmacological therapies. The limited availability of effective pharmacological interventions can be partially explained by insufficient knowledge regarding delirium pathophysiology, the multifactorial construct behind delirium occurrence, and the low methodological quality of previous studies.[112] Providers should adapt screening methods, preventive strategies, and management protocols to their settings, developing a delirium care plan for older adults that is both feasible and effective in the long run.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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AUTHOR'S CONTRIBUTION

FBG: conceptualization, methodology, visualization, writing - original draft, writing - review & editing. TJAS: conceptualization, methodology, supervision, writing - review & editing. REVC: methodology, writing - original draft, writing - review & editing. SKI: conceptualization, supervision, writing - review & editing.

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