Delirium

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Contents

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Learning Objectives

- Learn the relevance of delirium in terms of epidemiology, prognosis, and mortality, particularly after hospital admission and during the intensive care unit (ICU) stay
- Understand the pathophysiological basis of delirium, including the importance of risk and precipitant factors
- Recognize the clinical features of delirium, especially on elderly, and the major differential diagnoses
- Appropriately investigate the causes of delirium and identify specific treatments
- Learn the differences between nonpharmacologic and pharmacologic management of delirium

35.1 Introduction

Delirium represents a common medical condition which affects the old and very old patient in a hospital setting, particularly with cognitive impairment. It is characterized by disorganized thinking, inattention, and an altered level of consciousness. Delirium shows a fluctuating course during the acute phase. It might be underdiagnosed, due to the variability of its clinical features. In fact, it can manifest as an overactive or as an underactive form. Physicians could also observe a mixed form.

The onset of a confusional state in hospitalized older people is derived by the interruption of their daily routine, environmental modifications, and loss of orientation. Sleep deprivation, untreated pain, drugs, and medical devices, including bladder catheters, are precipitating factors for delirium.

Considering the complicated assessment of all risk and precipitating factors and the consequent delay of its resolution, delirium can lead to a longer stay and a higher risk of mortality [1], particularly on ICU.

Preventing delirium should be a fundamental goal for clinicians who approach this issue. Early mobilization, reduction of physical restraints, use of hearing and visual aids, and environmental actions to avoid sleep deprivation could represent some strategies in the nonpharmacological management of delirium.

Pain assessment is an important step in the process of care. Finally, treatment with neuroleptic drugs is often mandatory in the acute phase of delirium.

35.2 Definition and Classification

Delirium could be imagined as a cerebral insufficiency, with a fluctuating course, that occurred to people affected by an acute clinical illness, especially with cognitive disorders.

According to fifth edition of the Statistical Manual of Mental Disorders (DSM-5), delirium is based on:

- Disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment). The disturbance develops over a short period of time (usually hours to few days), represents an acute change from baseline attention and awareness, and tends to fluctuate during the course of a day.
- An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).

The disturbances are not better explained by another preexisting, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.

There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct consequence of a medical condition.

Delirious patients also present behavioral disorders. Although not essential criteria for the diagnosis of delirium, psychomotor activities, emotional disturbances, and sleep interruption are common features of a confusional state. The two delirium phenotypes are the hyperactive patient and the hypoactive one [2].

The hyperactive delirious patient shows euphoria and agitation, with psychomotor manifestations. He is not collaborating and does not respond easily to medications. This kind of confusional state is associated with hospitalization, environmental modification, untreated pain, and medical devices.

The hypoactive delirious patient tends to exhibit lowers levels of attention, even if he is awake. It is usual to see daytime sleepiness. The typical trait is the exhausted ability to react to external stimuli. Hypoactive delirium derives from an acute illness. It does not require medications, but the management of the underlying acute disease is fundamental for the resolution of delirium, especially because this form of confusional state is associated with higher risk of mortality.

The mixed form includes both positive and negative symptoms. Emotional manifestations concern hallucinations, fear, and delusions.

35.3 Epidemiology

Confusional states are mainly observed during hospitalization. Delirium determines a longer stay than usual and consequent increase of the costs [3]. Potentially, all hospitalized patients present high risk of delirium, especially after surgery [4]. Among very old patients admitted at hospital, one third of them might develop confusion during the stay. The incidence of delirium on elderly changes from 25% after major elective surgery to 50% after hip fracture repairing surgery or other high-risk procedures [2]. Approximately, 10–15% of older persons presenting to emergency departments manifest delirium in association to the main illness [5]. The rate of delirium mostly increases in the intensive care unit (ICU), and this issue often persists during the ICU stay [6]. Moreover, delirium in the ICU is associated with worse short-term outcomes [7] and three-times increased risk of death both during and after the ICU stay [8].

About long-term care, such as post-acute and end-of-life care settings, in which the majority of patients are frail, delirium is a frequent and very frequent complication, respectively.

35.4 Pathogenesis

The pathophysiology of delirium is partially clear, but there are some theories concerning the etiology of this issue. We can explain how delirium develops with three mechanisms: alteration in neurotransmission, inflammation, and the connection between risk and precipitating factors.

Neurotransmitters act both on subcortical and cortical brain areas. Neuroimaging and somatosensory evoked potentials have shown the role of subcortical zones (such as pontine reticular formation, basal ganglia, and thalamus) in the onset of confusional state. In fact, attention and arousal are mediated by truncus encephali. Moreover, persons affected by clinical conditions associated with lesions on subcortical areas, like Parkinson disease or subcortical stroke, are susceptible for delirium. On the other side, electroencephalography (EEG) shows that delirium is associated with altered cortical function, that is, the slowdown of the dominant alpha rhythm and the onset of slow-wave activity, which is not physiological. Attention is governed by cortical functions, particularly in the frontal lobes. Thus, we can suppose that delirious patients with inattention might have altered pathways on these regions.

Acetylcholine seems to participate in the pathogenesis of delirium. We know how this neurotransmitter plays a fundamental role in Alzheimer disease, in which there is loss of cholinergic neurons. Some neuroleptic and cardiovascular medications, such as clozapine, olanzapine, and atropine, exhibit anticholinergic activity; at therapeutic doses, their serum concentration on elderly is likely to increase [9]. These considerations might explain why polymedicated older people affected by Alzheimer disease are at high risk to manifest delirium. Moreover, in some precipitating conditions for delirium, such as hypoxia and hypoglycemia, the acetylcholine synthesis decreases. Nevertheless, anticholinergic inhibitors do not prevent delirium [10].

The altered serum concentrations of other neurotransmitter, such as dopamine, gamma-aminobutyric acid (GABA), glutamate, melatonin, somatostatin, endorphins, serotonin, histamine, and norepinephrine, have been seen. Drugs that act against these molecules can develop delirium-like symptoms. The most described pathophysiological mechanisms for these neurotransmitters are: increased synthesis of dopamine, glutamate, or norepinephrine; reduced melatonin availability; and excess or deficiency, depending on symptoms presentation, of GABA, serotonin, and histamine concentration [11].

None of these altered pathways might develop the clinical manifestation of delirium alone. It is more reasonable that more than one abnormal mechanism is involved in the pathogenesis of delirium.

Inflammation develops in specific clinical situations, such as infections, cancer, surgery, or after falls. The interleukins and tumor necrosis factor-alpha levels increase during the onset of delirium, especially with hyperactive forms. Moreover, inflammation may alter the blood-brain barrier, and consequently it can promote the activity of cytokines and drugs on central nervous system.

Different clinical factors can participate in the pathogenesis of confusional states. At first, we must consider those *risk factors* (► Box 35.1) which expose patients to major vulnerability. The most common chronic diseases associated with delirium are dementia, other cerebral disorders, and advanced cancer. Among acute illnesses, we must mention stroke, hip fracture, and dehydration. Depression, drugs, and alcohol addiction represent other risk factors for confusional states. Advanced age, if interested with multimorbidity and polypharmacy, makes a person more prone to complications. Malnutrition and sarcopenia can worsen the functional state. Generally, frail people present reduced tolerance to exogenous factors, which determines adverse health outcomes, including delirium.

Risk factors, if connected with precipitating factors, cause the onset of delirium. In ► Box 35.2 we can mention all the recognized precipitating factors among very

older people, both out or during the hospital stay. Drugs represent the most common reason for the onset of delirium. Antipsychotics are effective in the resolution of acute psychomotor disorders, but they can also increase the risk of delirium. Sedative-hypnotics, skeletal muscle relaxers, and opioids can cause confusional states. Generally, the risk of delirium increases as much as the number of prescribed medications augments. Among acute disorders, we can include fever, infections, heart failure, hypoxemia, and electrolyte disorders. If pain is untreated or undertreated, it might precipitate delirium. Hospitalization exposes to alteration in daily routine, particularly for people with reduced autonomy and cognitive impairment. Environmental modifications are fundamental in the onset of delirium. Sharing room with other patients and sleep deprivation should be considered. Finally, but not less important, physical restraints and all medical devices, such as urinary catheters, nasogastric tubes, central and peripheral venous catheters, oxygen devices, and tracheostomy, precipitate delirium.

Box 35.1 Risk Factors for Delirium

Aging
Cerebral disorders
Dementia
Brain cancer
Stroke
Multimorbidity
Polypharmacy
Reduced functional state
Malnutrition
Sarcopenia
Frailty
Advanced cancer
Hip fracture
Dehydration
Depression
Drugs or alcohol addiction

Box 35.2 Precipitating Factors for Delirium on Very Old Patient

Drugs

Analgesics (opioids, NSAIDs)

Antibiotics and antivirals (cephalosporins, penicillins, fluoroquinolones, linezolid, metronidazole, aminoglycosides, isoniazid, rifampin, sulfonamides, acyclovir)

Anticonvulsants (carbamazepine, levetiracetam, phenytoin, valproate)

Antidepressants (mirtazapine, selective serotonin reuptake inhibitors, tricyclic antidepressants)

Antihistamines

Antipsychotics

Cardiovascular drugs (atropine, beta blockers, antiarrhythmics, clonidine, digoxin, diuretics)

Corticosteroids

Diphenhydramine
Dopamine agonists (levodopa, pramipexole, ropinirole, amantadine)
Gastrointestinal drugs (antiemetics, loperamide, scopolamine, histamine-2 receptor blockers)
Hypoglycemics
Sedative-hypnotics (barbiturates, benzodiazepines)
Skeletal muscle relaxers
Other drugs (lithium, disulfiram, phenothiazines, cholinesterase inhibitors)
Drugs side effects
Hyperammonemia from valproic acid
Serotonin syndrome
Drugs of abuse and poisons
Ethanol
Hallucinogens
Heroin
Others (carbon monoxide, methanol, ethylene glycol)
Pain
Fever
Infections
Pneumonia
Urinary tract infections
Sepsis
Encephalitis
Meningitis
Abdominal infections
Hypoxemia
Electrolyte disorders
Hypoglycemia
Hypovolemia
Myocardial infarction
Acute organ failure
Head injury
Major trauma
Hospitalization
Hip surgery
Major surgery
Environmental modifications
Sleep deprivation
Physical restraints
Medical devices
Urinary catheters
Peripheral venous catheters
Central venous catheters
Nasogastric tubes
Oxygen devices
Tracheostomy
Monitoring devices
Urinary retention
Fecal impaction

35.5 Clinical Presentation

The diagnosis of delirium is not self-evident, due to the complex variety of presentation, as it can manifest in different ways, and often requires an experienced clinician. Among younger people, an underlying illness is more likely to be found; on elderly, an acute disease might not manifest itself except for behavioral disorders. As discussed before, delirium can manifest with hypoactive or hyperactive form [12]. The first one is the most common phenotype on very old people, and it is characterized by lethargy, inability to be alert when awake, and reduced psychomotor functions. These alterations can be confused with depressed mood or fatigue; for this reason, it is often not recognized. On the other side, the hyperactive form manifests itself with symptoms of agitation, increased alertness, and often hallucinations. Moreover, patients may fluctuate from the hypoactive to the hyperactive phenotype (mixed motor type). The mixed form represents a critical diagnostic challenge for physician, to differentiate it from psychotic illnesses and mood disorders. The hallmarks of delirium are the acute onset and the disturbance of attention. One of the first manifestations of delirium is an altered level of consciousness and the inability to main-

tain attention (e.g., easy distractibility). However, assessing the delirious patient's attention is not simple, especially if the cognitive status before the acute event is unknown. The role of caregivers is often necessary, to assess what the patient's functional level was before delirium has started. The onset of this confusional state is generally abrupt, occurring within hours or days. A critical aspect is the fluctuating course, with symptoms having significant variations within 24 hours, with alternating moments of lucidity and severe exacerbation of delirium. The worst moments for the onset of symptoms are the evening or nighttime hours, while during daily hours a normal and lucid state is typical. These fluctuations do not help the clinician during the assessment of delirium. A delirious patient also shows easily distraction, fails to perform complex tasks, and does not follow the thread of a conversation. He may present with disorganization of thought, which evolve into non-fluent, incoherent, and disorganized speech. Other signs might include temporospatial disorientation, memory alterations, psychomotor agitation, perceptual alterations, sleep-wake cycle alterations, and emotional instability. Perceptual alterations might be visual, auditory, or somatosensory hallucinations, with little insight or misinterpretations of objects or people (i.e., mistaking one person or an object for another). Delirium can be often preceded by a prodromal phase, including easy irritability, mood alterations, restlessness, alterations in sleep-wake rhythm, and hypersensitivity to sound or light.

35.6 Diagnosis

Detecting the clinical history of delirium is fundamental in the process of diagnosis. During the first evaluation, preexisting cognitive status and changes of mental status must be investigated. It is critical to search for a possible cause of delirium and evaluate every acute reported symptom, such as pain or dysuria. It is important to investigate those symptoms/signs appeared during the last hours or days, medications or their recent changes, and the previous history, evaluating any previous episode and comorbidities. In an estimated 70% of cases, the clinician does not recognize delirium. The diagnosis of delirium is primarily clinical, and it is often difficult to do a history collection and a careful cognitive assessment. Evaluation scales might help on this phase.

35.6.1 Physical Examination

The physical examination will investigate any detectable causes, such as signs of infection, dehydration, focal neurologic changes, or thermal changes. It may be complex to make a completely objective assessment in a patient who is poorly cooperating. Furthermore, it is important to pay attention on the physiological changes among elderly, which might alter the clinical presentation of common diseases. Some examples are infections, such as sepsis, which can manifest with a temperature lower than 38.5°, acute coronary syndrome that might arise without chest pain, or pneumonia with any auscultatory or radiographic changes. Moreover, older persons with delirium are unable to report pain. Neurological objective examination, although it may be altered and tainted by the presence of inattention and altered consciousness, may reveal focal neurological signs of new onset, such as cranial nerve or visual field

alterations, or multisegmental disorders, such as myoclonus or tremor. Some specific signs, such as multifocal myoclonus, asterixis, or postural action tremor, are usually associated with a metabolic/toxic cause of delirium.

35.6.2 Evaluation Scales

In order to obtain a correct diagnosis, the various aspects of delirium must be considered. For this purpose, the use of evaluation scales can be helpful. There are several assessment scales, both for identification of delirium and identification of its severity. Among identification scales, the most known one is the Confusion Assessment Method (CAM) [13], of which some variants have been validated depending on the setting where it is performed (e.g., CAM-ICU in the intensive care unit, CAM-ED and B-CAM in emergency rooms, and NH-CAM in nursing homes). The 3D-CAM takes 3 min to perform it and evaluates the cardinal and accessory clinical features of delirium. Another quick and simple test is the 4AT scale that is based on four items, and its purpose is to identify the presence of delirium. Tools for assessing the severity of delirium include the Delirium Index, the Memorial Delirium Assessment Scale, and the Delirium Rating Scale. Each scale has strengths and limitations, so it is important that the choice of a scale is made by experienced clinicians.

35.6.3 Searching for Precipitating Factors

As part of the initial evaluation of a patient with delirium, it is critical to search potential causes of delirium. It is important to identify life-threatening conditions and exclude confounding factors or possible alternative diagnoses. The most common causes of delirium are postoperative status, infections (e.g., respiratory inflammation, urinary tract infection), pain syndromes, alterations in hydro-electrolyte balance, metabolic disorders (e.g., hypoglycemia, uremia, liver failure), hypoperfusion states such as shock, and withdrawal or toxicity of certain medications.

35.6.4 Laboratory and Instrumental Tests

Nowadays, there is no specific diagnostic test for delirium. The choice to perform specific tests depends on clinical picture. They might be useful to identify the underlying cause of delirium. We can mention some common laboratory and instrumental tests, usually performed to achieve the diagnosis of the underlying illness: complete blood count; renal, liver, and pancreatic function; serum electrolytes; blood glucose; inflammatory markers; chest x-ray; electrocardiogram (EKG); urinalysis; and arterial blood gas test. Culture tests should be requested only in the suspicion of an ongoing infectious state. Other blood tests should be considered patient by patient, and they might include vitamins (e.g., B12), thyroid and adrenal hormones, blood ammonium, plasma drug assays, and screening for specific infectious diseases (e.g., syphilis). In selected cases, such as a patient with febrile delirium or neurologic signs, some tests like brain imaging, lumbar puncture, or electroencephalogram (EEG) might be performed.

Table 35.1 Main clinical differences between delirium and dementia

	Delirium	Dementia
Onset	Acute (hour/days)[a]	Progressive, insidious (months/years)
Attention	Impaired (fluctuating)[a]	Stable
Orientation	Impaired (but fluctuating)	Normal until late stage (less fluctuating)
Course in a day	Fluctuating	No major changes
Consciousness	Variable, from lethargic to hyperalert	Normal until late stage
Hallucination	Visual (auditory)	Sometimes
Memory	Impaired commonly	Prominent impairment
Speech	Disorganized, illogical, incoherent	Aphasia, anomia
Delusions	Common	Common

[a]Hallmark of delirium

35.7 Differential Diagnosis

It is not easy to differentiate a chronic confusional state, as dementia can be, from delirium alone or delirium superimposed on dementia. However, delirium differs from dementia in some clinical features (Table 35.1). Cognitive impairment has a more progressive and insidious onset, where fluctuations are, if present, very nuanced. The Lewy body dementia has more pronounced fluctuations in attention, but visual hallucinations (especially animal images) are more frequent and typical. Some psychiatric disorders might enter in differential diagnosis with delirium, such as acute psychosis or depressive disorder. A particular phenomenon, still poorly understood, is sundowning, typical of patients with dementia, in which the deterioration occurs in the evening hours and it can be confused with delirium.

35.8 Prevention

Prevention is a fundamental aspect to avoid the onset of delirium, particularly for very old people, admitted on hospital setting. A wide set of nonpharmacologic measures and individualized approaches might reduce the risk of confusional state. These strategies aim to provide supportive and regenerative care, prevent cognitive and physical decline, and minimize or eliminate precipitating factors. Some of the interventions that can help to reduce the risk of delirium are descripted below, and they can be applied also during the ICU stay.

Several procedures are specific to hospitalized patients which include reducing the length of stay in the emergency room, preventing falls in patients with a reduced functional state, and creating specialized spaces for hospitalized patients with delir-

ium (delirium room). Furthermore, the activation of geriatric counseling in some contexts (e.g., postoperative states after hip fracture surgery) could be important in the process of recovery. No medications have shown to prevent delirium. Currently, several classes of drugs could be effective in preventing delirium. Some of these include antipsychotics, dexmedetomidine, melatonin and melatonin agonists, gabapentinoids, and cholinesterase inhibitors. Nevertheless, we suggest focusing on multicomponent, nonpharmacologic interventions to modify risk factors and reduce the incidence of delirium [14].

Practical Implications

To prevent delirium, we can suggest some strategies:

- Try to avoid exposure to some instrumental devices that may contribute to the development of delirium (e.g., indwelling bladder catheters)
- Remove precipitating factors, physical restraints, indwelling catheter, conditions of impaired visual or auditory function, and treat pain as soon as possible
- Limit immobilization as much as possible (as in postoperative bedding), encouraging early mobilization (even from the first postoperative day), with the activation of motor rehabilitation services
- Limit sleep deprivation and promote physiological sleep, particularly in hospitalized patients, by limiting medical and nursing interventions at night and reducing noise and any source of sleep disturbance
- Avoid or monitor closely categories of drugs or substances that may facilitate the onset of delirium (e.g., benzodiazepines, opioids, antidepressants, dopamine agonists)
- Ensure adequate hydration
- Promote moderate cognitive stimulation through regular family visits, especially for patients with cognitive impairment (but overstimulation is not recommended)
- Use reorientation procedures, such as providing tools like clocks and calendars
- Ensure the availability and easy access to non-threatening personal effects

35.9 Management

The management of delirium consists into two main components that happen simultaneously: supportive therapy and assessment of the underlying cause.

35.9.1 Etiological Treatment

Once the potential cause of delirium is identified, therapy is needed. The treatment of the underlying condition might be pharmacologic or nonpharmacologic, and that is specific to each hypothesized cause, such as analgesics for pain, antibiotic therapy for infections, fluid replacement for dehydration, drug removal, or antidote for drug toxicity.

35.9.2 Supportive Therapy: Nonpharmacological Treatment

Nonpharmacologic treatment is the first-line choice in the management of delirium itself. This type of intervention includes reorientation and behavioral practices, for example, allowing as soon as possible family members to be close to the patient, or showing calendars, clocks, objects from the patient's home. It is important that the patient with hearing or visual impairments has hearing aids or glasses. Communication with the delirious patients is also critical: reassure and calm them, attempt reorientation, and explain where they are and what is happening. These patients could be able to appreciate specific aspects of the communication: a calmly and quietly speech, nonverbal language, sitting close to the patient, maintaining eye contact, smiling, and appearing friendly. On the other hand, superficial, hostile, hasty, heedless, or surly attitudes will most likely be counterproductive. Temporary use of physical restraints is allowed if they are the only available way to ensure the patient's safety. Therefore, it is advisable to promote the patient's mobility and autonomy as much as possible, reducing bedridden time and placing personal belongings. Other relevant factors to consider are good ambient illumination, preferably natural, during daylight hours, whereas it is important to limit light sources and noise during nighttime hours. Other strategies to improve sleep quality in a nonpharmacological way are music and bright light therapy. To achieve these objectives, "delirium rooms" are increasingly common and specifically created for this type of patient. Although there are conflicting data, it seems that nonpharmacological interventions can reduce the duration and occurrence of delirium [14, 15].

35.9.3 Supportive Therapy: Pharmacological Treatment

Pharmacologic management is based on symptomatic treatments (Table 35.2). Drugs need to be administered in the hyperactive delirium. On hypoactive delirious patients, there is no agreement on the use of antipsychotics or psychostimulants.

Antipsychotic Medications

The use of these medications for the treatment of delirium is off-label. This class of drugs is effective in delirium and psychomotor agitation to prevent the patient from harming themselves. The most frequently used drug is haloperidol [16], which can be administered orally or parenterally, either intramuscularly or intravenously; however, the latter is to be reserved in patients in whom the rapid onset of drug effect is required, paying attention to the risk of polymorphic ventricular tachycardia and sudden death. The initial haloperidol dose must be low (0.25–10.5 mg), repeatable every 30 min, until sedation is achieved or up to a maximum of 5 mg per day. However, older patients never treated with antipsychotic treatment require a maximum initial daily dosage of 3–5 mg. A maintenance dose, corresponding to half of the loading dose, should be administered in the course of the next 24 h. Then, it might be scaled up over the next 48 h as agitation resolves.

Continuous or prophylactic administration of haloperidol is not advisable. In any case, the time of haloperidol administration should be as short as possible

Table 35.2 Main antipsychotic medications for delirium in older adults

Pharmacological treatment	Dose	Mechanism of action	Focus on	Geriatric considerations
Haloperidol	**PO**: Initial 0.5–0.1 mg (may repeat every 30 min) **IM/IV**: 0.125–0.25 mg (may repeat every 30 min) Max: 5 mg/day **Maintenance dose**: Half loading dose in multiple doses over the next 24 h, with subsequent tapering in 48–72 h	**Blockade of brain dopamine receptor D2**	Extrapyramidal syndrome (dystonia, dyskinesia, parkinsonism, akathisia, dysphagia) is dose related QT prolongation, cardiac arrhythmia, and cardiac arrest Pneumonia Leukopenia and thrombocytopenia Neuroleptic malignant syndrome Seizures Glycemic and lipid parameters and weight gain Electrolytes (hyponatremia/SIADH) Sexual dysfunction Hypothermia *Not indicated in Parkinson disease and Lewy body dementia*	Beers criteria: High risk medication (increased risk of cerebrovascular accident, cognitive decline, and mortality)
Risperidone	**PO**: 0.5–1 mg every 4 h, max 2–3 mg/day	**Antagonism of 5-HT2, dopamine-D2, alpha 1, alpha 2 adrenergic and histaminergic receptors** Low affinity for 5-HT1a, 5-HT1c, 5-HT1d and dopamine-D1	Extrapyramidal syndrome (dystonia, dyskinesia, parkinsonism, akathisia, dysphagia) is dose related QT prolongation, cardiac arrhythmia, and cardiac arrest Pneumonia Leukopenia and thrombocytopenia Neuroleptic malignant syndrome Angioedema Glycemic and lipid parameters and weight gain Orthostatic hypotension, syncope, falling Sexual dysfunction Hypothermia	Beers criteria: High risk medication (increased risk of cerebrovascular accident, cognitive decline, and mortality)

Table 35.2 (continued)

Pharmacological treatment	Dose	Mechanism of action	Focus on	Geriatric considerations
Quetiapine	**PO/nasogastric tube**: Initial 12.5–25 mg once/twice daily. Increase gradually based on response	**Antagonism of 5-HT2, dopamine-D2, alpha 1, alpha 2 adrenergic, histaminergic receptors, dopamine-D1**	Extrapyramidal syndrome (dystonia, dyskinesia, parkinsonism, akathisia, dysphagia) is dose related QT prolongation, cardiac arrhythmia, and cardiac arrest Leukopenia and thrombocytopenia Neuroleptic malignant syndrome Orthostatic hypotension, syncope, falling Sexual dysfunction Glycemic and lipid parameters and weight gain Anticholinergic syndrome (constipation, urinary retention, xerostomia, blurred vision)	Beers criteria: High risk medication (increased risk of cerebrovascular accident, cognitive decline, and mortality) May be used with more safety in Parkinson's disease
Olanzapine	**PO/IM**: 2.5 mg once daily	**Strong antagonism of 5-HT2a, 5-HT2c, dopamine-D1–4, histamine H1, alpha1-adrenergic receptors. Moderate antagonism 5-HT3, muscarinic M1–5**	Extrapyramidal syndrome (dystonia, dyskinesia, parkinsonism, akathisia, dysphagia) is dose related QT prolongation, cardiac arrhythmia, and cardiac arrest Leukopenia and thrombocytopenia Neuroleptic malignant syndrome Orthostatic hypotension, syncope, falling Sexual dysfunction Glycemic and lipid parameters and weight gain Anticholinergic syndrome (constipation, urinary retention, xerostomia, blurred vision) Hypersensitivity reactions	Beers criteria: High risk medication (increased risk of cerebrovascular accident, cognitive decline, and mortality)

because of the increased risk of mortality and stroke in patients with dementia. Strong antipsychotics, such as haloperidol, expose to an increased risk of extrapyramidal effects and acute dystonia. These effects are dose-dependent and occur for doses greater than 4–5 mg per day. In addition, especially in elderly patients, this drug can accumulate on the body, and side effects can develop with submaximal doses. Also, its use in patients with Parkinson's disease is not recommended. Atypical antipsychotics such as quetiapine, risperidone, and olanzapine have been shown to have fewer side effects and similar efficacy [17]. However, haloperidol remains the most widely used drug because of the greater clinical experience with its use [18]. Some evidence, however, seems to indicate that antipsychotics might prolong the duration of delirium.

▪▪ Benzodiazepines

This class of drugs is not recommended as a first-line therapy for delirium. Benzodiazepines, such as lorazepam, have a rapid onset of pharmacologic effects. However, they can cause worsening delirium, paradoxical agitation, and excessive sedation, particularly on elderly. An exception is delirium caused by alcohol or drug withdrawal, seizures, or when antipsychotics are contraindicated. In this case, we suggest to consider low-dose lorazepam (0.5 mg). It is important to remember that benzodiazepines are chronically used by older patients, and we need to pay attention to the risk of withdrawal syndrome when modifying such therapy.

▪▪ Others

Other drugs have been studied in the past, such as cholinesterase inhibitors, propofol, dexmedetomidine, selective serotonin reuptake inhibitors, and clonidine. Studies conducted have shown conflicting results, and there is no consensus on their use in delirium treatment.

35.9.4 Special Circumstances: End-Life Patients

Delirium in palliative care is common; more than 80% of terminally ill patients develop delirium, either in the hyperactive or hypoactive form. It is essential to involve both patient and family on establishing the goals of treatments, assessing the needs of the patient and his family, and discussing together the intensity and appropriateness of possible medical treatments. As already mentioned, the cause of delirium is often identifiable and removable, but in some cases, particularly in palliative care settings, it may result in the practice of invasive procedures. Nonpharmacological treatment is the first-line recommended approach also on these patients [19]. Sedation should be considered, but it will affect the interaction with family members. Medications used in this context are primarily antipsychotics, especially haloperidol. If sedation is required, lorazepam is the first-line agent, with a starting dose of 0.5–1 mg, either orally or parenterally, which is short-acting and easily titrated.

35.10 Prognosis

Older and very older adults are highly susceptible to worse outcomes from delirium: increased risk for mortality, cognitive decline, institutionalization, and prolonged hospitalization. Delirium appears to be an independent marker of mortality at 6–12 months after hospitalization [20]. In addition, delirium sequelae may persist for a long time. Some studies have shown that some degree of cognitive dysfunction was present even at 12 months, especially if an underlying cognitive impairment was present. Furthermore, although delirium has always been considered a transient and reversible condition, in some cases, delirium can persist for a prolonged time, even for months, while some studies indicate that about 20% of patients have complete resolution of symptoms within the first few months after the acute event. Finally, a clear correlation between the severity of the clinical picture and outcomes has not yet been demonstrated. However, a report indicated that patients with severe delirium following femoral fracture surgery have a higher mortality rate and a subsequent admission to a nursing home [21].

Conclusion

Delirium represents a common complication for the elderly patient with an acute disease. It is associated with worse outcomes and higher risk of mortality. Older and very older persons are more susceptible to delirium due to the higher incidence of dementia, reduced functional state, or multimorbidity. Preventing delirium among people with those risk factors for the onset of confusional state should not be underestimated. All the probable precipitating factors for the onset of delirium must be investigated to perform an appropriate approach to this issue. Some interventions to reduce the risk of delirium can be applied in every hospital department, including ICU. Management of delirium concerns the resolution of precipitating factors and the treatment of delirium itself both with nonpharmacological and pharmacological therapies.

Take-Home Messages

- Delirium mainly affects hospitalized older people with previous cognitive impairment.
- Delirium is associated with a longer stay and increased risk of mortality.
- Untreated pain, infections, and major surgery might precipitate delirium. The use of medical devices is less tolerated by vulnerable people.
- Management of the underlying cause is fundamental in the process of care, both for community dwelling and hospitalized patients.
- Treatments with drugs for delirium itself must not be the only strategy for the recovery of old delirious patients.
- Preventing delirium is fundamental for clinicians who approach the old and the very old patient. Environmental actions to facilitate orientation, physiologic sleep, avoiding physical restraints, and promoting early mobilization should be considered, also on ICU.

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