10 Delirious Patients

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Delirium has likely replaced syphilis as "the great imitator" because its varied presentations have led to misdiagnoses among almost every major category of mental illness. Delirium is a syndrome caused by an underlying physiologic disturbance and marked by a fluctuating course, with impairments in consciousness, attention, and perception. Delirium thus is often mistaken for depression when the patient has a withdrawn or flat affect, for mania when the patient has agitation and confusion, for psychosis when the patient has hallucinations and paranoia, for anxiety when the patient has restlessness and hypervigilance, for dementia when the patient has cognitive impairments, and for substance abuse when the patient has impairment in consciousness. With so diverse an array of symptoms, delirium assumes a position of diagnostic privilege in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV),[1] in that almost no other diagnosis can be made in its presence.

Perhaps even more noteworthy, delirium is a signifier of often serious somatic illness.[2] Delirium has been associated with increased length of stay in hospitals[3] and with an increased cost of care.[4,5] Among intensive care unit (ICU) patients, prospective studies have noted that delirium occurs in 31% of admissions[6]; when intubation and mechanical ventilation are required, the incidence soars to 81.7%.[7]

Sometimes, delirium is refered to as an acute confusional state, a toxic-metabolic encephalopathy, or acute brain failure; unquestionably, it is the most common cause of agitation in the general hospital. Delirium ranks second only to depression on the list of all psychiatric consultation requests. Given its prevalence and its importance (morbidity and mortality), the American Psychiatric Association issued practice guidelines for the treatment of delirium in 1999.[8]

Placed in this context, the consequences of misdiagnosis of delirium can be severe; prompt and accurate recognition of this syndrome is paramount for all clinicians.

DIAGNOSIS

The essential feature of delirium, according to the DSM-IV, is a disturbance of consciousness that is accompanied by cognitive deficits that cannot be accounted for by past or evolving dementia (Table 10–1).[1] Disturbance of the sleep–wake cycle is also common, sometimes with nocturnal worsening (sundowning) or even by a complete reversal of the night–day cycle, though, despite previous postulation, sleep disturbance alone does not cause delirium.[9] Similarly, the term *ICU psychosis* has entered the medical lexicon; this is an unfortunate misnomer because it is predicated on the belief that the environment of the ICU is capable of inducing delirium and that the symptomatology of delirium is limited to psychosis.[9] Despite wide variation in the presentation of the delirious patient, the hallmarks of delirium, although perhaps less immediately apparent, remain quite consistent from case to case.

Both Chedru and Geschwind[10] and Mesulam and coworkers[11] regard impaired attention as the main deficit of delirium. This inattention (along with an acute onset, waxing and waning course, and overall disturbance of consciousness) forms the core features of delirium, whereas other related symptoms, such as withdrawn affect, agitation, hallucinations, and paranoia, serve as a frame that can sometimes be so prominent as to detract from the picture itself.

Psychotic symptoms (such as visual or auditory hallucinations and delusions) are common among patients with delirium.[12] Sometimes the psychiatric symptoms are so bizarre or so offensive (e.g., an enraged and paranoid patient shouts that pornographic movies are being made in the ICU) that diagnostic efforts are distracted. The hypoglycemia of a man with diabetes can be missed in the emergency department (ED) if the accompanying behavior is threatening, uncooperative, and resembling that of an intoxicated person.

Although agitation can distract practitioners from making an accurate diagnosis of delirium, disruptive behavior alone will almost certainly garner some attention. The hypoactive presentation of delirium is more insidious, because the patient is often thought to be depressed or anxious because of the medical illness. Studies of quietly delirious patients show the experience to be as disturbing as the agitated variant[13]; quiet delirium is still a harbinger of serious medical pathology.[14,15]

The core similarities found in cases of delirium have led to postulation of a final common neurologic pathway for its symptoms. Current understanding of the neurophysiologic basis of delirium is one of hyperdopaminergia and hypocholinergia.[16] The ascending reticular activating system (RAS) and its bilateral thalamic projections regulate alertness, with neocortical and limbic inputs to this system

TABLE 10–1 DSM-IV Diagnostic Criteria for Delirium

A disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention
A change in cognition (e.g., memory deficit, disorientation, or a language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia
A disturbance that develops over a short period (usually hours to days) and tends to fluctuate during the course of the day
Evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiologic consequences of a general medical condition

DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition.

controlling attention. Because acetylcholine is the primary neurotransmitter of the RAS, medications with anticholinergic activity can interfere with its function, resulting in the deficits in alertness and attention that are the heralds of delirium. Similarly, it is thought that loss of cholinergic neuronal activity in the elderly (e.g., resulting from microvascular disease or atrophy) is the basis for their heightened risk of delirium. Release of endogenous dopamine due to oxidative stress is thought to be responsible for the perceptual disturbances and paranoia that so often lead to mislabeling the delirious patient "psychotic." As we discuss later, cholinergic agents (e.g., physostigmine) and dopamine blockers (e.g., haloperidol) have proved efficacious in managing delirium.

Early detection of changes in cognition can be key to timely identification and treatment of delirium (and perhaps of a heretofore undiagnosed somatic illness responsible for the delirium). Unfortunately, several studies have revealed that physicians who are not psychiatrists are quite unreliable in their ability to accurately identify delirium in their patients, and most patients referred to psychiatric consultation services with purported depression are ultimately found to have delirium. Because consultation psychiatrists cannot perform repeated examinations on all patients admitted to the general hospital (even on those at high risk for delirium), a number of screening protocols designed to be serially administered by nursing staff have been developed and validated for use. Some of the most commonly used of these scales are summarized in Table 10–2.[17–23]

DIFFERENTIAL DIAGNOSIS

As useful as screening protocols may be, treatment relies on a careful diagnostic evaluation; there is no substitute for a systematic search for the specific cause of delirium. The temporal relationship to clinical events often gives the best clues to potential causes. For example, a patient who extubated himself was almost certainly in trouble before self-extubation. When did his mental state actually change? Nursing notes should be studied to help discern the first indication of an abnormality (e.g., restlessness, mild confusion, or anxiety). If a time of onset can be established as a marker, other events can be examined for a possible causal relationship to the change in mental state. Initiation or discontinuation of a drug, the onset of fever or hypotension, or the acute worsening of renal function, if in proximity to the time of mental status changes, become likely culprits.

TABLE 10–2 Delirium Assessment Tools

TOOL	STRUCTURE	NOTES
Confusion Assessment Method (CAM)[17]	Full scale of 11 items Abbreviated algorithm targeting four cardinal symptoms	Intended for use by nonpsychiatric clinicians
Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[18]	Algorithm targeting four cardinal symptoms	Designed for use by nursing staff in the ICU
Intensive Care Delirium Screening Checklist (ICDSC)[19]	Eight-item screening checklist	Bedside screening tool for use by nonpsychiatric physicians or nurses in the ICU
Delirium Rating Scale (DRS)[20]	Full scale of 10 items Abbreviated seven- or eight-item subscales for repeated administration	Provides data for confirmation of diagnosis and measurement of severity
Delirium Rating Scale—Revised–98 (DRS-R-98)[21]	Sixteen-item scale that can be divided into a three-item diagnostic subscale and a thirteen-item severity subscale	Revision of DRS is better suited to repeat administration
Memorial Delirium Assessment Scale (MDAS)[22]	Ten-item severity rating scale	Grades severity of delirium once diagnosis has been made
Neecham Confusion Scale[23]	Ten-item rating scale	Designed for use by nursing staff Primarily validated for use in elderly populations in acute medical or nursing home setting

ICU, Intensive care unit.

Without a convincing temporal connection, the cause of delirium may be discovered by its likelihood in the unique clinical situation of the patient. In critical care settings, as in EDs, there are several (life-threatening) states that the clinician can consider routinely. These are states in which intervention needs to be especially prompt because failure to make the diagnosis may result in permanent central nervous system (CNS) damage. These conditions are Wernicke's disease, hypoxia, hypoglycemia, hypertensive encephalopathy, hyper- or hypothermia, intracerebral hemorrhage, meningitis or encephalitis, poisoning (exogenous or iatrogenic), and status epilepticus. These conditions are usefully recalled by the mnemonic device "WHHHHHIMPS" (Table 10–3). Other less urgent but still acute conditions that require intervention include subdural hematoma, septicemia, subacute bacterial endocarditis, hepatic or renal failure, thyrotoxicosis or myxedema, delirium tremens, anticholinergic psychosis, and complex partial seizures. If these conditions are not already ruled out, they are easy to verify. A broad review of conditions commonly associated with delirium is provided by the mnemonic "I WATCH DEATH" (Table 10–4).

Bacteremia commonly clouds a patient's mental state. In prospectively studied seriously ill hospitalized patients, delirium was commonly correlated with bacteremia.[24] In that study, the mortality of septic patients with delirium was higher than that in septic patients with a normal mental status. In the elderly, regardless of the setting, the onset of confusion should trigger concern about infection. Urinary tract infections (UTIs) and pneumonias are among the most common infections in older patients, and when bacteremia is associated with a UTI, confusion is the presenting feature nearly one third (30%) of the time.[25] Once a consultant has eliminated these common conditions as possible causes of a patient's disturbed brain function, there is time enough for a more systematic approach to the differential diagnosis. A comprehensive differential diagnosis, similar to the one compiled by Ludwig[26] (slightly expanded in Table 10–5) is recommended. A quick review of this list is warranted even when the consultant is relatively sure of the diagnosis.

To understand the acute reaction of the individual patient, one should begin by completely reviewing the medical record. Vital signs can reveal periods of hypotension or fever. The highest temperature recorded will also be key. Operative procedures and the use of anesthetics can also induce a sustained period of hypotension or reveal unusually large blood loss that requires replacement. Laboratory values should be scanned for abnormalities that could be related to an encephalopathic state.

TABLE 10–3 Life-Threatening Causes of Delirium: WHHHHIMPS

Wernicke's disease
Hypoxia
Hypoglycemia
Hypertensive encephalopathy
Hyperthermia or hypothermia
Intracerebral hemorrhage
Meningitis or encephalitis
Poisoning (exogenous or iatrogenic)
Status epilepticus

TABLE 10–4 Conditions Commonly Associated with Delirium: "I WATCH DEATH."

CATEGORY	CONDITIONS
Infectious	Encephalitis, meningitis, syphilis, pneumonia, urinary tract infection
Withdrawal	From alcohol or sedative–hypnotics
Acute metabolic	Acidosis, alkalosis, electrolyte disturbances, liver or kidney failure
Trauma	Heat stroke, burns, following surgery
CNS pathology	Abscesses, hemorrhage, seizure, stroke, tumor, vasculitis, or normal-pressure hydrocephalus
Hypoxia	Anemia, carbon monoxide poisoning, hypotension, pulmonary embolus, lung or heart failure
Deficiencies	Of vitamin B_{12}, niacin, or thiamine
Endocrinopathies	Hyper- or hypoglycemia, hyper- or hypoadrenocorticism, hyper- or hypothyroidism, hyper- or hypoparathyroidism
Acute vascular	Hypertensive encephalopathy or shock
Toxins or drugs	Medications, pesticides, or solvents
Heavy metals	Lead, manganese, or mercury

The old chart, no matter how thick, cannot be overlooked without risk. Some patients have had psychiatric consultations for similar difficulties on prior admissions. Others, in the absence of psychiatric consultations, have caused considerable trouble for their caregivers. Similar to a patient's psychiatric history, the family psychiatric history can help make a diagnosis, especially if a major mood or anxiety disorder, alcoholism, schizophrenia, or epilepsy is present.

Examination of current and past medications is essential because pharmacologic agents (in therapeutic doses, in overdose, or with withdrawal) can produce psychiatric symptoms. These medications must be routinely reviewed, especially in patients whose drugs have been stopped because of surgery or hospitalization or whose drug orders have not been transmitted during transfer between services. Of all causes of an altered mental status, use of and withdrawal from drugs are probably the most common. Some, such as lidocaine, are quite predictable in their ability to cause encephalopathy; the frequency and severity of symptoms are dose-related. Other agents, such as antibiotics, usually cause delirium only in someone whose brain is already vulnerable, as in a patient with a low seizure threshold.[27] Table 10–6 lists some drugs used in clinical practice that have been associated with delirium.

The number of drugs that can be involved either directly or indirectly (e.g., because of drug interactions) is numerous. Fortunately, certain sources provide regular review of published summaries and drug updates.[28] Although physicians are usually aware of these hazards,

TABLE 10–5 Differential Diagnosis of Delirium

GENERAL CAUSE	SPECIFIC CAUSE
Vascular	Hypertensive encephalopathy Cerebral arteriosclerosis Intracranial hemorrhage or thrombosis Emboli from atrial fibrillation, patent foramen ovale, or endocarditic valve Circulatory collapse (shock) Systemic lupus erythematosus Polyarteritis nodosa Thrombotic thrombocytopenic purpura Hyperviscosity syndrome Sarcoid
Infectious	Encephalitis Bacterial or viral meningitis, fungal meningitis (*cryptococcal, coccidioidal, Histoplasma*) Sepsis General paresis Brain, epidural, or subdural abscess Malaria Human immunodeficiency virus Lyme disease Typhoid fever Parasitic (*toxoplasma, trichinosis, cysticercosis, echinococcosis*) Behçet's syndrome Mumps
Neoplastic	Space-occupying lesions, such as gliomas, meningiomas, abscesses Paraneoplastic syndromes Carcinomatous meningitis
Degenerative	Senile and presenile dementias, such as Alzheimer's or Pick's dementia Huntington's chorea Creutzfeldt-Jakob disease Wilson's disease
Intoxication	Chronic intoxication or withdrawal effect of sedative–hypnotic drugs, such as bromides, opiates, tranquilizers, anticholinergics, dissociative anesthetics, anticonvulsants, carbon monoxide from burn inhalation
Congenital	Epilepsy Postictal states Complex partial status epilepticus Aneurysm
Traumatic	Subdural and epidural hematomas Contusion Laceration Postoperative trauma Heat stroke Fat emboli syndrome
Intraventricular	Normal pressure hydrocephalus
Vitamin deficiency	Thiamine (Wernicke–Korsakoff syndrome) Niacin (pellagra) B_{12} (pernicious anemia)
Endocrine-metabolic	Diabetic coma and shock Uremia Myxedema Hyperthyroidism, Parathyroid dysfunction Hypoglycemia Hepatic or renal failure Porphyria Severe electrolyte or acid and base disturbances Paraneoplastic syndrome Cushing's or Addison's syndrome Sleep apnea Carcinoid Whipple's disease
Metals	Heavy metals (lead, manganese, mercury) Other toxins
Anoxia	Hypoxia and anoxia secondary to pulmonary or cardiac failure, anesthesia, anemia
Depression—other	Depressive pseudodementia, hysteria, catatonia

Modified from Ludwig AM: *Principles of clinical psychiatry*, New York, 1980, The Free Press.

a common drug, such as meperidine, when used in doses greater than 300 mg/day for several days, causes CNS symptoms because of the accumulation of its excitatory metabolite, normeperidine, which has a half-life of 30 hours and causes myoclonus (the best clue of normeperidine toxicity), anxiety, and ultimately seizures.[29] The usual treatment is to stop the offending drug or to reduce the dosage; however, at times this is not possible. Elderly patients and those with mental retardation or a history of significant head injury are more susceptible to the toxic actions of many of these drugs.

Psychiatric symptoms in medical illness can have other causes. Besides the abnormalities that can arise from the effect of the patient's medical illness (or its treatment) on the CNS (e.g., the abnormalities produced by systemic lupus erythematosus or high-dose steroids), the disturbance may be the effect of the medical illness on the patient's mind (the subjective CNS), as in the patient who thinks he or she is "washed up" after a myocardial infarction, quits, and withdraws into hopelessness. The disturbance can also arise from the mind, as a conversion symptom or as malingering about pain to get more narcotics. Finally, the abnormality may be the result of interactions between the sick patient and his or her environment or family (e.g., the patient who is without complaints until the family arrives, at which time the patient promptly looks acutely distressed and begins to whimper continuously). Nurses are commonly aware of these sorts of abnormalities, although the abnormalities might go undocumented in the medical record.

TABLE 10–6 Drugs used in Clinical Practice that Have Been Associated with Delirium

Antiarrhythmics
Disopyramide
Lidocaine
Mexiletine
Procainamide
Propafenone
Quinidine
Tocainide

Antibiotics
Aminoglycosides
Amodiaquine
Amphotericin
Cephalosporins
Chloramphenicol
Gentamicin
Isoniazid
Metronidazole
Rifampin
Sulfonamides
Tetracyclines
Ticarcillin
Vancomycin

Anticholinergics
Atropine
Benztropine
Diphenhydramine
Eye and nose drops
Scopolamine
Thioridazine
Trihexyphenidyl

Tricyclic Antidepressants
Amitriptyline
Clomipramine
Desipramine
Imipramine
Nortriptyline
Protriptyline
Trimipramine

Anticonvulsants
Phenytoin

Antihypertensives
Captopril
Clonidine
Methyldopa
Reserpine

Antiviral Agents
Acyclovir
Interferon
Ganciclovir
Nevirapine

Barbiturates

β-blockers
Propranolol
Timolol

Cimetidine, ranitidine

Digitalis preparations

Disulfiram

Diuretics
Acetazolamide

Dopamine agonists (central)
Amantadine
Bromocriptine
Levodopa
Selegiline

Ergotamine

GABA agonists
Baclofen
Benzodiazepines
Zaleplon
Zolpidem

Immunosuppressives
Aminoglutethimide
Azacytidine
Chlorambucil
Cytosine arabinoside (high dose)
Dacarbazine
FK-506
5-Fluorouracil
Hexamethylmelamine
Ifosfamide
Interleukin-2 (high dose)
L-Asparaginase
Methotrexate (high dose)
Procarbazine
Tamoxifen
Vinblastine
Vincristine

Monoamine oxidase inhibitors
Tranylcypromine
Phenelzine
Procarbazine

Narcotic analgesics
Meperidine (normeperidine)
Pentazocine
Podophyllin (topical)

Nonsteroidal antiinflammatory drugs
Ibuprofen
Indomethacin
Naproxen
Sulindac

Other medications
Clozaril
Cyclobenzaprine
Lithium
Ketamine
Sildenafil
Trazodone
Mefloquine

Sympathomimetics
Aminophylline
Amphetamine
Cocaine
Ephedrine
Phenylephrine
Phenylpropanolamine
Theophylline

Steroids, ACTH

Adapted from Cassem NH, Lake CR, Boyer WF: Psychopharmacology in the ICU. In Chernow B, editor: *The pharmacologic approach to the critically ill patient*, Baltimore, 1995, Williams & Wilkins, pp 651–665; and Drugs that may cause psychiatric symptoms, *Med Letter Drugs Ther* 44:59–62, 2002.
ACTH, Adrenocorticotropic hormone; *GABA*, gamma aminobutyric acid.

THE EXAMINATION OF THE PATIENT

Appearance, level of consciousness, thought, speech, orientation, memory, mood, judgment, and behavior should all be assessed. In the formal mental status examination (MSE), one begins with the examination of consciousness. If the patient does not speak, a handy common-sense test is to ask oneself, "Do the eyes look back at me?" One could formally rate consciousness by using the Glasgow Coma Scale (Table 10–7), a measure that is readily understood by consultees in other specialties.[30]

If the patient can cooperate with an examination, attention should be examined first because if this is disturbed, other parts of the examination may be invalid. One can ask the patient to repeat the letters of the alphabet that rhyme with "tree." (If the patient is intubated, ask that a hand or finger be raised whenever the letter of the recited alphabet rhymes with "tree.") Then the rest of the MSE can be performed. The Folstein Mini-Mental State Examination (MMSE),[31] which is presented in Table 4–8, is usually included. Specific defects are more important than is the total score. Other functions (such as writing, which Chedru and Geschwind[10] considered to be one of the most sensitive indicators of impairment of consciousness) are often abnormal in delirium. Perhaps the most dramatic (though difficult to score objectively) test of cognition is the clock drawing test, which can provide a broad survey of the patient's cognitive state (Figure 10–1).[32] A more-recently developed and validated bedside test, the Montreal Cognitive Assessment (MoCA),[33] usefully incorporates some aspects of the MMSE (i.e., tests of memory, attention, and orientation) with tests of more complex visuospatial and executive function (including clock drawing and an adaptation of the trail making B task). Although not specifically validated for detecting delirium, the MoCA (available at www.mocatest.org) has been consistently shown to have greater sensitivity than the MMSE for mild cognitive impairment in a variety of conditions and typically requires less than 10 minutes to administer.

The patient's problem can involve serious neurologic syndromes as well; however, the clinical presentation of the patient should direct the examination. In general, the less responsive and more impaired the patient is, the more one should look for *hard signs*. A directed search for an abnormality of the eyes and pupils, nuchal rigidity, hyperreflexia (withdrawal), hung-up reflexes (myxedema), one-sided weakness or asymmetry, gait (normal pressure hydrocephalus), Babinski's reflexes, tetany, absent vibratory and position senses, hyperventilation (acidosis, hypoxia, or pontine disease), or other specific clues can help verify or reject hypotheses about causality that are stimulated by the abnormalities in the examination.

TABLE 10–7 Glasgow Coma Scale

CRITERION	SCORE
Eye opening (E)	
Spontaneous	4
To verbal command	3
To pain	2
No response	1
Motor (M)	
Obeys verbal command	6
Localizes pain	5
Flexion withdrawal	4
Abnormal flexion (decortication)	3
Extension (decerebration)	2
No response	1
Verbal (V)	
Oriented and converses	5
Disoriented and converses	4
Inappropriate words	3
Incomprehensible sound	2
No response	1
Coma Score = (E + M + V)	**Range 3 to 15**

From Bastos PG, Sun X, Wagner DP et al: Glasgow Coma Scale score in the evaluation of outcome in the intensive care unit: findings from the Acute Physiology and Chronic Health Evaluation III study, *Crit Care Med* 21:1459–1465, 1993.

Frontal lobe function deserves specific attention. Grasp, snout, palmomental, suck, and glabellar responses are helpful when present. Hand movements thought to be related to the premotor area (Brodmann's area 8) can identify subtle deficiencies. The patient is asked to imitate, with each hand separately, specific movements. The hand is held upright, a circle formed by thumb and first finger ("okay" sign), then the fist is closed and lowered to the surface on which the elbow rests. In the Luria sequence, one hand is brought down on a surface (a table or one's own leg) in three successive positions: extended with all five digits parallel ("cut"), then as a fist, and then flat on the surface ("slap"). Finally, both hands are placed on a flat surface in front of the patient, one flat on the surface, the other resting as a fist. Then the positions are alternated between right and left hands, and the patient is instructed to do likewise.

For verbally responsive patients, their response to the "Frank Jones story" can be gauged (I have a friend, Frank Jones, whose feet are so big he has to put his pants on over his head. How does that strike you?). Three general responses are given. Type 1 is normal: The patient sees the incongruity and smiles (a limbic response) and can explain (a neocortical function) why it cannot be done. Type 2 is abnormal: The patient smiles at the incongruity (a limbic connection), but cannot explain why it cannot be done. Type 3 is abnormal: The patient neither gets the incongruity nor can explain its impossibility.

Laboratory studies should be carefully reviewed, with special attention paid to indicators of infection or metabolic disturbance. Toxicology screens are also usually helpful in allowing the inclusion or exclusion of substance intoxication or withdrawal from the differential diagnosis. Neuroimaging can prove useful in detecting intracranial processes that can result in altered mental status. Of all the diagnostic studies available, the electroencephalogram (EEG) may be the most useful tool in the diagnosis of delirium. Engel and Romano[34] reported in 1959 their (now classic) findings on the EEG in delirium, namely, generalized slowing to the theta-delta range in the delirious patient, the consistency of this finding despite wide-ranging underlying conditions, and resolution of this slowing with effective treatment of the delirium. EEG findings might even clarify the etiology of a delirium, because delirium tremens is associated with low-voltage fast activity superimposed on slow waves, sedative–hypnotic toxicity produces fast beta activity (>12 Hz), and hepatic encephalopathy is classically associated with triphasic waves.[35]

SPECIFIC MANAGEMENT STRATEGIES FOR DELIRIUM

Thoughts about (and treatment of) delirium have changed dramatically in the past several decades. In the 1970s, atropine was routinely administered to newly admitted

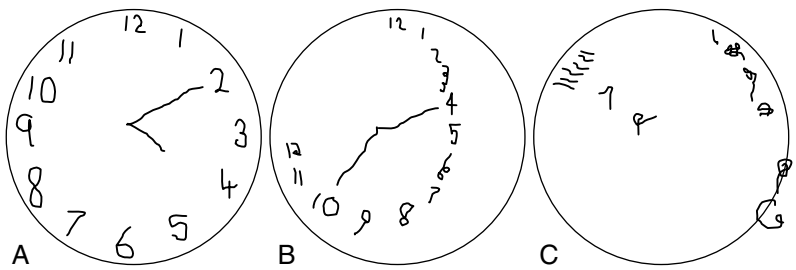

Figure 10–1. The clock drawing test. The patient is provided with a circular outline and asked to draw the numbers as they appear on the face of a clock. Once the numbering is complete, the patient is asked to set the hands to a particular time (often "ten past" the hour to test if the patient can suppress the impulse to include the number ten). **A,** This drawing demonstrates good planning and use of space. **B,** This drawing features some impulsiveness because the numbers are drawn out without regard for actual location, and the time "ten past four" is represented by hands pointing to the digits ten and four. Note the perseveration indicated by the extra loops on the digits *3* and *6*. Impulsiveness and perseveration indicate frontal lobe dysfunction. **C,** This drawing demonstrates gross disorganization, although the patient took several minutes to draw the clock and believed it to be a good representation.

coronary care unit (CCU) patients with bradycardia. Some patients, particularly older ones with preexisting organic brain disease, developed delirium. For such patients, parenteral propantheline bromide (Pro-Banthine), a quaternary ammonium compound that does not cross the blood–brain barrier and is equally effective in treating bradycardia, was substituted. This approach may still be taken, but problems are seldom so simple. Often the drugs that cause delirium (such as lidocaine or prednisone), cannot be changed without causing harm to the patient. Alternatively, pain can cause agitation in a delirious patient. Morphine sulfate can relieve pain but can unfortunately lead to decreases in blood pressure and respiratory rate.

Psychosocial or environmental measures are rarely effective in the treatment of a *bona fide* delirium of uncertain or unknown cause. Nevertheless, it is commendable to have hospital rooms with windows, calendars, clocks, and a few mementos from home on the walls[36]; soft and low lighting at night helps sundowners; and, most of all, a loving family in attendance reassures and reorients the patient. The psychiatric consultant is often summoned because psychosocial measures have failed to prevent or to treat the patient's delirium. Restraints (e.g., Posey vests; geriatric chairs; helmets; locked leather restraints for application to one or more extremities, chest, and even head) are also available and quite useful to protect patients from inflicting harm on themselves or staff. One or several of these is often in place when the consultant arrives. One hoped-for outcome of the consultation is that the use of these devices can be reduced or eliminated. The unfortunate misnomer *chemical restraint* is often applied to the most helpful class of drugs for delirium, neuroleptics. However, physicians do not use chemical restraints (i.e., tear gas, pepper spray, mace, or nerve gas) in the treatment of agitated patients.

When the cause of the delirium seems straightforward, the treatment revolves around resolution or reversal of the underlying cause. A discovered deficiency can be replaced (e.g., of blood, oxygen, thiamine, vitamin B_{12}, levothyroxine, or glucose). Pathologic conditions can be treated (e.g., volume replacement for hypotension, diuretics for pulmonary edema, antibiotics for infection, calcium for hypocalcemia, or dialysis for acute lithium toxicity). Implicated drugs, such as meperidine and cimetidine, can be stopped or reduced.

Specific antidotes can reverse the delirium caused by some drugs. Flumazenil and naloxone reverse the effects of benzodiazepines and opioid analgesics, respectively. However, caution is required because flumazenil can precipitate seizures in a benzodiazepine-dependent patient, and naloxone can also precipitate narcotic withdrawal in a narcotic-dependent patient.

Anticholinergic delirium can be reversed by intravenous (IV) physostigmine in doses starting at 0.5 to 2 mg. Caution is essential with use of this agent because the autonomic nervous system of the medically ill is generally less stable than it is in a healthy patient who has developed an anticholinergic delirium as a result of a voluntary or accidental overdose. Moreover, if there is a reasonably high amount of an anticholinergic drug on board that is clearing from the system slowly, the therapeutic effect of physostigmine, although sometimes quite dramatic, is usually short lived. The cholinergic reaction to intravenously administered physostigmine can cause profound bradycardia and hypotension, thereby multiplying the complications.[37,38] A continuous IV infusion of physostigmine has been successfully used to manage a case of anticholinergic poisoning.[39] Because of the diagnostic value of physostigmine, one might wish to use it even though its effects will be short-lived. If one uses an IV injection of 1 mg of physostigmine, protection against excessive cholinergic reaction can be provided by preceding this injection with an IV injection of 0.2 mg of glycopyrrolate. This anticholinergic agent does not cross the blood–brain barrier and should protect the patient from the peripheral cholinergic actions of physostigmine.

DRUG MANAGEMENT

Definitive treatment of delirium requires identification of the underlying somatic etiology, but all too often the cause of delirium is not readily identified or treated. These situations call for management of the symptoms of delirium until a more specific and effective treatment can be initiated. Opioids, benzodiazepines, neuroleptics, barbiturates, neuromuscular-blocking agents, inhalant anesthetics, and assorted other agents (such as propofol, ketamine, isoflurane, chloral hydrate, and clonidine), are available (alone or in creative combinations).

Benzodiazepines (e.g., diazepam 2.5 mg IV or midazolam 0.5 to 1 mg) are often effective in mild agitation in the setting of withdrawal from drugs that work at the alcohol, benzodiazepine, and barbiturate receptor. Morphine is also often used because it calms agitation and is easily reversed if hypotension or respiratory depression ensues. Especially in higher doses, these agents can cause or exacerbate confusion in older patients. This occurs much less often with neuroleptics, unless thioridazine (which has potent anticholinergic properties) is used.

Neuroleptics are the agent of choice for delirium. Haloperidol is probably the antipsychotic most commonly used to treat agitated delirium in the critical care setting; its effects on blood pressure, pulmonary artery pressure, heart rate, and respiration are milder than those of the benzodiazepines, making it an excellent agent for delirious patients with impaired cardiorespiratory status.[40]

Although haloperidol can be administered orally or parenterally, acute delirium with extreme agitation typically requires use of parenteral medication. IV administration is preferable to intramuscular (IM) administration because drug absorption may be poor in distal muscles if delirium is associated with circulatory compromise or with borderline shock. The deltoid is probably a better IM injection site than the gluteus muscle, but neither is as reliable as the IV route. Second, because the agitated patient is commonly paranoid, repeated painful IM injections can increase the patient's sense of being attacked by enemies. Third, IM injections can complicate interpretations of muscle enzyme studies if enzyme fractionation is not readily available. Fourth, and most important, haloperidol is less likely to produce extrapyramidal side effects (EPS) when given IV than when given IM or by mouth (PO), at least for patients without a prior serious psychiatric disorder.[41]

In contrast to the immediately observable sedation produced by IV benzodiazepines, IV haloperidol has a mean

distribution time of 11 minutes in normal volunteers[42]; this may be even longer in critically ill patients. The mean half-life of IV haloperidol's subsequent, slower phase is 14 hours. This is still a more rapid metabolic rate than the overall mean half-lives of 21 and 24 hours for IM and PO doses. The PO dose has about half the potency of the parenteral dose, so 10 mg of PO haloperidol corresponds to 5 mg given IV or IM.

Haloperidol has not been approved by the Food and Drug Administration (FDA) for IV administration. However, any approved drug can be used for a nonapproved indication or route if justified as "innovative therapy." For critical care units desirous of using IV haloperidol, one approach is to present this to the hospital's institutional review board (IRB) or human studies committee with a request to use the drug with careful monitoring of results based on the fact that it is the drug of choice for the patient's welfare, it is the safest drug available for this purpose, and it is justifiable as innovative therapy. After a period of monitoring, the committee can choose to make the use of the drug routine in that particular hospital.

Over decades of clinical use, IV haloperidol has been associated with few side effects on blood pressure, heart rate, respiratory rate, or urinary output and has been linked with few EPS. The reason for the latter is not known. Studies of the use of IV haloperidol in psychiatric patients have not shown that these side effects were fewer. They rarely appear after IV administration in medically ill patients probably because many of the medically ill patients have other medications in their system, especially benzodiazepines (which protect against EPS), or because patients with psychiatric disorders are more susceptible to EPS.[41]

Before administering IV haloperidol, the IV line should be flushed with 2 mL of normal saline. Phenytoin precipitates with haloperidol, and mixing the two in the same line must be avoided. Occasionally, haloperidol also precipitates with heparin, and because many lines in critical care units are heparinized, the 2-mL flush is advised. The initial bolus dose of haloperidol usually varies from 0.5 to 20 mg; usually 0.5 mg (for an elderly person) to 2 mg is used for mild agitation, 5 mg is used for moderate agitation, and 10 mg for severe agitation. A higher initial dose should be used only when the patient has already been unsuccessfully treated with reasonable doses of haloperidol. To adjust for haloperidol's lag time, doses are usually staggered by at least a 30-minute interval. If one dose (e.g., a 5-mg dose) fails to calm an agitated patient after 30 minutes, the next higher dose, 10 mg, should be administered. Calm is the desired outcome. Partial control of agitation is usually inadequate, and settling for this only prolongs the delirium or guarantees that excessively high doses of haloperidol will be used after the delirium is controlled.

Haloperidol can be combined every 30 minutes with simultaneous parenteral lorazepam doses (starting with 1 to 2 mg). Because the effects of lorazepam are noticeable within 5 to 10 minutes, each dose can precede the haloperidol dose, be observed for its impact on agitation, and be increased if it is more effective. Some believe that the combination leads to a lower overall dose of each drug.[43]

After calm is achieved, agitation should be the sign for a repeat dose. Ideally the total dose of haloperidol on the second day should be a fraction of that used on day 1. After complete lucidity has been achieved, the patient needs to be protected from delirium only at night, by small doses of haloperidol (1 to 3 mg), which can be given orally. As in the treatment of delirium tremens, the consultant is advised to stop the agitation quickly and completely at the outset rather than barely keep up with it over several days. The maximum total dose of IV haloperidol to be used as an upper limit has not been established, although IV administration of single bolus doses of 200 mg have been used,[44] and more than 2000 mg has been used in a 24-hour period. The highest requirements have been seen with delirious patients on the intra-aortic balloon pump.[45] A continuous infusion of haloperidol has also been used to treat severe, refractory delirium.[46] It has previously been argued that (despite strong empirical clinical evidence) high-dose haloperidol made little pharmacologic sense, given the high rates of dopamine receptor blockade at relatively low doses. In vitro research has revealed that the butyrophenone class of neurolpetics (haloperidol and droperidol) might protect neurons from oxidative stress resulting from interactions at the sigma receptor.[47,48] These interactions might provide the physiologic basis for the clinical benefits of high-dose haloperidol.[49]

When delirium does not respond and agitation is unabated, one might wonder if the neuroleptic (e.g., haloperidol) is producing akathisia. The best indication as to whether the treatment is causing agitation is the patient's description of an irresistible urge to move—usually the limbs, lower more often than upper. If dialogue is possible, even nodding yes or no (provided that the patient understands the question) can confirm or exclude this symptom. If the patient cannot communicate, limited options remain: to decrease the dose or to increase it and judge by the response. In our experience, it is far more common for the patient to receive more haloperidol and to improve.

Hypotensive episodes following the administration of IV haloperidol are rare and almost invariably result from hypovolemia. Ordinarily, this is easily checked in ICU patients who have in-dwelling pulmonary artery catheters, but because agitation is likely to return, volume replacement is necessary before one administers further doses. Local caustic effects on veins do not arise. IV haloperidol is generally safe for epileptic patients and for patients with head trauma, unless psychotropic drugs are contraindicated because the patient needs careful neurologic monitoring. Although IV haloperidol may be used without mishap in patients receiving epinephrine drips, after large doses of haloperidol a pressor other than epinephrine (e.g., norepinephrine) should be used to avoid unopposed β-adrenergic activity. IV haloperidol does not block a dopamine-mediated increase in renal blood flow. It also appears to be the safest agent for patients with chronic obstructive pulmonary disease.

As with all neuroleptic agents, IV haloperidol has been associated with the development of torsades de pointes (TDP).[50–54] The reasons for this are unclear, although particular caution is urged when levels of potassium and magnesium are low (because these deficiencies independently predict TDP), when a baseline prolonged QT interval is noted, when hepatic compromise is present, or when a specific cardiac abnormality (e.g., mitral valve prolapse or a dilated ventricle) exists. Progressive QT widening after administration of haloperidol should alert one to

the danger, however infrequent it may be in practice (4 of 1100 cases in one unit).[51] Delirious patients who are candidates for IV haloperidol require careful screening. Serum potassium and magnesium should be within normal range, and a baseline electrocardiogram (ECG) should be checked for the pretreatment QT interval corrected for heart rate (QTc). If necessary, potassium and magnesium shoud be repleted and the QTc and levels of potassium and magnesium should be monitored regularly for the duration of neuroleptic treatment. QT interval prolongation occurs in some patients with alcoholic liver disease; this finding is associated with adverse outcomes (e.g., sudden cardiac death).[55] Several other commonly used medications also carry the potential for QTc prolongation (Table 10–8). Medication lists should be reviewed closely for other agents that could be discontinued or therapeutically exchanged if QTc prolongation becomes a concern.

Other available parenteral first-generation neuroleptics for treatment of agitation are perphenazine, thiothixene, trifluoperazine, fluphenazine, and chlorpromazine. Perphenazine is approved for IV use as an antiemetic. Chlorpromazine is extremely effective, but its potent α-blocking properties can be dangerous for critically ill patients. When administered IV or IM, it can abruptly decrease total peripheral resistance and cause a precipitous fall in cardiac output. Nevertheless, used IV in small doses (10 mg) it can be safe and effective in the treatment of delirium.

The availability of injectable formulations of olanzapine and ziprasidone has prompted a growing interest in using the second-generation antipsychotics in managing delirium.[56] Risperidone has the most available data supporting its use, and multiple studies show it to be efficacious and safe for treating delirium[57–59]; one small randomized double-blind comparative study found no significant difference in efficacy compared with haloperidol.[60] The other members of this class (olanzapine, ziprasidone, quetiapine, clozapine, and aripiprazole) have far less supporting evidence, though some small studies seem to indicate some promise for management of delirium.[61–65] Agranulocytosis associated with clozapine and the resultant regulation of its use effectively eliminates any routine application of it in managing delirium. All drugs in this class feature an FDA black box warning indicating an increased risk of death when used to treat behavioral problems in elderly patients with dementia. Similar warnings regarding a potential increased risk of cerebrovascular events are reported for risperidone, olanzapine, and aripiprazole. One study examining the mean prolongation of the QTc for various neuroleptic agents on a per-dose-equivalent basis revealed that haloperidol was associated with the lowest increase of all the drugs tested.[66] With decades of clinical experience in the use of haloperidol, and a dearth of available data on these newer agents, haloperidol remains the agent of choice for treating delirium.

To date, there are few published data to support pharmacologic prophylaxis of delirium for the critically ill, although one randomized, double-blind, placebo-controlled study examining the preoperative use of haloperidol in elderly patients undergoing hip surgery indicated decreases in the severity and duration of delirium and length of hospital stay but no statistically significant decrease in the actual incidence of delirium.[67] A double-blind, randomized, placebo-controlled study involving the prophylactic administration of olanzapine to patients undergoing joint replacement surgery demonstrated a decreased incidence of delirium and more frequent discharge to home (as opposed to a rehabilitation hospital) when they received olanzapine before surgery.[68] There is also some limited evidence suggesting that the pro-cholinergic action of cholinesterase inhibitors provides some protection against the development of delirium.[69,70]

TABLE 10–8 Non-Neuroleptic Medications Associated with Prolongation of the QT Interval

ANTIARRYTHMICS	ANTIINFECTIOUS	OTHER
Amiodarone	Atazanavir	Alfuzosin
Disopyramide	Azithromycin	Amantadine
Dofetilide	Chloroquine	Arsenic trioxide
Flecainide	Clarithromycon	Bepridil
Ibutilide	Erythromycin	Chloral hydrate
Procainamide	Foscarnet	Cisapride
Quinidine	Gatifloxacin	Dolasetron
Sotalol	Gemifloxacin	Felbamate
	Halofantrine	Granisetron
	Levofloxacin	Indapamide
	Moxifloxacin	Isradipine
	Ofloxacin	Lapatinib
	Pentamidine	Levomethadyl
	Sparfloxacin	Lithium carbonate
	Telithromycin	Methadone
	Voriconazole	Nicardipine
		Octreotide
		Ondansetron
		Oxytocin
		Probucol
		Ranolazine
		Sunitinib
		Tacrolimus
		Tizanidine
		Vardenafil
		Venlafaxine

DELIRIUM IN SPECIFIC DISEASES

Critically ill patients with human immunodeficiency virus (HIV) infection may be more susceptible to the EPS of haloperidol and to neuroleptic malignant syndrome (NMS),[71–74] leading an experienced group to recommend use of molindone.[74] Molindone is associated with fewer of such effects; it is available only as an oral agent, and it can be prescribed from 5 to 25 mg at appropriate intervals or, in a more acute situation, 25 mg every hour until calm is achieved. Risperidone (0.5 to 1 mg per dose) is another recommended oral agent. If parenteral medication is required, 10 mg of chlorpromazine has been effective. Perphenazine is readily available for parenteral use as well, and 2-mg doses can be used effectively.

Patients with Parkinson's disease pose a special problem because dopamine blockade aggravates their condition. If oral treatment of delirium or psychosis is possible, clozapine, starting with a small dose of 6.25 or 12.5 mg,

is probably the most effective agent available that does not exacerbate the disease. With the risk of agranulocytosis attendant to the use of clozapine, quetiapine can play a valuable role in this population because its very low affinity for dopamine receptors is less likely to exacerbate this disorder.[75]

IV benzodiazepines (particularly diazepam, chlordiazepoxide, and lorazepam) are routinely used to treat agitated states, particularly delirium tremens, and alcohol withdrawal.[76] Neuroleptics have also been used successfully, and both have been combined with clonidine. IV alcohol is also extremely effective in treating alcohol withdrawal states, particularly if the patient does not seem to respond as rapidly as expected to higher doses of benzodiazepines. The inherent disadvantage is that alcohol is toxic to liver and brain, although its use can be quite safe if these organs do not show already extensive damage, and it is sometimes quite safe even when they do. Nonetheless, use of IV alcohol should be reserved for extreme cases of alcohol withdrawal when other, less-toxic measures have failed. A 5% solution of alcohol mixed with 5% dextrose in water run at 1 mL per minute often achieves calm quickly. Treatment pathways have been developed to provide nonpsychiatric clinicians with guidance on the management of alcohol withdrawal,[77] though care must always be taken to ensure that benzodiazepines are not inappropriately administered because they almost certainly exacerbate a delirium that results from any other cause.[78]

Propofol is now commonly used to sedate critically ill patients and can also be extremely effective in managing agitation.[79–81] It has moderate respiratory depressant and vasodilator effects, although hypotension can be minimized by avoiding boluses of the drug. Impaired hepatic function does not slow metabolic clearance, but clearance does decline with age, and its half-life is significantly longer in the elderly. This drug's rapid onset and short duration make it especially useful for treating short periods of stress. When rapid return to alertness from sedation for an uncompromised neurologic examination is indicated, propofol is a nearly ideal agent[82]; however, its use in treating a prolonged delirious state has specific disadvantages.[83] Delivered as a fat emulsion containing 0.1 g of fat per milliliter, propofol requires a dedicated IV line, and drug accumulation can lead to a fat-overload syndrome that has been associated with overfeeding and with significant CO_2 production, hypertriglyceridemia, ketoacidosis, seizure activity 6 days after discontinuation, and even fatal respiratory failure.[83–85] Obese patients provide a high volume of distribution, and their doses should be calculated using estimated lean, rather than actual, body mass. If the patient is receiving fat by parenteral feeding, this must be accounted for or eliminated and adequate glucose infusion must be provided to prevent ketoacidosis. Although no clear association has been demonstrated with addiction, tolerance, or withdrawal, doses seem to require escalation after 4 to 7 days' infusion. Seizures seen after withdrawal or muscular rigidity during administration are poorly understood. The drug is costly, especially when used for prolonged infusions.

Dexmedetomidine is a selective α_2-adrenergic agonist used for sedation and analgesia in the ICU setting. Its action on receptors in the locus ceruleus results in anxiolysis and sedation, and agonism of spinal cord receptors provides analgesia. This unique mechanism of action allows effective management in agitation without the risks of respiratory depression, dependence, and deliriogenesis associated with the benzodiazepines traditionally employed in the ICU.[86] Its relative lack of amnestic effect might further limit its use as monotherapy in the treatment of the delirious patient owing to an increased likelihood of distressing recollections persisting from the period of sedation.[87] In current practice, dexmedetomidine can serve as a useful (but costly) adjunct agent to quell agitation when more traditional approaches have met with limited success.

Drug infusions may be more effective and efficient than intermittent bolus dosing because the latter can intensify side effects (such as hypotension), waste time of critical care personnel, and permit more individual error. The contents of the infusion can address simultaneously multiple aspects of a patient's difficulties in uniquely appropriate ways. The report of the sufentanil, midazolam, and atracurium admixture for a patient who required a temporary biventricular assist device is an excellent example of multiple-drug infusion and creative problem-solving.[88,89]

CONCLUSION

Of all psychiatric diagnoses, delirium demands the most immediate attention because delay in identifying and treating delirium might allow the progression of serious and irreversible pathophysiologic changes. Unfortunately, delirium is all too often underemphasized, misdiagnosed, or altogether missed in the general hospital setting.[90–92] Indeed, it was not until their most recent editions that major medical and surgical texts corrected chapters indicating that delirium was the result of anxiety or depression, rather than an underlying somatic cause that required prompt investigation. In the face of this tradition of misinformation, it often falls to the psychiatric consultant to identify and manage delirium while alerting and educating others to its significance.

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