PRACTICE GUIDELINE FOR THE
Treatment of Patients With Delirium

WORK GROUP ON DELIRIUM

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STATEMENT OF INTENT

The American Psychiatric Association (APA) Practice Guidelines are not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual patient and are subject to change as scientific knowledge and technology advance and practice patterns evolve. These parameters of practice should be considered guidelines only. Adherence to them will not ensure a successful outcome for every individual, nor should they be interpreted as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgment regarding a particular clinical procedure or treatment plan must be made by the psychiatrist in light of the clinical data presented by the patient and the diagnostic and treatment options available.

This practice guideline has been developed by psychiatrists who are in active clinical practice. In addition, some contributors are primarily involved in research or other academic endeavors. It is possible that through such activities some contributors, including work group members and reviewers, have received income related to treatments discussed in this guideline. A number of mechanisms are in place to minimize the potential for producing biased recommendations due to conflicts of interest. Work group members are selected on the basis of their expertise and integrity. Any work group member or reviewer who has a potential conflict of interest that may bias (or appear to bias) his or her work is asked to disclose this to the Steering Committee on Practice Guidelines and the work group. Iterative guideline drafts are reviewed by the Steering Committee, other experts, allied organizations, APA members, and the APA Assembly and Board of Trustees; substantial revisions address or integrate the comments of these multiple reviewers. The development of the APA practice guidelines is not financially supported by any commercial organization.

More detail about mechanisms in place to minimize bias is provided in a document available from the APA Department of Quality Improvement and Psychiatric Services, "APA Guideline Development Process."

This practice guideline was approved in December 1998 and published in May 1999.

INTRODUCTION

This practice guideline seeks to summarize data regarding the care of patients with delirium. It begins at the point where the psychiatrist has diagnosed a patient as suffering from delirium according to the DSM-IV criteria for the disorder. The purpose of this guideline is to assist the psychiatrist in caring for a patient with delirium.

Psychiatrists care for patients with delirium in many different settings and serve a variety of functions. In many cases, a psychiatrist will serve as a consultant to the attending physician and will not have primary responsibility for the patient. This guideline reviews the treatment that patients with delirium may need. The psychiatrist should either provide or advocate for the appropriate treatments. In addition, many patients have comorbid conditions that cannot be described completely with one DSM diagnostic category. Therefore, the psychiatrist caring for patients with delirium should consider, but not be limited to, the treatments recommended in this practice guideline.

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DEVELOPMENT PROCESS

This practice guideline was developed under the auspices of the Steering Committee on Practice Guidelines. The process is detailed in a document available from the APA Department of Quality Improvement and Psychiatric Services: the "APA Guideline Development Process." Key features of the process include the following:

- a comprehensive literature review (description follows) and development of evidence tables;
- initial drafting by a work group that included psychiatrists with clinical and research expertise in delirium;
- the production of multiple drafts with widespread review, in which 12 organizations and over 83 individuals submitted comments (see Section VI);
- approval by the APA Assembly and Board of Trustees; and
- planned revisions at 3- to 5-year intervals.

A computerized search of the relevant literature from MEDLINE, PsycINFO, and EMBASE was conducted.

The first literature search was conducted by searching MEDLINE, using PubMed, for the period 1966 to April 1996 and used the keywords "organic mental disorders," "psychotic," "delirium," "delusions," "acute organic brain syndrome," "alcohol amnestic disorder," "psychoses," "substance-induced," and "intensive care psychosis" with "haloperidol," "droperidol," "antipsychotic agents," "physostigmine," "tacrine," "cholinergic agents," "benzodiazepines," "thiamine," "folic acid," "vitamin b 12," "vitamins," "morphine," "paralysis," "electroconvulsive therapy," "risperidone," and "neuroleptic malignant syndrome." A total of 954 citations were found.

A second search in MEDLINE was completed for the period 1995 to 1998 and used the key words "delirium," "dementia," "amnestic," "cognitive disorders," and "delusions" with "haloperidol," "droperidol," "antipsychotic agents," "physostigmine," "tacrine," "cholinergic agents," "benzodiazepines," "vitamins," "morphine," "paralysis," "electroconvulsive therapy," "risperidone," and "neuroleptic malignant syndrome." A total of 1,386 citations were found.

The literature search conducted by using PsycINFO covered the period 1967 to November 1998 and used the key words "delirium" and "treatment & prevention" with "psychosocial," "behavioral," "restraint," "seclusion," "isolation," "structure," "support," "sensory deprivation," "orient," "reorient," and "delirium tremens." A total of 337 citations were found.

An additional literature search was conducted by using EMBASE for the period 1985 to November 1998 and used the key word "delirium" with "vitamins," "morphine," "paralysis," "electroconvulsive therapy," and "neuroleptic malignant syndrome." A total of 156 citations were found.

I. SUMMARY OF RECOMMENDATIONS

The following executive summary is intended to provide an overview of the organization and scope of recommendations in this practice guideline. The treatment of patients with delirium requires the consideration of many factors and cannot be adequately reviewed in a brief summary. The reader is encouraged to consult the relevant portions of the guideline when specific treatment recommendations are sought. This summary is not intended to stand on its own.

▶ A. CODING SYSTEM

Each recommendation is identified as falling into one of three categories of endorsement, indicated by a bracketed Roman numeral following the statement. The three categories represent varying levels of clinical confidence regarding the recommendations:

[I]   Recommended with substantial clinical confidence.
[II] Recommended with moderate clinical confidence.
[III] May be recommended on the basis of individual circumstances.

▶ B. GENERAL CONSIDERATIONS

Delirium is primarily a disturbance of consciousness, attention, cognition, and perception but can also affect sleep, psychomotor activity, and emotions. It is a common psychiatric illness among medically compromised patients and may be a harbinger of significant morbidity and mortality. The treatment of patients with delirium begins with an essential array of psychiatric management tasks designed to provide immediate interventions for urgent general medical conditions, identify and treat the etiology of the delirium, ensure safety, and improve the patient's functioning. Environmental and supportive interventions are also generally offered to all patients with delirium and are designed to reduce factors that may exacerbate delirium, to reorient patients, and to provide them with support. Somatic interventions largely consist of pharmacologic treatment with high-potency antipsychotic medications. Other somatic interventions may be of help in particular cases of delirium due to specific etiologies or with particular clinical features.

1. Psychiatric management

Psychiatric management is an essential feature of treatment for delirium and should be implemented for all patients with delirium [I]. The specific tasks that constitute psychiatric management include the following: coordinating the care of the patient with other clinicians; identifying the underlying cause(s) of the delirium; initiating immediate interventions for urgent general medical conditions; providing treatments that address the underlying etiology of the delirium; assessing and ensuring the safety of the patient and others; assessing the patient's psychiatric status and monitoring it on an ongoing basis; assessing individual and family psychological and social characteristics; establishing and maintaining a supportive therapeutic stance with the patient, the family, and other clinicians; educating the patient, family, and other clinicians regarding the illness; and providing postdelirium management to support the patient and family and providing education regarding risk factors for future episodes.

2. Environmental and supportive interventions

These interventions are generally recommended for all patients with delirium [I]. Environmental interventions are designed to reduce or eliminate environmental factors that exacerbate delirium.

They include providing an optimal level of environmental stimulation, reducing sensory impairments, making environments more familiar, and providing environmental cues that facilitate orientation. Cognitive-emotional supportive measures include providing patients with reorientation, reassurance, and information concerning delirium that may reduce fear or demoralization. In addition to providing such supportive interventions themselves, it may be helpful for psychiatrists to inform nursing staff, general medical physicians, and family members of their importance.

3. Somatic interventions

The choice of somatic interventions for delirium will depend on the specific features of a patient's clinical condition, the underlying etiology of the delirium, and any associated comorbid conditions [I]. Antipsychotic medications are often the pharmacologic treatment of choice [I]. Haloperidol is most frequently used because it has few anticholinergic side effects, few active metabolites, and a relatively small likelihood of causing sedation and hypotension. Haloperidol may be administered orally, intramuscularly, or intravenously and may cause fewer extrapyramidal symptoms when administered intravenously. Haloperidol can be initiated in the range of 1–2 mg every 2–4 hours as needed (0.25–0.50 mg every 4 hours as needed for elderly patients), with titration to higher doses for patients who continue to be agitated. For patients who require multiple bolus doses of antipsychotic medications, continuous intravenous infusions of antipsychotic medication may be useful (e.g., haloperidol bolus, 10 mg i.v., followed by continuous intravenous infusion of 5–10 mg/hour; lower doses may be required for elderly patients). For patients who require a more rapid onset of action, droperidol, either alone or followed by haloperidol, can be considered. Recently some physicians have used the newer antipsychotic medications (risperidone, olanzapine, and quetiapine) in the treatment of patients with delirium. Patients receiving antipsychotic medications for delirium should have their ECGs monitored [I]. A QTc interval greater than 450 msec or more than 25% over baseline may warrant a cardiology consultation and reduction or discontinuation of the antipsychotic medication.

Benzodiazepine treatment as a monotherapy is generally reserved for delirium caused by withdrawal of alcohol or sedative-hypnotics [I]. Patients with delirium who can tolerate only lower doses of antipsychotic medications may benefit from the combination of a benzodiazepine and antipsychotic medication [III].

Other somatic interventions may be considered for patients with delirium who have particular clinical conditions or specific underlying etiologies. Cholinergics such as physostigmine may be useful in delirium known to be caused specifically by anticholinergic medications [II]. Paralysis, sedation, and mechanical ventilation may be required for agitated patients with delirium and hypercatabolic conditions [III]. Palliative treatment with opiates may be needed by patients with delirium for whom pain is an aggravating factor [III]. Multivitamin replacement should be given to patients with delirium for whom there is the possibility of B vitamin deficiencies (e.g., those who are alcoholic or malnourished) [II].

II. DISEASE DEFINITION, EPIDEMIOLOGY, AND NATURAL HISTORY

▶ ## A. DEFINITION AND CLINICAL FEATURES

The essential features of delirium include disturbances of consciousness, attention, cognition, and perception. The disturbance develops over a short period of time (usually hours to days)

and tends to fluctuate during the course of the day. Following are the DSM-IV criteria for delirium (1):

A. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.
B. A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.
C. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.

According to DSM-IV, delirium frequently represents a sudden and significant decline from a previous level of functioning and cannot be better accounted for by a preexisting or evolving dementia. There is usually evidence from the history, physical examination, or laboratory tests that the delirium is a direct physiological consequence of a general medical condition, substance intoxication or withdrawal, use of a medication, toxin exposure, or a combination of these factors. The disorders included in the DSM-IV delirium section have a common symptom presentation of a disturbance in consciousness and cognition but are differentiated by etiology:

1. Delirium due to a general medical condition.
2. Substance-induced delirium.
3. Delirium due to multiple etiologies.
4. Delirium not otherwise specified.

The disturbance in consciousness or arousal can be manifested by a reduced clarity or awareness of the environment that does not reach the level of stupor or coma. In addition, the ability to focus, sustain, or shift attention is frequently impaired and may result in the patient's being easily distracted.

There is also an accompanying decline in other areas of cognition. Cognitive deficits can include memory and visuoconstructional impairment, disorientation, or language disturbance. Memory impairment is most commonly evident in recent memory. Disorientation is usually manifested as disorientation to time (e.g., thinking it is morning in the middle of the night) or place (e.g., thinking one is at home rather than in the hospital). Disorientation to other persons occurs commonly, but disorientation to self is rare. It may be difficult for the clinician to fully assess cognitive function because the patient is inattentive and incoherent. Obtaining information from the medical chart, medical staff, and other informants, particularly family members, is often helpful in these circumstances.

Dysarthria is a frequent speech and language disturbance, and dysnomia (i.e., impaired ability to name objects), dysgraphia (i.e., impaired ability to write), or even frank aphasia may be observed.

Perceptual disturbances may include misinterpretations, illusions, or hallucinations. For example, the patient may see the nurse mixing intravenous solutions and conclude the nurse is trying to poison him or her (misinterpretation); the folds of the bedclothes may appear to be animate objects (illusion); or the patient may see a group of people around the bed when no one is actually there (hallucination). Although visual misperceptions and hallucinations are most common in delirium, auditory, tactile, gustatory, and olfactory misperceptions or hallucinations can also occur. Misperceptions range from simple and uniform to highly complex. A patient with delirium may have a delusional conviction of the reality of a hallucination and exhibit emotional and behavioral responses consistent with the hallucination's content.

B. ASSOCIATED FEATURES

Other commonly associated features of delirium include disturbances of sleep, psychomotor activity, and emotion. Disturbances in the sleep-wake cycle observed in delirium include daytime sleepiness, nighttime agitation, and disturbances in sleep continuity. In some cases, complete reversal of the night-day sleep-wake cycle or fragmentation of the circadian sleep-wake pattern can occur.

Delirium is often accompanied by disturbed psychomotor activity. Lipowski (2, 3) clinically described two subtypes of delirium based on psychomotor activity and arousal levels. These delirium subtypes included the "hyperactive" (or agitated, hyperalert) subtype and the "hypoactive" (lethargic, hypoalert) subtype. Others have included a "mixed" delirium subtype with alternating features of both. Ross et al. (4) suggested that the hyperactive form is more often characterized by hallucinations, delusions, agitation, and disorientation, while the hypoactive form is characterized by confusion and sedation and is less often accompanied by hallucinations, delusions, or illusions. Comparable levels of cognitive impairment have been observed with both motor subtypes.

The delirious individual may also exhibit emotional disturbances, such as anxiety, fear, depression, irritability, anger, euphoria, and apathy. There may be affective lability, with rapid and unpredictable shifts from one emotional state to another.

Depending on the etiology, delirium can be associated with a number of nonspecific neurological abnormalities, such as tremor, myoclonus, asterixis, and reflex or muscle tone changes. For example, nystagmus and ataxia may accompany delirium due to medication intoxications; cerebellar signs, myoclonus, and generalized hyperreflexia may be seen with lithium intoxication; cranial nerve palsies may occur with Wernicke's encephalopathy; and asterixis may be observed with renal or hepatic insufficiency. The background rhythm seen on EEG is typically abnormal, usually showing generalized slowing. However, in alcohol or sedative-hypnotic withdrawal, the EEG usually shows fast activity. In addition, laboratory findings that are characteristic of associated or etiological general medical conditions (or intoxication or withdrawal states) may be seen.

C. DIFFERENTIAL DIAGNOSIS

The differential diagnosis of patients with features of delirium is discussed in the delirium section of DSM-IV. The most common issue in differential diagnosis is whether the patient has dementia rather than delirium, has delirium alone, or has a delirium superimposed on a preexisting dementia. Cognitive disturbances, such as memory impairment, are common to both delirium and dementia; however, the patient with dementia usually is alert and does not have the disturbance of consciousness or arousal that is characteristic of delirium. The temporal onset of cognitive deficit symptoms and the temporal course and reversibility of cognitive impairments are helpful in distinguishing between delirium and dementia. The severity of delirium symptoms characteristically fluctuates during a 24-hour period, while dementia symptoms generally do not. Information from medical records, other caregivers, and family members may be helpful in determining whether a dementia was present before the onset of a delirium.

D. PREVALENCE AND COURSE

The prevalence of delirium in the hospitalized medically ill ranges from 10% to 30%. In the hospitalized elderly, the delirium prevalence ranges from 10% to 40% (2). As many as 25% of hospitalized cancer patients (5) and 30%–40% of hospitalized AIDS patients (6) develop delirium. As many as 51% of postoperative patients develop delirium (7), and up to 80% of patients with terminal illnesses develop delirium near death (8). Patients who have just had

surgery, particularly cardiotomy, hip surgery, or a transplant, and patients with burns, dialysis, or central nervous system lesions are at increased risk for delirium.

Some patients manifest subclinical delirium or prodromal symptoms such as restlessness, anxiety, irritability, distractibility, or sleep disturbance in the days before the onset of overt delirium. Prodromal symptoms may progress to full-blown delirium over 1–3 days. The duration of symptoms of delirium has been reported to range from less than 1 week to more than 2 months (9–14). Typically the symptoms of delirium resolve within 10–12 days; however, up to 15% of patients with delirium have symptoms that persist for up to 30 days and beyond (10). Elderly patients with delirium may be more likely to have a prolonged course, with symptom durations frequently exceeding 1 month (11, 12).

While the majority of patients recover fully, delirium may progress to stupor, coma, seizures, or death, particularly if untreated. Full recovery is less likely in the elderly, with estimated rates of full recovery by the time of discharge varying from 4% to 40% (9, 15). Persistent cognitive deficits are also quite common in elderly patients recovering from delirium, although such deficits may be due to preexisting dementia that was not fully appreciated (9). Similarly, in a study of delirium in AIDS patients Fernandez et al. (16) found that only 27% had complete recovery of cognitive function, possibly because of underlying AIDS dementia.

Delirium in the medically ill is associated with significant morbidity. Medically ill patients, particularly the elderly, have a significantly increased risk of developing complications, such as pneumonia and decubitus ulcers, resulting in longer hospital stays (17, 18). In postoperative patients, delirium is a harbinger of limited recovery and poor long-term outcome. Patients who develop delirium, particularly after orthopedic surgery, are at increased risk for postoperative complications, longer postoperative recuperation periods, longer hospital stays, and long-term disability (19, 20). Seizures may occur in delirium, particularly among patients with alcohol or sedative-hypnotic withdrawal, cocaine intoxication, head trauma, hypoglycemia, strokes, or extensive burns (21).

Delirium in the medically ill is also associated with an increased mortality rate (22, 23). Elderly patients who develop delirium during a hospitalization have been estimated to have a 22%–76% chance of dying during that hospitalization (22, 24). Patients who develop delirium during a hospitalization also have a very high rate of death during the months following discharge. Several studies suggest that up to 25% of patients with delirium die within 6 months and that their mortality rate in the 3 months after diagnosis is 14 times as high as the mortality rate for patients with affective disorders (25, 26).

▶ E. CAUSES

The disorders included in the delirium section of DSM-IV have a common symptom presentation but are differentiated according to presumed etiology (see Table 1 for a list of common etiologies).

1. Due to a general medical condition

In determining that delirium is due to a general medical condition, the clinician must first establish the presence of a general medical condition and then establish that the delirium is etiologically related. A careful and comprehensive assessment is necessary to make this judgment. A temporal association between the onset, exacerbation, or remission of the general medical condition and that of the delirium is a helpful guide. Evidence from the literature that suggests the condition in question can be directly associated with the development of delirium is also useful. Delirium can be associated with many different general medical conditions, each of which has characteristic physical examination and laboratory findings. When these are present they may help confirm the relationship between delirium and the general medical condition. General medical conditions commonly causing delirium are shown in Table 1.

TABLE 1. Underlying Conditions Commonly Associated With Delirium

Type	Disorder
Central nervous system disorder	Head trauma
	Seizures
	Postictal state
	Vascular disease (e.g., hypertensive encephalopathy)
	Degenerative disease
Metabolic disorder	Renal failure (e.g., uremia)
	Hepatic failure
	Anemia
	Hypoxia
	Hypoglycemia
	Thiamine deficiency
	Endocrinopathy
	Fluid or electrolyte imbalance
	Acid-base imbalance
Cardiopulmonary disorder	Myocardial infarction
	Congestive heart failure
	Cardiac arrhythmia
	Shock
	Respiratory failure
Systemic illness	Substance intoxication or withdrawal
	Infection
	Neoplasm
	Severe trauma
	Sensory deprivation
	Temperature dysregulation
	Postoperative state

2. Due to substance use or withdrawal

Delirium is frequently due to substance use or withdrawal (27). Substances with the potential to cause delirium include both agents that are not usually regarded as having psychoactive properties and those with established psychoactive properties. Delirium that occurs during substance intoxication may arise within minutes to hours after ingestion of high doses of drugs such as cocaine or hallucinogens; other drugs, such as alcohol, barbiturates, or meperidine, may cause delirium after intoxication is sustained for several days. During substance intoxication, the potential for additional agents with anticholinergic activity to cause delirium is increased. Usually the delirium resolves as the intoxication ends or within hours to days thereafter. Delirium associated with substance withdrawal develops as fluid and tissue concentrations of the substance decrease after reduction of sustained, high-dose use of certain substances. Substance-withdrawal delirium can also occur after the reduction of lower doses in patients having poor clearance, experiencing drug interactions, or taking combinations of drugs. The duration of the delirium usually varies with the half-life of the substance involved. Longer-acting substances usually are associated with less severe but more protracted withdrawal and may not have an onset of withdrawal symptoms for days or weeks after use of the substance is discontinued. Substance-withdrawal delirium may continue for only a few hours or may persist for as long as 2–4 weeks.

Table 2 lists substances associated with delirium, including substances of abuse, prescription medications, and toxins.

3. Due to multiple etiologies

Delirium, particularly in the critically ill and in elderly hospitalized patients, often has multiple etiologies (25). Francis and Kapoor (28) found that while 56% of elderly patients with delirium

TABLE 2. Substances That Can Cause Delirium Through Intoxication or Withdrawal

Category	Substance
Drugs of abuse	Alcohol
	Amphetamines
	Cannabis
	Cocaine
	Hallucinogens
	Inhalants
	Opioids
	Phencyclidine
	Sedatives
	Hypnotics
	Other
Medications	Anesthetics
	Analgesics
	Antiasthmatic agents
	Anticonvulsants
	Antihistamines
	Antihypertensive and cardiovascular medications
	Antimicrobials
	Antiparkinsonian medications
	Corticosteroids
	Gastrointestinal medications
	Muscle relaxants
	Immunosuppressive agents
	Lithium and psychotropic medications with anticholinergic properties
Toxins	Anticholinesterase
	Organophosphate insecticides
	Carbon monoxide
	Carbon dioxide
	Volatile substances, such as fuel or organic solvents

had a single definite or probable etiology for delirium, the remaining 44% had an average of 2.8 etiologies per patient.

4. Due to unspecified etiology

Occasionally, no clear etiology is immediately apparent. Often, unrecognized medication use or substance abuse is the cause of an intoxication or withdrawal delirium, and sometimes a rare cause of delirium, such as disseminated intravascular coagulation, is eventually revealed. There has been some controversy as to whether particular settings can themselves cause delirium (e.g., there has been speculation that the intensive care environment can cause "intensive care unit psychosis"). Koponen et al. (11) found a clear organic etiology in 87% of patients with delirium, and they found relatively little evidence that delirium was caused primarily by environmental factors.

► F. USE OF FORMAL MEASURES

Although standard psychiatric, general medical, and neurological histories and examinations are usually sufficient to diagnose and evaluate the severity of delirium, they can be supplemented by assessments using formal instruments. A large number of delirium assessment methods have

been designed, some intended for clinical evaluations and others for research. Detailed reviews of the psychometric properties of instruments, as well as suggestions for choosing among instruments for particular clinical evaluations or research purposes, are available (29–31). Four types of instruments are briefly mentioned in the following sections: tests that screen for delirium symptoms, delirium diagnostic instruments, delirium symptom severity ratings, and some experimental laboratory tests.

1. Screening instruments

Several tools have been developed to screen for delirium symptoms among patients, and most have been designed to be administered by nursing staff. These may aid in the recognition of delirium, especially in nursing homes, where physician visits are less frequent. The number of delirium symptoms covered, the specificity of items for delirium, and the complexity of administration all vary. Screening instruments include the Clinical Assessment of Confusion–A (CAC-A) (32), the Confusion Rating Scale (CRS) (33), the MCV Nursing Delirium Rating Scale (MCV-NDRS) (34), and the NEECHAM Confusion Scale (35).

2. Diagnostic instruments

Investigators have designed a variety of instruments to make a formal diagnosis of delirium. These instruments consist of operationalized delirium criteria from a variety of diagnostic systems, often in the form of a checklist incorporating information from patient observation and the medical record (e.g., DSM-III-R, DSM-IV, ICD-9, and ICD-10). The rate of delirium diagnosis obtained by using these diagnostic instruments varies according to both the diagnostic system that was used and the particular way in which the authors chose to operationalize the criteria. One structured diagnostic interview schedule, the Delirium Symptom Interview (DSI), can be administered by lay interviewers and used in epidemiological studies (36). Other delirium diagnostic instruments include the Confusion Assessment Method (CAM) (37), Delirium Scale (Dscale) (38), Global Accessibility Rating Scale (GARS) (39), Organic Brain Syndrome Scale (OBS) (40), and Saskatoon Delirium Checklist (SDC) (41).

3. Delirium symptom severity rating scales

Several instruments have been developed to rate the severity of delirium symptoms. Ratings are generally based both on behavioral symptoms and on confusion and cognitive impairment. Rating the severity of delirium over time may be useful for monitoring the effect of an intervention or plotting the course of a delirium over time. These scales have also been used to make the diagnosis of delirium by considering patients with scores above a specified cutoff to have the diagnosis. Such rating scales include the Delirium Rating Scale (DRS) (42) and the Memorial Delirium Assessment Scale (MDAS) (43).

4. Laboratory tests

Several laboratory evaluations have been investigated for possible use in evaluating delirium. With the exception of the EEG, these tests are experimental and currently appropriate only for research purposes. For several decades, investigators have observed EEG changes in patients with delirium (44). EEG changes consist mainly of generalized slowing, although low-voltage fast activity is seen in some types of delirium, such as delirium tremens (45). The presence of EEG abnormalities has fairly good sensitivity for delirium (in one study, the sensitivity was found to be 75%), but their absence does not rule out the diagnosis; thus, the EEG is no substitute for careful clinical observation. Among the experimental laboratory tests that have been investigated for use in delirium, those that appear to show some promise include brain imaging (46, 47) and measures of serum anticholinergic activity (48).

III. TREATMENT PRINCIPLES AND ALTERNATIVES

Several therapeutic modes are employed in the treatment of delirium and are discussed in this section. First, the cornerstone of treatment, psychiatric management, is defined and its components are described. Treatment of the delirium itself involves a set of environmental and supportive interventions and specific pharmacologic treatments. Environmental manipulations are generally designed to help reorient the patient and modulate the degree of stimulation. Supportive measures are designed to provide patient, family, and friends with both reassurance and education regarding the nature, temporal course, and sequelae of delirium.

▶ A. PSYCHIATRIC MANAGEMENT

Psychiatric management involves an array of tasks that the psychiatrist should seek to ensure are performed for all patients with delirium. A psychologically informed understanding of the patient and the family may facilitate these tasks. These tasks are designed to facilitate the identification and treatment of the underlying cause(s) of delirium, improve the patient's level of functioning, and ensure the safety and comfort of patients and others. In many cases, the psychiatrist will be part of, or a consultant to, a multidisciplinary team and should encourage the administration of the full range of needed treatments.

1. Coordinate with other physicians caring for the patient

Delirium frequently heralds a medical emergency, and patients are usually managed in an acute-care hospital setting. For some patients with milder symptoms, once the etiology of delirium has been identified and general medical management has begun, psychiatric and general medical management can take place in an alternative setting (e.g., skilled nursing facility, home, hospice). The psychiatrist is commonly asked to consult when a patient develops delirium on a general medical or surgical unit in the hospital; however, delirium may also present as an emergency in either the psychiatric outpatient or inpatient setting.

The appropriate treatment of delirium involves interventions to search for and correct underlying causes, as well as relieve current symptoms. Joint and coordinated management of the patient with delirium by the psychiatrist and internist, neurologist, or other primary care or specialty physicians will frequently help ensure appropriate comprehensive evaluation and care.

2. Identify the etiology

An essential principle in the psychiatric management of delirium is the identification and correction of the etiologic factors. Careful review of the patient's medical history and interview of family members or others close to the patient may provide some direction. Appropriate laboratory and radiological investigations such as those listed in Table 3 may be necessary to determine the underlying cause(s) of delirium. The choice of specific tests to be undertaken will depend on the results of the clinical evaluation.

3. Initiate interventions for acute conditions

A patient with delirium may have life-threatening general medical conditions that demand therapeutic intervention even before a specific or definitive etiology is determined. In addition to ensuring that diagnostic tests essential to identifying the cause of delirium are ordered, when acting as a consultant, the psychiatrist should raise the level of awareness of the general medical staff concerning the potential morbidity and mortality associated with delirium. Increased observation and monitoring of the patient's general medical condition should include frequent monitoring of vital signs, fluid intake and output, and levels of oxygenation. A patient's medications should be carefully reviewed; nonessential medications should be discontinued, and doses of needed medications should be kept as low as possible.

TABLE 3. Assessment of the Patient With Delirium

Domain	Measure
Physical status	History
	Physical and neurological examinations
	Review of vital signs and anesthesia record if postoperative
	Review of general medical records
	Careful review of medications and correlation with behavioral changes
Mental status	Interview
	Cognitive tests (e.g., clock face, digit span, Trailmaking tests)
Basic laboratory tests—consider for all patients with delirium	Blood chemistries: electrolytes, glucose, calcium, albumin, blood urea nitrogen (BUN), creatinine, SGOT, SGPT, bilirubin, alkaline phosphatase, magnesium, PO_4
	Complete blood count (CBC)
	Electrocardiogram
	Chest X-ray
	Measurement of arterial blood gases or oxygen saturation
	Urinalysis
Additional laboratory tests— ordered as indicated by clinical condition	Urine culture and sensitivity (C&S)
	Urine drug screen
	Blood tests (e.g., venereal disease research laboratory [VDRL], heavy metal screen, B_{12} and folate levels, lupus erythematosus [LE] prep, antinuclear antibody [ANA], urinary porphyrins, ammonia, human immunodeficiency virus [HIV])
	Blood cultures
	Measurement of serum levels of medications (e.g., digoxin, theophylline, phenobarbital, cyclosporine)
	Lumbar puncture
	Brain computerized tomography (CT) or magnetic resonance imaging (MRI)
	Electroencephalogram (EEG)

Source. From guidelines by Trzepacz and Wise (49).

4. Provide other disorder-specific treatment

The goal of diagnosis is to discover reversible causes of delirium and prevent complications through prompt treatment of these specific disorders. One must give a high priority to identifying and treating such disorders as hypoglycemia, hypoxia or anoxia, hyperthermia, hypertension, thiamine deficiency, withdrawal states, and anticholinergic-induced or other substance-induced delirium. Examples of specific reversible causes of delirium and treatments for these disorders appear in Table 4.

5. Monitor and ensure safety

Behavioral disturbances, cognitive deficits, and other manifestations of delirium may endanger patients or others. Psychiatrists must assess the suicidality and violence potential of patients and implement or advocate interventions to minimize these risks (e.g., remove dangerous items, increase surveillance and supervision, and institute pharmacotherapy). Suicidal behaviors are often inadvertent in delirium and occur in the context of cognitive impairment and/or in response to hallucinations or delusions. Additional assessments of a patient's risk for falls, wandering, inadvertent self-harm, etc., should also be made with appropriate measures taken to ensure safety.

TABLE 4. Examples of Reversible Causes of Delirium and Their Treatments

Condition	Treatment
Hypoglycemia or delirium of unknown etiology where hypoglycemia is suspected	Tests of blood and urine for diagnosis Thiamine hydrochloride, 100 mg i.v. (before glucose) 50% glucose solution, 50 ml i.v.
Hypoxia or anoxia (e.g., due to pneumonia, obstructive or restrictive pulmonary disease, cardiac disease, hypotension, severe anemia, or carbon monoxide poisoning)	Immediate oxygen
Hyperthermia (e.g., temperature above 40.5°C or 105°F)	Rapid cooling
Severe hypertension (e.g., blood pressure of 260/150 mm Hg) with papilledema	Prompt antihypertensive treatment
Alcohol or sedative withdrawal	Appropriate pharmacologic intervention Thiamine, intravenous glucose, magnesium, phosphate, and other B vitamins, including folate
Wernicke's encephalopathy	Thiamine hydrochloride, 100 mg i.v., followed by thiamine daily, either intravenously or orally
Anticholinergic delirium	Withdrawal of offending agent In severe cases, physostigmine should be considered unless contraindicated

Whenever possible, means other than restraints, such as sitters, should be used to prevent the delirious patient from harming himself or herself, others, or the physical environment. Restraints themselves can increase agitation or carry risks for injuries and should be considered only when other means of control are not effective or appropriate (50). A patient who is restrained should be seen as frequently as is necessary to monitor changes in the patient's condition (51). The justification for initiating restraints and continuing use of restraints should be documented in the patient's medical record. Additional rules may apply in some jurisdictions, and the psychiatrist should become familiar with applicable regulations and institutional policies (52).

6. Assess and monitor psychiatric status

The psychiatrist must periodically assess the patient's delirium symptoms, mental status, and other psychiatric symptoms. The symptoms and behavioral manifestations of delirium can fluctuate rapidly, and regular monitoring will allow for the adjustment of treatment strategies.

Important behavioral issues that must be addressed include depression, suicidal ideation or behavior, hallucinations, delusions, aggressive behavior, agitation, anxiety, disinhibition, affective lability, cognitive deficits, and sleep disturbances. It is helpful to record serial assessments of mental status and symptoms over time, as these may indicate the effectiveness of interventions and new or worsening medical conditions. A structured or semistructured instrument, such as those described in Section II.F, may aid in the systematic completion of this task.

7. Assess individual and family psychological and social characteristics

Knowledge of the patient's and the family's psychodynamic issues, personality variables, and sociocultural environment may aid in dealing effectively with specific anxieties and reaction patterns on the part of both the patient and the family. This understanding may be based on prior acquaintance with the patient, current interviews or interaction with the patient or family, and/or history from the family.

8. Establish and maintain alliances

It is important for the psychiatrist who is treating the patient with delirium to establish and maintain a supportive therapeutic stance. Understanding the underlying affect, concerns, and premorbid personality of the patient is frequently helpful in maintaining a supportive alliance. A solid alliance with the family is also desirable, as family members are a critical source of potential support for patients and information on patients who may be unable to give reliable histories. Establishing strong alliances with the multiple clinicians and caregivers frequently involved in the care of delirious medically ill patients is also crucial.

9. Educate patient and family regarding the illness

Educating patients and families regarding delirium, its etiology, and its course is an important role for psychiatrists involved in the care of patients with delirium. Patients may vary in their ability to appreciate their condition; however, providing reassurance that delirium is usually temporary and that the symptoms are part of a medical condition may be extremely beneficial to both patients and their families. Specific educational and supportive interventions are discussed in more detail in the following paragraphs.

Nursing staff make frequent observations of patients over time, which places them in an excellent position to detect the onset and monitor the course of delirium. Education of nursing staff on each shift regarding the clinical features and course of delirium can be an important task for psychiatrists.

Because of the behavioral problems accompanying delirium, there may be a tendency for some general medical physicians to overlook underlying general medical problems contributing to a patient's delirium and to consider the problem to be entirely in the realm of the psychiatrist. In such instances, providing education to other physicians regarding the underlying physiological etiologies of delirium may be an important task for the psychiatrist.

10. Provide postdelirium management

Following recovery, patients' memory for the experience and events of the delirium is variable. Some patients gradually or abruptly lose all apparent recall of the delirious experience, while others have vivid, frightening recollections. Explanations regarding delirium, its etiology, and its course should be reiterated. Supportive interventions that are a standard part of psychiatric management following a traumatic experience should be used for those with distressing postdelirium symptoms. Following recovery, all patients who have experienced delirium should be educated about the apparent cause of their delirium (when this could be identified) so that the patient, family, and subsequent physicians can be made aware of risk factors that may lead to delirium in the future. Psychotherapy focused on working through the experience of the delirium may, at times, be necessary to resolve anxiety, guilt, anger, depression, or other emotional states. These states may be compounded by the patient's preexisting psychological, social, or cultural characteristics.

▶ B. ENVIRONMENTAL AND SUPPORTIVE INTERVENTIONS

1. Environmental interventions

Management of delirium includes a specific array of interventions by nursing, psychological, general medical, and psychiatric staff that can be broadly categorized as environmental interventions. The general goals are to reduce environmental factors that exacerbate delirium, confusion, and misperception while providing familiarity and an optimal level of environmental stimulation. While there is no empirical evidence that the environment by itself causes delirium, certain environmental conditions may exacerbate delirium.

"Timelessness" in hospital intensive care units (ICUs) (i.e., a similar environment regardless of the time of day) appears to contribute to disorganization of sleep-wake cycles, which in turn aggravates fatigue and confusion. Some ICUs have introduced windows, while others change the lighting to cue night versus day. The ICU can be a very noisy environment, with beeps, alarms, pumps, respirators, overhead paging, resuscitation efforts, etc. The confused patient with delirium may become overstimulated by too much noise, and efforts should be made to reduce this whenever possible. On the other hand, understimulation from the environment may leave the patient with delirium undistracted from his or her own internal disorganized perceptions and thoughts; too quiet an environment may exacerbate delirium. It is important to provide a regular amount of modest stimulation (vocal, visual, tactile) to the patient with delirium.

Delirium can also be aggravated by sensory impairments, including visual impairment (53) and auditory impairment (54). By restoring a patient's glasses or hearing aid, one may substantially reduce the manifestations of delirium. Ensuring that there is an analog clock and a calendar that the patient can see will further facilitate orientation. Steps that render the environment more familiar and less alien, such as bringing in family photographs or favorite objects from home (e.g., stuffed animals) or actually having family members there when possible, are also helpful. Especially in a room that may be dark at night, night-lights can help reduce anxiety.

There is some empirical evidence that these environmental interventions can reduce the severity of delirium and improve outcomes (55–58). While there are no large, rigorous, randomized controlled trials, these environmental interventions are widely endorsed because of clinical experience and the lack of adverse effects. Although the value of environmental interventions is widely recognized, they remain substantially underutilized (59).

2. Structure and support for the patient

Nursing, psychological, general medical, and psychiatric staff and family members can also provide cognitive-emotional support designed to strengthen any retained adaptive cognitive functioning that the patient possesses. The goal of these interventions is to reduce anxiety and the unfamiliar while providing understanding and support.

Central to providing cognitive and emotional support are efforts to deal with disorientation. All who come in contact with the patient should provide reorientation, which entails reminding the patient in an unpressured manner of where he or she is, the date and time, and what is happening to him or her.

The patient's emotional reaction to symptoms of delirium can itself be a significant aggravating factor. The patient should be told that the symptoms are temporary and reversible and do not reflect a persistent psychiatric disorder. Similarly, the perception of cognitive deficits may lead patients to conclude that they have suffered brain damage. Unless the delirium is thought to be due to a major stroke or injury or to another event that may cause permanent brain injury, all who have contact with the patient should reassure her or him that these deficits are common and reversible symptoms associated with the particular illness, surgery, or other treatment.

There have been no large clinical trials examining the efficacy of cognitive and emotional support in delirium. However, as with environmental interventions, increased use of these currently underutilized supportive measures has been encouraged on the basis of clinical experience, common sense, and lack of adverse effects (59).

3. Support and education for the family

Educating patients' friends and family about delirium is extremely helpful since they may have the same worries as the patient (e.g., the patient has a permanent psychiatric illness or is brain damaged) and become frightened and demoralized instead of being hopeful and encouraging the patient (60).

It may be useful to recommend that family and friends spend time in the patient's room and bring familiar objects from home to help orient the patient and help him or her feel secure.

▶ C. SOMATIC INTERVENTIONS

The primary treatment of the symptoms of delirium is largely pharmacologic. The high-potency antipsychotic medication haloperidol is most frequently employed, although other pharmacologic and somatic interventions have been used in particular instances. Recently, there has been increased use of risperidone (61, 62). The available studies of the efficacy and other outcomes from use of these treatments for patients with delirium are reviewed in this section.

Several important points should be considered when evaluating the evidence for specific somatic interventions. While haloperidol has been the most studied pharmacologic treatment, few studies have used a standardized definition of delirium (e.g., based on DSM-IV criteria). In addition, few investigations have used reliable and valid delirium symptom rating measures to assess symptom severity before and after intervention.

For somatic treatments other than haloperidol, there have been no large, prospective trials or studies including a control group. Information regarding the efficacy of these treatments comes mainly from small case series or case reports; interpretation of the results from many of these case presentations is also made difficult by the use of nonstandardized definitions of delirium or informal measures of delirium symptom severity.

1. Antipsychotics

a) Goals and efficacy

Antipsychotics have been the medication of choice in the treatment of delirium. Evidence for their efficacy has come from numerous case reports and uncontrolled trials (63, 64). A series of controlled trials also showed that antipsychotic medications can be used to treat agitation and psychotic symptoms in medically ill and geriatric patient populations (65–69). However, most of these trials were not conducted with patients who had clearly or consistently defined delirium; in some studies, agitation and disorientation were the sole criteria and symptom assessments ranged from questionnaires to simple identification without symptom descriptions.

A randomized, double-blind, comparison trial by Breitbart et al. (70) identified delirium by using standardized clinical measures, and it demonstrated the clinical superiority of antipsychotic medications over benzodiazepines in delirium treatment. The Delirium Rating Scale, Mini-Mental State examination, and DSM-III-R were used to make the diagnosis in 244 hospitalized AIDS patients. The subjects were randomly assigned to one of three medications: chlorpromazine, haloperidol, and lorazepam. There were statistically significant decreases in scores on the Delirium Rating Scale after 2 days in the haloperidol and chlorpromazine groups but not in the lorazepam group (the mean decreases in scores were 8.0, 8.5, and 1.0, respectively). The improvement in delirium symptoms observed among those treated with antipsychotic medications occurred quickly, usually before the initiation of interventions directed at the medical etiologies of the delirium.

Droperidol, a butyrophenone with a rapid onset of action and relatively short half-life that is more sedating than haloperidol, has also been found to be an effective treatment for hospitalized patients with agitation, although not necessarily delirium (71). Results of two double-blind clinical trials comparing droperidol to haloperidol suggest that a more rapid response may be obtained with droperidol. Resnick and Burton (72) reported that 30 minutes after intramuscular injections, 81% of patients initially treated with 5 mg of haloperidol required a second injection, compared to only 36% of patients initially given 5 mg of droperidol. Thomas and colleagues (69), comparing 5 mg i.m. of droperidol to 5 mg i.m. of haloperidol, found significantly decreased combativeness among the droperidol treatment group after 10, 15, and 30 minutes. There has been very little study of the newer antipsychotic medications (risperidone, olanzapine, and quetiapine) in the treatment of delirium. Although there have been several case reports of use of risperidone for patients with delirium (61, 62, 73, 74), there have been no published clinical trials of any of the new antipsychotic medications for patients with delirium.

b) Side effects

Phenothiazines can be associated with sedation, anticholinergic effects, and α-adrenergic blocking effects that can cause hypotension; each of these side effects may complicate delirium. Butyrophenones, particularly haloperidol and droperidol, are considered the safest and most effective antipsychotics for delirium. Haloperidol, a high-potency dopamine-blocking agent with few or no anticholinergic side effects, minimal cardiovascular side effects, and no active metabolites, has generally been considered the antipsychotic medication of first choice in the treatment of delirium. High-potency antipsychotic medications also cause less sedation than the phenothiazines and therefore are less likely to exacerbate delirium. Although droperidol may have the advantages of a more rapid onset of action and a shorter half-life than haloperidol, droperidol is associated with greater sedation and hypotensive effects (75).

The use of antipsychotic medications can be associated with neurological side effects, including the development of extrapyramidal side effects, tardive dyskinesia, and neuroleptic malignant syndrome. However, there is some evidence to suggest that extrapyramidal side effects may be less severe when antipsychotic medications are administered intravenously (76). One case series involved 10 consecutive general medical inpatients receiving doses of oral or intravenous haloperidol at approximately 10 mg/day. Four patients were given intravenous medication, and six were given oral doses. Although delirium was not identified as the reason for treatment, five patients met diagnostic criteria by description. There was no significant difference in the incidence of akathisia, but the group receiving intravenous medication experienced less severe extrapyramidal symptoms. Neither method of administration resulted in acute dystonic reactions or changes in blood pressure or pulse rate (76).

Haloperidol used in the treatment of delirium has been found in some instances to lengthen the QT interval, which can lead to torsades de pointes, a form of polymorphic ventricular tachycardia that can degenerate to ventricular fibrillation and sudden death. Estimates of the incidence of torsades de pointes among patients with delirium treated with intravenous haloperidol have ranged from four out of 1,100 patients (77) to eight out of 223 patients (78). Although development of this serious event has been associated with higher intravenous doses (>35 mg/day) of haloperidol, it is important to note that torsades de pointes has also been reported with low-dose intravenous haloperidol and oral haloperidol as well (78, 79). Droperidol has also been associated with lengthening of the QT interval, and it may also be associated with torsades de pointes and sudden death.

Other side effects of antipsychotic medication use can rarely include lowering of the seizure threshold, galactorrhea, elevations in liver enzyme levels, inhibition of leukopoiesis, neuroleptic malignant syndrome, and withdrawal movement disorders.

c) Implementation

Although different antipsychotic medications can be given orally, intramuscularly, or intravenously, in emergency situations or when there is lack of oral access, intravenous administration may be most effective. In addition, as described in the preceding section on side effects, there is some evidence that antipsychotic medications may cause less severe extrapyramidal side effects when administered intravenously (76). Intravenous administration of haloperidol has not yet received approval by the Food and Drug Administration (FDA).

There have been few studies to determine the optimal doses of antipsychotic medications in the treatment of delirium. On the basis of doses used in several studies, starting haloperidol in the range of 1–2 mg every 2–4 hours as needed has been suggested (80). Low doses, for example as low as 0.25–0.50 mg of haloperidol every 4 hours as needed, have been suggested for elderly patients (81). On the other hand, severely agitated patients may require titration to higher doses. Bolus intravenous haloperidol doses exceeding 50 mg with total daily doses up to 500 mg have been reported, and they were associated with minimal effects on heart rate, respiratory rate, blood pressure, and pulmonary artery pressure and minimal extrapyramidal side effects (82, 83).

Several studies (75, 84) have examined the use of continuous intravenous infusions of haloperidol or droperidol among agitated medically ill patients who have required multiple bolus intravenous injections of antipsychotic medications. The results indicate that this means of administration can be safe and may help avoid some of the complications associated with repeated bolus dosing (e.g., hypotension). The authors of one study (84) recommended continuous infusion of haloperidol for patients who required more than eight 10-mg haloperidol boluses in 24 hours or more than 10 mg/hour for more than 5 consecutive hours. They suggested initiating haloperidol with a bolus dose of 10 mg followed by continuous infusion at 5–10 mg/hour.

Because antipsychotic medications used in the treatment of delirium have occasionally been found to lengthen the QT interval, possibly leading to torsades de pointes, ventricular fibrillation, and sudden death, recommendations for medication management include a baseline ECG with special attention paid to the length of the QTc interval. A prolongation of the QTc interval to greater than 450 msec or to greater than 25% over that in previous ECGs may warrant telemetry, a cardiology consultation, and dose reduction or discontinuation (85, 86). It has also been recommended that serum levels of magnesium and potassium be monitored in critically ill patients, especially those whose baseline QTc interval is 440 msec or longer, those who are receiving other drugs that increase the QT interval, or those who have electrolyte disturbances (87).

2. Benzodiazepines

a) Goals and efficacy

Few controlled studies have evaluated the efficacy of benzodiazepines as a monotherapy (i.e., not in combination with other pharmacotherapies) for the treatment of delirium. The limited data that are available suggest that benzodiazepine monotherapy may be ineffective as a treatment for general cases of delirium caused by a variety of etiologies. For example, the comparison by Breitbart et al. (70), described in Section III.C.1, indicated that lorazepam, given alone, was less effective as a treatment for delirium than either haloperidol or chlorpromazine.

Although there appears to be little evidence to support the use of benzodiazepines alone for general cases of delirium, there may be certain types of delirium for which benzodiazepines have advantages and are preferable. For example, benzodiazepines are the treatment of choice for delirium related to alcohol or benzodiazepine withdrawal. Other specific clinical circumstances in which benzodiazepines may be useful include instances when there is a need for a medication that can raise the seizure threshold (unlike antipsychotics, which lower the seizure threshold) or when anticholinergic side effects or akathisia associated with antipsychotics would seriously exacerbate a patient's condition.

There have been several reports of the combination of antipsychotics and benzodiazepines for the treatment of delirium, and the results indicate that this combination may decrease medication side effects and potentially increase clinical effectiveness in special populations, for example severely ill cancer patients or AIDS patients. Results of several open studies using intravenous haloperidol along with intravenous lorazepam suggest that the combined treatment is more efficacious, with a shorter duration of the delirium and fewer extrapyramidal symptoms, than intravenous haloperidol alone (16, 63, 88). Most of these studies defined delirium according to DSM criteria but did not use standardized assessment tools.

b) Side effects

The adverse effects of benzodiazepines on mental status have received some attention. Marcantonio et al. (89) demonstrated an association between benzodiazepine use and postoperative delirium in a prospective study of psychoactive medications given to patients admitted for elective noncardiac procedures. Long-acting benzodiazepines in particular posed problems. Benzodiazepines have been associated with sedation, behavioral disinhibition, amnesia, ataxia, respiratory depression, physical dependence, rebound insomnia, withdrawal reactions, and delirium. Geri-

atric populations are at greater risk for the development of these complications; children and adolescents may also be at increased risk for disinhibition reactions, emotional lability, increased anxiety, hallucinations, aggression, insomnia, euphoria, and incoordination (16, 90, 91).

Benzodiazepines are generally contraindicated in delirium from hepatic encephalopathy due to accumulation of glutamine, which is related chemically to γ-aminobutyric acid (GABA). Benzodiazepines should also be avoided, or used with caution, in patients with respiratory insufficiency. For patients who have hepatic insufficiency or are taking other medications metabolized by the cytochrome P450 system, benzodiazepines that are predominantly metabolized by glucuronidation (lorazepam, oxazepam, and temazepam) should be used when a benzodiazepine is required.

c) Implementation

When benzodiazepines are used, relatively short-acting medications with no active metabolites (e.g., lorazepam) should be selected.

Few studies have investigated the optimal dose of benzodiazepines for the treatment of delirium. However, the dose must be carefully considered, given the possibility that benzodiazepines may exacerbate symptoms of delirium. In cases of delirium due specifically to alcohol or sedative-hypnotic withdrawal, higher doses of benzodiazepines and benzodiazepines with longer half-lives may be required.

In a report of a case series of 20 critically ill cancer patients for which benzodiazepines and antipsychotics were administered together, Adams et al. (63) suggested that treatment be started with 3 mg i.v. of haloperidol followed immediately by 0.5–1.0 mg i.v. of lorazepam. Additional doses and the frequency are then titrated to the patient's degree of improvement. For example, Adams et al. stated that if little or no improvement is observed within 20 minutes, an additional dose of 5 mg i.v. of haloperidol and 0.5–2.0 mg i.v. of lorazepam can be given. In some cases of severe agitation, the eventual doses of both medications have been quite large (e.g., daily doses of lorazepam between 20 and 30 mg and of haloperidol between 100 and 150 mg).

3. Cholinergics

a) Goals and efficacy

Anticholinergic mechanisms have been implicated in the pathogenesis of many medication-induced deliriums. In addition, anticholinergic mechanisms may be involved in delirium from hypoxia, hypoglycemia, thiamine deficiency, traumatic brain injury, and stroke (49). However, cholinergic medications have been used in a very limited fashion to treat delirium, almost exclusively in cases of delirium clearly caused by anticholinergic medications. Physostigmine, a centrally active cholinesterase inhibitor, has been used most often, with tacrine and donepezil receiving less attention.

In one prospective study (92), physostigmine reversed delirium among 30 patients in a postanesthesia recovery room, in whom either atropine or scopolamine had caused the delirium. In four single case reports of delirium diagnosed by clinical interviews, physostigmine reversed the delirium resulting from ranitidine (93), homatropine eyedrops (94), benztropine (95), and meperidine (96).

In a single case study (97), tacrine reversed delirium induced by anticholinergic medication. Newer cholinesterase inhibitors with fewer side effects than tacrine have not been studied for treatment of delirium.

b) Side effects

Many side effects of cholinesterase inhibitors are caused by cholinergic excess; such effects include bradycardia, nausea, vomiting, salivation, and increased gastrointestinal acid. Physostigmine can cause seizures, particularly if intravenous administration is too rapid (98). Tacrine has

been associated with asymptomatic increases in liver enzyme levels. A threefold increase has been observed in approximately 30% of patients and is generally reversible with discontinuation of treatment; 5%–10% of patients develop more marked (e.g., tenfold) but still generally reversible increases in liver enzyme levels that warrant discontinuation of tacrine treatment (99).

c) Implementation

Physostigmine is usually administered parenterally. Doses that have been used in studies of delirium have included intravenous or intramuscular injections ranging from 0.16 to 2.00 mg and continuous intravenous infusions of 3 mg/hour (92–96).

In the single case study of tacrine used to reverse delirium induced by anticholinergic medication, 30 mg i.v. was used (97).

4. Vitamins

Certain vitamin deficiencies are commonly described as causing delirium. Consequently, one would expect such deliria to reverse at least to some extent with repletion of the deficient vitamin. Although this has not been subjected to rigorous trials, there are some case reports and case series supporting this effect. A malnourished hemodialysis patient with nicotinamide deficiency had a paranoid delirium that responded to parenteral nicotinamide, 500 mg/day (100). Bahr et al. (101) reported that of two chronic alcoholic patients with B vitamin deficiency, malnutrition, and central pontine myelinolysis, one improved quickly with intravenous vitamins. Thiamine deficiency delirium (DSM-III-R) was treated with vitamin B complex in six of 13 elderly medically ill patients, but only one patient had a dramatic response to treatment (102).

In one randomized controlled trial (103), 26 elderly patients undergoing orthopedic surgery received treatment with intravenous vitamins B and C preoperatively and postoperatively and were compared to 32 age-matched surgical control subjects who did not receive vitamins. There was no difference between the intervention and control groups in the incidence of postoperative confusion (39% versus 38%) or in the preoperative thiamine status as determined by serum assays.

In general, any patient with delirium who has a reason to be B vitamin deficient (e.g., alcoholic or malnourished) should be given multivitamin replacement.

5. Morphine and paralysis

Hypoxia, fatigue, and the metabolic consequences of overexertion all exacerbate delirium. Such hypercatabolic conditions are likely to accompany certain causes of agitated delirium (e.g., hyperdynamic heart failure, adult respiratory distress syndrome, hyperthyroid storm). For such patients and for any cases of agitated delirium unresponsive to other pharmacologic interventions, the patient may require a paralytic agent and mechanical ventilation. This improves oxygenation and reduces skeletal muscle exertion. The patient is usually heavily sedated. Morphine (or other opiate) is also an important palliative treatment in cases of delirium where pain is an aggravating factor (104). However, some opiates can exacerbate delirium, particularly through their metabolites, which possess anticholinergic activity (89). Among opiates, meperidine and fentanyl are particularly anticholinergic.

6. ECT

ECT has not been shown to be an effective treatment for general cases of delirium. Earlier case reports and case series had significant limitations: standardized diagnostic criteria and rating scales were not used; patients with schizophrenia, mania, postpartum psychosis, or psychotic depression were included and diagnosed with delirium because they had disorganized thinking and cognition; and few details concerning the manner in which ECT was performed were provided (105–111).

There is limited evidence for ECT as a treatment for particular cases of delirium due to specific etiologies. MEDLINE literature searches identified two case reports of ECT use for the delirium that is a component of neuroleptic malignant syndrome. In one study (112), the delirium symptoms improved in 24 of 29 patients with neuroleptic malignant syndrome who were treated with ECT. In the second study (113), 26 of 31 patients with neuroleptic malignant syndrome who were treated with ECT and hydration were described as having improved delirium symptoms. ECT has been studied in small samples of patients with delirium tremens. In one older study (109), 10 patients receiving ECT and conventional treatment had a shorter duration of delirium symptoms than 10 patients receiving conventional treatment alone (mean, 0.85 versus 2.8 days, respectively). In one case report (106), a patient with delirium tremens who had not responded to high-dose benzodiazepine treatment was described as recovering after ECT. In two case reports (114, 115), patients with protracted courses of delirium after traumatic brain injuries improved after receiving ECT. Because of the lack of compelling evidence, as well as the availability of alternative means of management, ECT is not presently used in the United States for treatment of delirium tremens.

In addition to the very limited evidence that ECT is an effective treatment for delirium, there may be considerable risks with ECT in medically unstable patients. For these reasons, ECT should be considered only rarely for patients with delirium due to specific etiologies such as neuroleptic malignant syndrome and should not be considered initially as a substitute for more conservative and conventional treatments. ECT itself may carry a risk of both postictal delirium (lasting minutes to hours) and interictal delirium (lasting days) after the procedure (116–120). Beyond that time period, ECT can also exacerbate cognitive deficits, such as memory impairment. Certain patient populations at higher risk for these adverse effects from ECT include patients with Parkinson's disease (particularly those taking carbidopa), Huntington's disease, or caudate or other basal ganglia strokes (119, 121–125).

IV. FORMULATION AND IMPLEMENTATION OF A TREATMENT PLAN

After the diagnosis of delirium is made (see Section II) a treatment plan is developed. The components of the treatment plan and factors that go into a psychiatrist's choice of treatment recommendations are discussed in this section. Although the treatment of delirium involves multiple modalities, certain components are essential and should be implemented with all patients. Other components of treatment may involve a choice between specific therapies, and this choice should be guided by a careful assessment of the patient's clinical condition, etiology, and comorbid conditions.

▶ A. PSYCHIATRIC MANAGEMENT

Psychiatric management is the cornerstone of successful treatment for delirium and should be implemented for all patients with delirium. The goals of psychiatric management are similar for all patients with delirium and involve facilitating the identification and treatment of underlying etiologies, improving patient functioning and comfort, and ensuring the safety of patients and others. The specific elements (see Section III.A) include coordinating care with other clinicians; ensuring that the etiology is identified; ensuring that interventions for acute conditions are initiated; ensuring that disorder-specific treatments are provided; monitoring and ensuring

safety; assessing and monitoring psychiatric status; establishing and maintaining supportive therapeutic alliances with patients, families, and other treaters; educating the patient and family regarding the illness; and postdelirium management.

▶ B. CHOICE OF SPECIFIC ENVIRONMENTAL AND SUPPORTIVE INTERVENTIONS

One aspect of the management of delirium involves environmental interventions and cognitive-emotional support provided by nursing, general medical, and psychiatric treaters. The general goals of environmental interventions are to remove factors that exacerbate delirium while providing familiarity and an optimal level of environmental stimulation; the general goals of supportive management include reorientation, reassurance, and education concerning delirium. Specific examples of environmental and supportive interventions are given in Section III.B. These interventions are recommended for all patients with delirium, on the basis of some formal evidence but mainly because of the value observed through clinical experience and the absence of adverse effects.

▶ C. CHOICE OF SOMATIC INTERVENTION

The specific features of a patient's clinical condition, the underlying cause(s) of the delirium, and associated conditions may be used by the psychiatrist to determine the choice of specific somatic therapy. Antipsychotic medications are the pharmacologic treatment of choice in most cases of delirium because of their efficacy in the treatment of psychotic symptoms. Haloperidol is most frequently used because of its short half-life, few or no anticholinergic side effects, no active metabolites, and lower likelihood of causing sedation. Haloperidol may be administered orally or intramuscularly, but it appears to cause fewer extrapyramidal side effects when administered intravenously. An optimal dose range for patients with delirium has not been determined. Initial doses of haloperidol in the range of 1–2 mg every 2–4 hours as needed have been used, and even lower starting doses (e.g., 0.25–0.50 mg every 4 hours as needed) are suggested for elderly patients. Titration to higher doses may be required for patients who continue to be agitated. Although total daily intravenous doses in the hundreds of milligrams have been given under closely monitored conditions, much lower doses usually suffice. Continuous intravenous infusions of antipsychotic medications can be used for patients who have required multiple bolus doses of antipsychotic medications. Initiating haloperidol with a bolus dose of 10 mg followed by continuous intravenous infusion of 5–10 mg/hour has been suggested. Droperidol, either alone or followed by haloperidol, can be considered for patients with delirium and acute agitation for whom a more rapid onset of action is required. The ECG should be monitored in patients receiving antipsychotic medications for delirium, and a QTc interval longer than 450 msec or more than 25% over baseline may warrant a cardiology consultation and consideration of discontinuation of the antipsychotic medication. The availability of new antipsychotic medications (risperidone, olanzapine, and quetiapine) with their different side effect profiles has led some physicians to use these agents for the treatment of delirium.

Benzodiazepines can exacerbate symptoms of delirium and, when used alone for general cases of delirium, have been shown to be ineffective. For these reasons, benzodiazepines as monotherapies are reserved for specific types of patients with delirium for which these medications may have particular advantages. For example, benzodiazepines are used most frequently to treat patients with delirium that has been caused by withdrawal of alcohol or benzodiazepines. When a benzodiazepine is used, medications such as lorazepam, which are relatively short-acting and have no active metabolites, are preferable. Combining a benzodiazepine with an antipsychotic medication can be considered for patients with delirium who can only tolerate

lower doses of antipsychotic medications or who have prominent anxiety or agitation. Combined treatment can be started with 3 mg i.v. of haloperidol followed immediately by 0.5–1.0 mg i.v. of lorazepam and then adjusted according to the patient's degree of improvement.

Other somatic interventions have been suggested for patients with delirium who have particular clinical conditions or specific underlying etiologies; however, few data are available regarding the efficacy of these interventions in treating delirium. There is some suggestion that cholinergics such as physostigmine and tacrine may be useful in delirium caused by anticholinergic medications. Agitated patients with delirium with hypercatabolic conditions (e.g., hyperdynamic heart failure, adult respiratory distress syndrome, hyperthyroid storm) may require paralysis and mechanical ventilation. For patients with delirium in whom pain is an aggravating factor, palliative treatment with an opiate such as morphine is recommended. ECT may be a treatment consideration in a few cases of delirium due to a specific etiology such as neuroleptic malignant syndrome; any potential benefit of ECT should be weighed against the risks of ECT for patients who are often medically unstable. Any patient with delirium with a reason to be deficient in B vitamins (e.g., alcoholic or malnourished) should be given multivitamin replacement.

▶ D. ISSUES OF COMPETENCY AND CONSENT

Decisions regarding the care of patients with delirium are often complex because of risks associated with treatments, and these decisions frequently have to be made quickly because of the seriousness of the underlying general medical conditions. Unfortunately, delirium intermittently affects consciousness, attention, and cognition and can impair a patient's decisional capacity (i.e., the ability to make decisions as determined by a clinician's evaluation) or competence (i.e., the ability to make decisions as determined by a court of law) (126, 127).

The presence or diagnosis of delirium does not in itself mean that a patient is incompetent or lacks capacity to give informed consent (128). Instead, a determination of decisional capacity or competence to give informed consent involves formal assessment of a patient's understanding about the proposed intervention (including the intervention's risks, benefits, and alternatives) and the consequences of the decisions to be made.

Decision-making guidelines have been suggested for patients with delirium who lack decisional capacity or competence to give informed consent (129). The urgency with which treatment is needed and the risks and benefits of treatments can be used by the treating physician to choose between several alternative courses of action. In medical emergencies requiring prompt intervention, the first alternative is to treat the patient with delirium without informed consent, under the common-law doctrine of implied consent (i.e., that treatment may be provided in medical emergencies without informed consent if it is appropriate treatment that a reasonable person would want). In nonemergency situations, the clinician should obtain input or consent from surrogates. Involving interested family members can be especially helpful for choosing among equally beneficial interventions that involve low or moderate risks. The opinion of a second clinician can be useful for making decisions involving more uncertainty or interventions associated with greater risks. Obtaining the consultation of a hospital's administrator, risk manager, or legal counsel may also provide a means for reassuring family members and the treatment team that reasonable decisions are being made. For decisions that involve significant risks or substantial disagreements involving family members, a court-appointed guardian can be sought if time permits. In more emergent cases, an urgent hearing with a judge may be required. All assessments of a patient's decisional capacity or competence and the reasons for a particular course of action should be documented in the patient's medical record.

V. CLINICAL FEATURES INFLUENCING TREATMENT

▶ ## A. COMORBID PSYCHIATRIC DISORDERS

Delirium is often misdiagnosed as depression or dementia. These disorders can be diagnosed during a delirium only when the patient's history reveals symptoms that clearly existed before the delirium onset. When delirium is comorbid with other psychiatric disorders, the delirium should be treated first and the treatments for these other disorders, such as antidepressant or anxiolytic medications, should be minimized or not begun until the delirium is resolved. Medications for psychiatric disorders can both be the cause of delirium and exacerbate or contribute to delirium from other causes.

▶ ## B. COMORBID GENERAL MEDICAL CONDITIONS

1. AIDS/HIV

Approximately 30%–40% of hospitalized AIDS patients develop delirium (6, 16, 70). Early reports concerning the increased sensitivity of AIDS patients to the extrapyramidal side effects of dopamine-blocking antipsychotic drugs have made clinicians cautious in using high doses of antipsychotics, such as haloperidol (130, 131). At lower doses, antipsychotics such as haloperidol and chlorpromazine have been demonstrated to be safe and effective with minimal extrapyramidal side effects (70).

2. Liver disease

The liver is the body's detoxifying organ for drugs and other molecules. Hepatic insufficiency significantly affects the metabolism of many medications. Most psychotropic medications undergo hepatic transformation. In addition, the liver produces albumin and other plasma proteins that transport bound medications in the bloodstream. When these protein levels decrease because of liver dysfunction, unbound medications can enter tissues at an accelerated rate—including crossing the blood-brain barrier—and can also be more available for catabolism or excretion. Thus, the former effect may alter therapeutic effects or cause side effects, while the latter may result in less therapeutic effect than expected at a given dose.

Haloperidol undergoes metabolism by the P450 2D6 enzyme system, which reduces it to reduced haloperidol. The latter is in equilibrium with the parent drug. In addition, glucuronidation is an important route of metabolism of haloperidol (132). This suggests that its pharmacokinetics in patients with liver insufficiency would be similar to those in other patients when used to treat delirium.

On the other hand, many benzodiazepines require oxidation by the liver. The exceptions are lorazepam, temazepam, and oxazepam, which require only glucuronidation. It is therefore preferred that benzodiazepines requiring only glucuronidation be used to treat delirium secondary to sedative-hypnotic or alcohol withdrawal in patients who have liver insufficiency. Of these, lorazepam is usually chosen because it is well absorbed when given orally, intramuscularly, or intravenously.

▶ ## C. ADVANCED AGE

The elderly are particularly vulnerable to delirium due to changes in brain function, multiple general medical problems, polypharmacy, reduced hepatic metabolism of medications, multi-

sensory declines, and brain disorders such as dementia. Conducting a careful medical evaluation that includes particular attention to a patient's level of oxygenation, possible occult infection (e.g., urinary tract infection), and the possible role of medications is an essential initial approach to the management of delirium in the elderly. Medications with anticholinergic effects are often the culprit; however, even medications not generally recognized as possessing anticholinergic effects (e.g., meperidine, digoxin, and ranitidine) can be responsible (133–135). Nursing home patients are at particular risk of delirium.

Low doses of antipsychotic medication usually suffice in treating delirium in elderly patients, for example, beginning with 0.5 mg haloperidol once or twice a day. The benefits of restraints may be greater for elderly patients than for younger patients because of the greater risk of falls and hip fractures in older populations; hip and other fractures often carry a grim prognosis for elderly patients, who may never return to independent functioning. On the other hand, the risks associated with restraints may be greater among the elderly, and other means to prevent falls should be considered if possible. When extrapyramidal side effects occur early in the treatment of delirium, Lewy body dementia should be considered in the differential diagnosis.

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Society of Adolescent Medicine
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VII. REFERENCES

The following coding system is used to indicate the nature of the supporting evidence in the references:

[A] *Randomized clinical trial.* A study of an intervention in which subjects are prospectively followed over time; there are treatment and control groups; subjects are randomly assigned to the two groups; both the subjects and the investigators are blind to the assignments.

[B] *Clinical trial.* A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally; study does not meet standards for a randomized clinical trial.

[C] *Cohort or longitudinal study.* A study in which subjects are prospectively followed over time without any specific intervention.

[D] *Case-control study.* A study in which a group of patients and a group of control subjects are identified in the present and information about them is pursued retrospectively or backward in time.

[E] *Review with secondary data analysis.* A structured analytic review of existing data (e.g., a meta-analysis or a decision analysis).

[F] *Review.* A qualitative review and discussion of previously published literature without a quantitative synthesis of the data.

[G] *Other.* Textbooks, expert opinion, case reports, and other reports not included above.

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