Delirium is a disorder that lies at the interface of psychiatry and medicine. It is an acute organic syndrome caused by an underlying medical condition and is defined clinically by disturbances in cognitive function, attention, and level of consciousness. Delirium is considered a syndrome because of the constellation of signs and symptoms associated with the disorder, coupled with a wide variety of potential etiologies.

Affecting a diverse population of patients, delirium is a prevalent disorder that is found in all health care settings. In elderly persons, it is one of the most frequent presenting symptoms of disease. In addition to being a common disorder, delirium is associated with adverse effects that can impact morbidity and mortality.

The syndrome of delirium has been known by many names over the years, including acute confusional state, postoperative psychosis, ICU psychosis, and acute brain failure. Most of these terms, however, are not associated with strict diagnostic criteria and thereby have clouded the diagnosis, management, and scientific research of delirium.

### Diagnostic Criteria

The *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* provides up-to-date diagnostic criteria for delirium (Table 1). These criteria allow for a common definition, improved classification, and more rigorous scientific study of this prevalent disorder.

The core symptoms of delirium are an impairment of level of consciousness and change in cognition that develops quickly and may fluctuate throughout the day. There must also be evidence that the disturbance in mental status is caused by a medical condition or a substance. The determined cause is then used to further classify the type of delirium that the patient is experiencing. This definition and classification allows the clinician to differentiate delirium from other medical and psychiatric disorders.

There are several clinical subtypes of delirium that are based on the disorder's motoric presentation. These subtypes of delirium are hypoactive, hyperactive, and mixed. The hypoactive subtype occurs in patients who appear apathetic, lethargic, and unaware. Given the quiet and withdrawn nature of their delirium, coupled with the lack of agitation, these patients' delirious states are often overlooked. Patients presenting with “failure to thrive,” for example, are often found to have hypoactive delirium on close examination in the emergency department (ED). In contrast, clinicians rarely have trouble identifying the behavioral components of the hyperactive subtype of delirium, which is associated with restlessness, hallucinations, delusions, combative, and wandering. Patients with the hyperactive subtype of delirium may present a danger to themselves or others if the agitation is severe. In the mixed subtype of delirium, the presentation may vary throughout the day, with alternating periods of hyperactivity and hypoactivity.

### Prevalence

Delirium is prevalent across clinical populations and settings. In elderly persons residing in the community, the prevalence of delirium has been reported to be approximately 1%. In patients presenting to the ED, the prevalence of delirium has been found to be between 10% and 24%. Medically hospitalized patients have a delirium prevalence of about 15%. However, prevalence may be higher in certain subsets of patients; for example, delirium may occur in more than 50% of elderly patients after hip fracture. Delirium is also prevalent in the subacute medical setting. One study estimated that 58% of patients in nursing homes have delirium, which represents a prevalence even higher than that in acute medical settings.

Despite the relatively high prevalence of delirium in clinical populations, its recognition by health care providers is often quite poor. Overall, delirium is not identified in 32% to 67% of elderly hospitalized patients. In addition, the hypoactive form of delirium is often mistaken for depression. Prospective studies have shown that up to 42% of patients referred for psychiatric consultation for evaluation of depression are subsequently given the diagnosis of delirium by a consulting psychiatrist.
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One study showed that in the ED, only 6 (17%) of 35 delirious patients were identified as having delirium (or equivalent diagnostic term) by the ED physician. Of the 35 delirious patients, 21 (60%) were admitted to the hospital, 13 (37%) were discharged from the ED, and 1 (3%) left the hospital against medical advice. In another prospective ED study, physicians only documented altered mental status in 28% of patients presenting with impaired mental status. Furthermore, specific mention of delirium, or an acceptable synonym, was noted in only about 17% of patients' charts. Cole identified 2 primary reasons for the failure of health care professionals to detect delirium. First, patients with delirium are expected to present with agitation and psychosis (the hyperactive form), whereas many patients with delirium present with the quietly confused form (the hypoactive form). Second, the waxing and waning mental status of delirium often confounds the diagnosis. Determining whether a patient has experienced an acute or subacute change in mental status is often difficult, especially in the ED setting, in which the patient is not known to the caregiver and there is often a profound lack of collateral history at presentation.

**CLINICAL SIGNIFICANCE**

Appropriate assessment and subsequent identification of delirium are important because delirium has multiple adverse effects on patient outcomes. Delirium can increase length of hospitalization, result in higher health care costs, and increase rates of nursing home placement. Delirium may also herald possible future cognitive decline. In addition, medical complications, such as decubitus ulcers, feeding issues, and urinary problems, have been reported to occur more frequently among patients with delirium compared with nondelirious controls.

Delirium also adversely affects patients' mortality rates. Inouye and colleagues found that delirium was associated with increased mortality in hospitalized elderly patients. This relationship remained even after controlling for patient age, sex, cognitive function, level of ability to perform activities of daily living, and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. In another study, delirium was associated with a mortality rate of 75% at 3 years, compared with a rate of 51% in elderly nondelirious controls, despite similar levels of medical comorbidity, physical functioning, and cognition between study groups. Identification of delirium during hospitalization, however, has been associated with improved clinical outcomes, such as decreased lengths of stay and lower mortality rates.

The importance of detecting delirium in the ED setting was described in a prospective cohort study that evaluated delirious and nondelirious patients who were discharged home instead of being admitted to the hospital. In this study, failure to detect delirium in the ED was associated with increased mortality at 6-month follow-up. This association remained even after adjustment for age, sex, comorbidity, cognitive status, functional level, and number of medications. Of importance, when delirium was identified, no difference in mortality was found between patients with delirium and those without.

Delirium can exert a psychological toll on the patient as well as the delirious patient's spouse and caregiver. Breitbart and colleagues prospectively interviewed cancer patients, their spouses, and their nurses after resolution of a delirium episode. Patients and nurses had high stress levels, but the spouses had the highest levels of distress associated with the delirium episode. Of the patients interviewed, 54% recalled their delirious state, with severity of delirium inversely related to level of recall.

**PATHOPHYSIOLOGY**

The exact cause of delirium is unknown, but the pathophysiology is likely multifactorial and complex. The development of delirium probably requires a susceptible person with predisposing traits or risk factors. This person then experiences some precipitating event that leads to the alteration of cerebral function and the development of delirium.

There are various theories about the pathophysiology of delirium, including abnormal cerebral metabolism and the dysfunction of specific neuronal pathways or brain regions. In addition, various neurotransmitters, mainly acetylcholine and dopamine, have been implicated in the development of delirious states. Evidence supports an underactivity of the cholinergic system or an overactivity of the dopaminergic systems (ie, low-acetylcholine or high-dopamine states) in the cause and clinical presentation of delirium. Infection or inflammation also may cause delirium through the action of cytokines, which may precipitate delirium by various mechanisms such as adversely affecting several neurotransmitters or directly inducing neurotoxic effects.

**DELIRIUM PRESENTATION**

The presentation of delirium is quite variable, with a wide variety of potential signs and symptoms that fluctuate in severity and character throughout a delirium episode. This inherent variability often leads to considerable diagnostic confusion and is likely a significant contributor to the poor identification of delirium in clinical settings. There are, however, some classic signs and symptoms associated with this neuropsychiatric disorder.
The onset of delirium is often acute and develops over a period of days. Once delirium is present, the severity often waxes and wanes, alternating between periods of relative clarity and periods of more severe confusion and impaired attention. Patients may experience a diurnal variation in symptomatology during the episode of delirium. A disrupted sleep-wake cycle is common in patients with delirium, with excess somnolence throughout the day and increased wakefulness and insomnia during the night. The term "sundowning" is often used to describe a pattern of increasing delirium symptomatology as the evening progresses.

Another hallmark of delirium is diffuse cognitive impairment. This cognitive deficit consists of an impairment in sensorium, or a clouding of consciousness, and is fundamentally a dysfunction of attention. Patients’ attentional deficits may range from a low level of arousal and somnolence to an easily distractible hyperactive state. Regardless of form, these altered mental states lead to a reduced ability to focus, sustain, or shift attention. These fundamental attentional impairments often negatively affect other areas of cognition, such as memory, orientation, and executive function. Patients in the midst of an episode of delirium may also experience myriad psychiatric symptoms. Certain aspects of a patient’s history and presentation may help the clinician differentiate a delirious state from affective or psychotic psychiatric disorders (Table 2). Disorganized or frankly illogical thought processes coupled with affective lability often occur during the course of delirium. Persons with delirium often have perceptual disturbances, such as illusions and hallucinations. Although these illusions and hallucinations may be auditory or visual, visual disturbances are more common during an episode of delirium and therefore should raise the suspicion of organicity whenever they occur. Delusions, often paranoid in nature, also can occur in patients with delirium, but the delusions are not as well formed and systematized as those seen in patients with schizophrenia. Neurological findings, such as language disturbances ranging from dysgraphia to aphasia, may occur in patients with delirium. Other nonspecific neurological findings, such as tremor, asterixis, and myoclonus, may also be observed in patients with delirium. In addition, primitive reflexes, such as the grasp, snout, or palmo-mental reflexes, may be found on careful neurological examination as frontal lobe inhibition of these reflexes fails.

**CAUSES OF DELIRIUM**

The potential causes of delirium are many. The presentation of delirium probably represents a cumulative insult to cortical function and a final common pathway in which various medical conditions affect cognition and attention. It is important for the clinician to attempt to identify whether delirium is secondary to a medical condition or the result of a medication side effect, substance intoxication, substance withdrawal, or multiple medical and toxic insults. Identification of the causes of delirium is imperative because management and reversal of these insults is the primary goal of delirium treatment. Unfortunately, delirium in elderly and critically ill persons is often complex and multifactorial, making this identification and treatment difficult. Delirium in most patients has multiple possible causes; fewer than 50% of delirium episodes are caused by a single insult. The recognition that the cause of delirium is usually multifactorial is important because the evaluation of delirium will often require thorough and repeated assessments of potential causative factors.

In the ED setting, whether medical or psychiatric, there are several emergent conditions that can cause delirium that need to be identified rapidly because failure to do so may lead to irreversible injury or death (Table 3). As a result of the potential morbidity and mortality associated with these conditions, medical evaluation directed toward identification of the likely emergent cause or causes needs to be completed. This assessment should begin as soon as delirium is suspected in the ED. The most common precipitants of a delirium episode are medications, infections, end-organ dysfunction (ie, cardiopulmonary, renal, or hepatic), electrolyte/metabolic derangement, and CNS disorders. Medications are commonly implicated in the development of delirium. A significant number of medications can cause a delirious state. However, certain medication classes are more notorious offenders than others. For example, narcotics, psychotropics, and medications with anticholinergic properties are common causative agents. Some medications that are not traditionally thought of as anticholinergic, such as digoxin and histamine receptor antagonists, possess anticholinergic activity and may contribute to the development of delirium. Infections as serious as sepsis or as varied as urinary tract infections, pneumonia, meningitis, and HIV infection may lead to delirium. Organ system dysfunction, such as pulmonary failure causing hypoxia, hepatic failure leading to hepatic encephalopathy, and renal failure resulting in uremia, may contribute to the occurrence of delirium as well. Other causes of delirium are endocrinopathies, such as hypoglycemia and thyroid perturbations, and metabolic derangements, such as hyponatremia or hypocalcemia. When metabolic derangements are involved, it is often the acuity of the change in electrolyte levels, rather than absolute levels,
that represents the greatest risk of development of delirium.\textsuperscript{1} Seizures, cerebrovascular accidents (ischemic or hemorrhage), traumatic brain injuries, subdural hematomas, brain tumors (primary or metastases), and vasculitic insults are all examples of CNS pathology that may lead to a patient presenting to the ED secondary to a delirious state.

The environment is rarely, if ever, the only precipitant to the development of delirium. Therefore, the descriptive terms once often used to describe delirium, such as ICU psychosis, are inappropriate. Such terms imply that the environment alone is responsible for the altered mental state. This flawed assumption may lead to the opinion that no further evaluation is required--a hazardous presumption because delirium is often the presenting syndrome for a wide variety of potentially dangerous medical conditions and therefore necessitates an appropriate medical evaluation.

**DIAGNOSTIC EVALUATIONS**

The first step in the evaluation of a patient experiencing an acute alteration in mental status is the recognition that delirium is present. Only after this pathology is recognized can appropriate evaluation and management commence. Therefore, delirium should always be suspected when a patient has an acute deterioration in behavior, function, or cognition.

Unfortunately, the assessment of delirious states is not evidence-based.\textsuperscript{13} The evaluation of delirium involves a careful and detailed search for potential causes and is fundamentally based on the patient's clinical presentation. The assessment requires a complete history directed toward establishing the course of the altered mental status. Once the time course of delirium is established, particular attention needs to be paid to events temporally related, and therefore potentially etiologically related, to the onset of delirium.

The cognitively impaired delirious patient may be unable to provide all the pertinent information required for a thorough history. Thus, a review of the available medical records in an attempt to establish a pertinent medical and psychiatric history of the patient along with the patient's cognitive and functional baseline is important. In the ED, the clinician should attempt to contact someone who may be able to provide this relevant information. Family, friends, police, and ambulance staff can provide invaluable collateral information about the presenting patient. Details of recent trauma or a history of similar presentations should be gathered. Because alcohol, illicit drugs, and medications (prescription and over-the-counter) are such common contributors to confusional states, a careful history to elicit recent use or changes in use of these substances needs to be taken.

A pertinent physical examination should be performed. Careful attention to vital signs for abnormalities that may explain the patient's delirious state, coupled with examination of the patient's nervous, cardiac, and pulmonary systems, is necessary. Assessment of the patient's mental status for behavioral signs consistent with delirium is also imperative. Evidence of inattention, confusion, impaired arousal, and illogical thought processes are often apparent during history taking and suggest the presence of delirium.

Testing a patient's cognitive status is also important because delirium is a disorder of impaired cognition. Simple bedside tests of cognition, such as the Folstein Mini-Mental State Examination, are helpful to document the presence of a cognitive disorder.\textsuperscript{36} This test, however, does not distinguish delirium from dementia. Tests such as digit span and naming the months of the year in reverse order may help document the attentional impairment present in delirium.

Various diagnostic and severity scales have been developed to assist clinicians in the diagnosis, assessment, and management of patients with delirium (Table 4). The Confusion Assessment Method\textsuperscript{37} (Table 5) has been tested in the ED setting and was found to be reliable, sensitive, specific, and easy to administer in this often hectic and clinically challenging environment.\textsuperscript{38} The laboratory evaluation of delirium should be based on the patient's presentation and thereby guided by clinical evidence toward potential causes of the confusional state (Table 6). Such evaluations should include a basic metabolic panel, a complete blood cell count, and a hepatic panel. A urinalysis with microscopic examination is a regular part of the examination, especially in the elderly. Tests of thyroid function and evaluation of vitamin B\textsubscript{12} and folate levels should also be performed, because thyroid dysfunction and deficiencies in vitamin B\textsubscript{12} and folate are associated with cognitive dysfunction. A serum or urine drug screen should be performed. Testing for syphilis and HIV infection may also be warranted.

Fever, leukocytosis, or an immunocompromised state may suggest an infectious cause and necessitate an appropriate evaluation, which can include blood cultures, chest radiograph, and a lumbar puncture. If there is a history of cardiac disease or suspicion of a cardiac event, an ECG and evaluation of cardiac enzyme levels should be performed. Evidence of a pulmonary process may require a chest radiograph and pulse oximetry or arterial blood gas test to complete the evaluation.

Measurement of serum levels of drugs that the patient may be taking, such as digoxin or...
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Antipsychotics. Hypoactive and hyperactive subtypes of delirium have been effectively managed with antipsychotic medications can help calm delirious patients and improve cognition. Toward the cornerstone of symptomatic delirium treatment and often help ameliorate the symptoms of delirium even before the underlying cause of delirium is identified and corrected (Table 7). Toward that end, antipsychotic medications can help calm delirious patients and improve cognition. Both hypoactive and hyperactive subtypes of delirium have been effectively managed with antipsychotics. Antipsychotics have been shown to be superior to benzodiazepines in delirium not caused by alcohol...
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Delirium: Acute Confusional States

or sedative-hypnotic withdrawal.\textsuperscript{51} Determination of the type and dose of antipsychotic medication to be used depends on multiple factors, including the patient's age, route of medication administration, degree of agitation, clinical setting, and risk of adverse effects.\textsuperscript{33} Regardless of which antipsychotic or dose is used, it is imperative to monitor patients closely for response and adverse effects. Once the delirium has cleared, a gradual tapering off of the antipsychotic medication should be initiated. **Typical antipsychotics.** Historically, the high-potency typical antipsychotic haloperidol is the medication most often chosen for the symptomatic management of delirium.\textsuperscript{53,54} It has the desirable characteristics of being virtually devoid of anticholinergic effects, hypotensive properties, cardiotoxicity, and respiratory suppression. In addition, haloperidol may be administered orally, intramuscularly, or intravenously, although the intravenous route is not approved by the FDA. Intravenous haloperidol is twice as potent as oral haloperidol.\textsuperscript{55} Despite this increased potency, intravenous haloperidol is associated with few of the extrapyramidal adverse effects that often complicate the use of oral or intramuscular haloperidol.\textsuperscript{56} Haloperidol's safety and effectiveness, even in very large doses, in seriously ill patients with delirium of varied causes is well represented in the literature.\textsuperscript{57-59}

The low-potency typical antipsychotics, such as chlorpromazine, are associated with hypotension and anticholinergic adverse effects, which make them suboptimal in the treatment of delirium. **Atypical antipsychotics.** The atypical antipsychotics have also been used to manage the psychiatric symptoms of delirium.\textsuperscript{60-64} The improved neurological tolerability of atypical antipsychotics led to their increased use across disciplines and diagnoses. A review of the literature by Schwartz and Masand\textsuperscript{65} suggests that the atypical antipsychotics are effective and well tolerated in the treatment of patients with delirium. However, this conclusion was recognized by the authors to be limited by the fact that the literature to date consists mostly of case reports, small case series, and a few open-label prospective trials.

**Adverse effects.** Extrapyramidal symptoms (EPS), such as dystonia, parkinsonism, and akathisia, are well-known adverse effects of antipsychotic medication. Antipsychotic-induced EPS may occur after both acute and long-term treatment. In addition, there is increasing recognition of the association between antipsychotic agents, prolongation of the QTc interval, and torsades de pointes.\textsuperscript{66} The American Psychiatric Association's guidelines for the management of delirium suggest that QTc prolongation of greater than 450 milliseconds or greater than 25% over baseline warrants close monitoring and potential medication change.\textsuperscript{67} Correcting concurrent electrolyte abnormalities and limiting the use of other medications that may prolong the QTc interval is also an important means of reducing the risk of potentially dangerous arrhythmias.

The FDA has recently placed a black box warning about the use of atypical antipsychotic drugs in elderly patients with dementia-related psychosis.\textsuperscript{68} The risk of briefly using an atypical antipsychotic in a delirious patient with a history of dementia is unclear and has not yet been studied to our knowledge. Because of the risk of increased mortality in this population, which led to the black box warning, prescribers should be vigilant in monitoring that the antipsychotic is tapered off as symptoms of delirium remit. In this way, the elderly patient with dementia is not unnecessarily exposed to a potentially hazardous medication longer than clinically necessary and appropriate. **Benzodiazepines.** Management of alcohol-withdrawal and sedative-hypnotic-withdrawal delirium states requires the use of benzodiazepines.\textsuperscript{69} Delirium associated with seizure activity is also appropriately managed with benzodiazepines. In addition, benzodiazepines may augment the effects of high-potency typical antipsychotics in patients with severe refractory delirium, thereby reducing the total dose of antipsychotic required and improving tolerability.\textsuperscript{70} Lorazepam has several advantages over other benzodiazepines in the ED setting in that it has a rapid onset of action, a short duration of action, and a lack of active metabolites. **CONCLUSION**

Delirium is an acute and fluctuating disturbance in consciousness, with resulting impairments in attention and cognition. It is a common yet often undiagnosed neuropsychiatric condition associated with significant negative effects on morbidity and mortality. Because delirium may be caused by potentially life-threatening medical conditions, prompt identification and treatment is imperative. The ED represents an excellent place to detect this dangerous disorder, initiate a workup, and begin clinical management. *

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