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Delirium in Elderly Patients

Delirium is a mental disorder characterized by disturbances in consciousness, orientation, memory, thought, perception, and behavior, of acute onset and fluctuating course. It occurs in hyperactive, hypoactive, or mixed forms, in up to 50% of elderly hospital inpatients, many with pre-existing dementia, and appears to be independently associated with significant increases in functional disability, length of hospital stay, rates of admission to long-term care institutions, rates of death, and healthcare costs. Despite its clinical importance, delirium is often not detected or it is misdiagnosed as dementia or other psychiatric illness even though there are potential strategies (e.g., screening by nurses, risk-factor assessment) and instruments that can improve detection and diagnosis. Although there has been limited progress in understanding the etiology, pathogenesis, assessment, and specific treatment of delirium, systematic detection and treatment programs appear to be beneficial for elderly surgical patients, as are preventive programs for elderly medical and surgical patients. Even now, there is probably enough evidence to recommend implementation of these two types of programs in acute-care hospitals.

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Delirium, one of the oldest disorders known to medicine, was well described 2,500 years ago in the medical writings of Hippocrates (1). It is characterized by disturbances in consciousness, orientation, memory, thought, perception, and behavior, of acute onset and fluctuating course (2–4). It occurs in hyperactive, hypoactive, or mixed forms in up to 50% of elderly hospitalized patients (5), many with pre-existing dementia (6), and is independently associated with poor outcomes (7–18). Despite its clinical importance, delirium is often not detected (19, 20), or it is misdiagnosed as dementia or other psychiatric illness, such as depression (21).

Clinical features

Acute Onset

The symptoms of delirium usually develop over hours-to-days, although onset may be abrupt.

Prodromal phase

When the onset is more gradual, the patient may report mild, transient symptoms, such as fatigue, decreased concentration, irritability, restlessness, anxiety, or depression. There may be mild cognitive impairment, perceptual disturbances, or hypersensitivity to light and sound. Commonly, there is daytime somnolence or a sleep disturbance. The disturbance may be limited to this mild prodromal phase or progress to a more florid picture.

Disorders of sleep and wakefulness

Delirium may first appear at night with fragmentation and reduction of sleep. Patients may wake from vivid dreams or nightmares in a disoriented or agitated state. They may describe their somnolent daytime experiences as "dreamlike," feeling they hover between sleep and wakefulness and have trouble distinguishing dreams from real perceptions.

Disturbance of consciousness

Although clouding of consciousness is purported to be a cardinal feature of delirium, it is difficult to define. Jaspers (22) distinguished two principal types of disturbed consciousness: 1) reduced consciousness (ranging between consciousness and unconsciousness); 2) clouded consciousness, with fragmentation of psychic experience and hallucinations. In DSM-IV (2), it is defined as reduced clarity of awareness, with reduced ability to focus, sustain, or shift atten-

tion. Traditionally, clinicians have relied on stimulus-response models of assessment of consciousness. For example, the patient may be hyperalert (overly sensitive to stimuli, easily startled), alert (normal), lethargic (drowsy, but easily aroused) or comatose (unarousable). The Glasgow Coma Scale (23) may be used to quantify level of consciousness.

INATTENTION

There is reduced ability to focus, sustain, or shift attention to external stimuli that may account for all other cognitive deficits. Distractibility and diminished concentration follow from inability to focus or sustain attention. Difficulties in selective attention enable external stimuli such as sounds, lights, or movements to interfere with cognitive processes. When attention shifts rapidly and unintentionally, registration of new information is impaired, leading to disorientation and memory deficits.

DISORDERS OF THOUGHT

Abnormalities in the form and content of thinking are prominent. The organization and utilization of information are impaired. Spontaneously, or in response to open-ended questions, thinking may become illogical or bizarre. The patient may be unable to make appropriate decisions, perform simple tasks, or maintain self-care. Judgment and insight may be poor.

The content of thought may be impoverished and stereotyped or abound with rich imagery and fantasies. Abstract thinking is often diminished. Delusions of persecution are prominent.

DISORDERS OF LANGUAGE

Language functions are often abnormal. Speech may be tangential, circumstantial, poorly organized, slowed, or slurred, with word-finding difficulties and paraphasias. We may also see poorly drawn and spatially aligned letters, syntactical and spelling errors, or reluctance to write.

IMPAIRMENT OF MEMORY AND ORIENTATION

There are disturbances of registration and recent and remote memory. Confabulation occurs in 8% to 15% of patients and most often concerns activities or discussions with friends that never took place. There may be a tendency to mistake the unfamiliar for the familiar. In severe cases, patients may not appreciate whether they are standing up or lying down, indoors or outdoors, dressed or undressed. Disorientation is most commonly manifested by mistakes in time, place, and sometimes person (24).

PERCEPTUAL DISTURBANCES

Beyond the hypersensitivity to sensory stimuli in the prodromal phase, perceptual abnormalities may extend to distortions, illusions, or frank hallucinations. Distortions, may include changes in size of objects (macropsia, micropsia), or in the shape, position, or motion of stationary objects, and derealization, depersonalization, and distortion of body image may also occur.

Illusions—misinterpretations of external sensory stimuli—may include mistaking a sound in the hall for a gunshot or seeing spots on the floor as crawling insects. Visual hallucinations, often occurring only at night, are common and range from simple shapes, lights, or colors to complex objects, insects, animals, ghost-like forms, or people. Auditory hallucinations are represented by simple sounds, music, or voices; tactile hallucinations are less common and may involve sensations of crawling insects, paresthesias, or pain. It must be stressed that delirious patients may perceive their hallucinations as real and respond in ways that may be disturbing to others or even life-threatening.

PSYCHOMOTOR DISTURBANCES

Three clinical variants of psychomotor behavior include hyperactive, hypoactive, and mixed forms. Hyperactive delirium, characterized by agitation, autonomic arousal, diaphoresis, tachycardia, dilated pupils, dry mouth, and tremor, occurs in 15%–21% of patients (11, 14, 25, 26). Hypoactive delirium, which may escape diagnosis because of its silent or passive presentation, occurs in 19%–71% of patients (11, 14, 25, 26). Mixed forms may occur in 43%–56% of patients (11, 14, 25). A small proportion (4%–14%) have no psychomotor disturbances (11, 14, 25). Some patients may present with falls or urinary or fecal incontinence.

Behavioral problems may be dangerous. Agitated patients run the risk of hip fractures or cardiovascular collapse. Homocidal or suicidal behavior may result from hallucinations or delusions. Hypoactive patients are also at risk for dehydration, malnourishment, or pressure sores.

EMOTIONAL DISTURBANCES

Fear, anxiety, and depression are very common symptoms of delirium. These symptoms are multidetermined, often influenced by the nature of the medical or surgical disorder, personality, premorbid

Table 1. DSM-IV Diagnostic Criteria for Delirium

1. Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain, or shift attention.
2. 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.
3. The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
4. There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

psychiatric disorder, current interpersonal relationships, and recent life events.

FLUCTUATION

Patients with delirium not only show a wide variation in the type and severity of symptoms, but unpredictable fluctuations. Symptoms may be intermittent and are often worse at night. During "lucid intervals," the patient may function at a normal level. These fluctuations may be observable during the course of a single clinical interview or over the course of 1 or more days (for example, in the morning a patient may be lucid, but in the evening, agitated and disoriented).

DIAGNOSIS

The clinical diagnosis is based on history from collateral sources (family members, caregivers, etc.) and bedside observations. DSM-IV criteria, presented in Table 1, appear to be the most inclusive set of criteria among elderly patients, compared with DSM-III, DSM-III-R, or ICD-10 criteria (27). Notably, different types of healthcare professionals can make an accurate diagnosis of delirium by use of structured instruments (28, 29). In one study, a nurse-clinician's diagnosis had a sensitivity of 89% and a specificity of 100%, compared with a consensus diagnosis involving the nurse and three psychiatrists (30). Three valid and reliable diagnostic instruments include the Confusion Assessment Method (29) the Delirium Rating Scale–Revised-98 (31) and the Delirium Symptom Interview (32). The first two instruments are easy to use in most clinical settings.

In practice, however, healthcare professionals often fail to detect and diagnose delirium (19, 20). There are two principal reasons for this: First, they expect delirium to present with agitation and hallucinations; but, in older patients, it often presents with decreased activity (the hypoactive form of delirium), which is overlooked. Second, the fluctuating nature of delirium may confound the diagnosis because healthcare professionals may fail to appreciate lucid intervals as characteristic of the disorder. Moreover, fluctuating manifestations may make delirium difficult for physicians to detect when they spend only a brief time with the patient. Nurses, who have contact with patients over the course of the day, typically document most confusional episodes (33, 34).

These two observations suggest strategies for improving detection and diagnosis. First, because cognitive dysfunction is often not apparent, the Short Portable Mental Status Questionnaire (35) or the Mini-Mental State Exam (36) should be used routinely to assess mental status; family members or caregivers who are capable of describing the patient's usual cognition and behavior should be interviewed. Second, nursing notes should be reviewed for symptoms, or nurses should be encouraged to document symptoms by use of reliable and valid instruments (37).

DIFFERENTIAL DIAGNOSIS

Delirium may be confused with dementia or functional psychiatric disorders. Clinical features that may be useful in distinguishing delirium from Alzheimer or Lewy-body dementia are presented in Table 2. One of the most challenging situations for the clinician is the dementia patient presenting with a sudden change in cognition or behavior. Many of these patients will prove to have a superimposed delirium. Notably, delirium is phenomenologically similar in patients with or without dementia (although patients with dementia have more symptoms) (38) and DSM-IV criteria are equally useful in diagnosing delirium in patients with or without dementia (27). However, rapid change in patients with dementia may be due to other psychiatric illness (e.g., delusional or depressive disorders) or reactions to stressful situations (such as pain, unfamiliar environment). Differentiating these possibilities is difficult when the patient is unable to provide an accurate history or cooperate with the examination. A reasonable approach is to assume that the new cognitive or behavioral problems are due to delirium until a thorough search rules out drug toxicity or medical illness.

Delirium is misdiagnosed as depression in up to 40% of cases (21). Agitated depression may present with cognitive disturbances, delusions, poor concentration, and fitful sleep; retarded depression

Table 2. Delirium Versus Alzheimer and Lewy Body Dementia

Clinical Features	Delirium	Alzheimer Dementia	Lewy Body Dementia
Onset	Acute	Insidious	Insidious
Duration of present illness	Hours, days	Months, years	Months, years
Consciousness	Hyperalert, alert, or hypoalert	Alert	Usually alert
Cognitive fluctuation	Frequent	Infrequent	Frequent (often minute-to-minute)
Symptom fluctuation	Frequent	Infrequent	Infrequent
Orientation	Impaired	Impaired	Impaired
Memory	Impaired (registration, recent, and remote)	Impaired (recent and, later, remote)	Impaired
Attention	Impaired	Intact	Frequent impairment
Visual hallucinations	Frequent, simple, or complex; transient	Occasional	Frequent, complex, and persistent
Thinking	Disorganized; delusions of persecution	Impoverished; delusions of persecution	Impoverished; delusions of persecution
Insight	May be present in lucid intervals	Usually absent	Usually absent
Sleep	Usually disturbed	Usually normal	—
Parkinsonism	Usually absent	Occasional	Frequent
Neuroleptic sensitivity	Infrequent	Infrequent	Frequent
Electroencephalogram	Marked slowing	Usually normal or mild slowing	—

may mimic hypoactive delirium, with slowed thinking, decreased concentration, and memory impairment. Depression, however, usually has a history of previous episodes, no fluctuations, and predominance of depressive feelings. Mania can simulate hyperactive delirium, with diminished attention, agitation, rapid fluctuations, and psychosis. However, there is usually a history of previous episodes and euphoria/irritability. In both depression and mania, the electroencephalogram (EEG) should be normal.

Schizophrenia may present with bewilderment, perceptual disturbances, and attention and memory impairments. However, schizophrenia is a long-standing illness, typically with an insidious onset. The sensorium is usually clear. Delusions tend to be highly systematized, bizarre, and uninfluenced by the environment. Delusions in delirium are usually poorly systematized, fleeting, and related to environmental stimuli.

PREVALENCE AND INCIDENCE

Delirium is a common disorder in elderly patients. At the time of admission to medical wards, between 15% and 20% of older patients meet criteria for delirium-prevalent cases (5, 12, 39–42). Most of these studies report a subsequent incidence during hospitalization (among patients free of delirium at admission) of 5% to 10%, although higher rates (20%–30%) have been reported (42). Delirium has been reported in 10%–15% of general-surgical patients, 30% of open-heart surgery patients, and over 50% of patients treated for hip fractures (5, 43–47). Studies among elderly emergency room (48–50) or community (51) subjects have reported prevalence rates of 5%–10% and 1%–2%, respectively.

RISK FACTORS

Despite the methodological limitations of most studies (retrospective, small sample size, mixing of prevalent and incident cases, no adjustment for confounding factors), consistent risk factors for delirium have been identified. Dementia is the strongest risk factor; 25% to 75% of patients with delirium have dementia (6), and the presence of dementia increases the risk of delirium by fivefold (52). Risk of delirium appears to be higher in patients with severe medical illness, comorbid psychiatric disorder, impaired physical functioning, male gender, abnormal

sodium levels, and hearing or vision impairment (52). Environmental factors, such as number of room changes and absence of a clock, watch, or reading glasses may also increase risk (53).

Nearly every class of drugs has the potential to cause delirium. The most important are anticholinergic drugs, sedative-hypnotics and narcotics. Susceptibility to these agents may depend on the presence of dementia or type and severity of medical illness, but a study of the relationship between anticholinergic drugs and severity of delirium symptoms reported no interaction with dementia (54).

Factors that increase the risk of delirium in surgical patients include dementia, low cardiac output, perioperative hypotension, postoperative hypoxia, and use of anticholinergic drugs (5, 43–47). Type of anesthetic (general versus local) does not appear to increase risk (55–57).

ETIOLOGY

The etiology of delirium is unknown, but is probably complex and multifactorial, involving the interaction of precipitating factors superimposed on a vulnerable patient with predisposing conditions.

PATHOGENESIS

The pathogenesis of delirium remains obscure. A structural brain lesion has not been identified, and neuroimaging studies have yet to show convincing results. Consequently, current knowledge of pathogenesis is based on evidence from electrophysiological and biochemical studies.

The EEG shows a diffuse slowing of cortical background activity and the appearance of delta and theta activity that correlates with degree of cognitive impairment, but is nonspecific in terms of underlying illness (58). Using experimental interventions (e.g., providing oxygen to hypoxic patients), the clinical and EEG manifestations of delirium can be reversed, demonstrating that one mechanism for delirium may be failure of cerebral oxidative metabolism (59).

Spectral analysis has confirmed the correlation between EEG slowing and cognitive impairment (60). Both quiet and hyperactive variants of delirium show similar patterns of EEG change. A notable exception, however, is delirium due to sedative drug or alcohol withdrawal, in which the EEG may appear normal or show low-voltage and relatively fast dysrhythmia. Studies using somatosensory, visual, and brainstem auditory evoked potentials in hepatic encephalopathy have demonstrated increased latency of characteristic waveforms, reflecting altered brainstem functioning (61, 62).

There is some evidence that delirium may be mediated by a failure of cholinergic transmission. Anticholinergic intoxication, which produces the behavioral and EEG manifestations of delirium, can be reversed with cholinesterase inhibitors (63, 64). Hypoxia or hypoglycemia decrease synthesis of acetylcholine (65). Serum anticholinergic activity is associated with delirium in medical (66, 67) and postoperative patients (68) and patients undergoing electroconvulsive therapy (69). Serum anticholinergic activity is associated with cognitive impairment in community subjects (70). Finally, anticholinergic drug scores correlate with severity of delirium symptoms (54).

Delirium may be due to the central nervous system effects of lymphokines. Clinical and EEG manifestations of delirium have been described in patients receiving alpha interferon (71, 72). Delirium occurred in half of patients treated with interleukin-2 and lymphokine-activated killer cells for advanced cancer; these effects were dose-related and cleared after stopping therapy (73). Other molecules (dopamine, noradrenaline, glutamate, serotonin, alpha-aminobutyric acid, tryptophan, cortisol and beta-endorphin, somatostatin, and phenylalanine metabolites) have been implicated, but the evidence is weak (74–79).

PROGNOSIS

Delirium in elderly patients has a poor prognosis. It is independently associated with significant increases in functional disability (7–9), length of hospital stay (10–14), rates of admission to long-term care institutions (7, 9, 10, 13) and rates of death (10, 12, 15). In 19 studies (7, 11–16, 41, 47, 56, 80–88), mean lengths of hospital stay were 8 to 32 days (median: 20 days); institutionalization rates at 1 and 6 months were 8% to 82% and 12% to 65%, respectively (median rates were 44% and 36%, respectively); mortality rates at 1 and 6 months were 0–65% and 14%–36%, respectively (median rates were 16% and 26%, respectively); rates of improvement in mental status at 1 month were 46% to 100% (median: 80%). Many patients still had symptoms of delirium 6 months later (83, 89). Across studies, only two characteristics were significantly related to outcomes. Admission from home was related to a higher rate of improvement in mental status at 1 month, and admission to a surgical unit was related to a lower mortality rate at 1 month. These results suggest that better premorbid functioning may be related to better outcomes. Age, frequency of dementia, patient

selection criteria, cause(s) of delirium, and length of follow-up were not related to outcomes. Quicker in-hospital recovery may be associated with better long-term outcomes (89).

ASSESSMENT

The medical assessment of delirium is not evidenced-based. At present, it involves a careful history and physical examination to search for conditions predisposing to, precipitating, or perpetuating the delirium (putative causes). Table 3 presents the most common conditions. The most important problems are medication toxicity, cardiorespiratory and neurologic disorders, and infections.

The history should establish the course of the mental status change and identify potential predisposing, precipitating, or perpetuating factors, such as recent medication changes or signs of medical illnesses. The physical examination should be comprehensive and should include a careful search for cardiorespiratory, neurologic, and infectious disorders.

Because medications contribute to up to 40% of cases of delirium (12, 13, 86), a review of current medications (including over-the-counter medications), particularly psychotropic, narcotic, and anticholinergic medications, is necessary. Other commonly prescribed drugs (e.g., digoxin, furosemide, cimetidine, prednisone) are reported to have anticholinergic properties (90), and should be examined closely. The potential interactions of all medications should be reviewed. The possibility of alcohol or sedative drug withdrawal should be considered even when autonomic signs are attenuated or absent.

The above assessment will probably identify most putative causes. Some authorities recommend a wide spectrum of routine testing, but a limited number of diagnostic studies (complete blood count, electrolytes, creatinine, urinalysis) will probably suffice for most patients. Other laboratory tests (e.g., glucose, calcium, phosphate, liver function tests, etc.) or a search for occult infection (e.g., chest radiography, selected cultures) may be indicated if the initial evaluation has not identified a putative cause. Notably, a putative cause may not be identified in 15% to 25% of patients (13, 91).

A controversial area involves determining which patients should have cerebrospinal (CSF) fluid examination, EEG, or brain imaging. Clearly, CSF examination should be carried out in the febrile patient whenever meningitis is suspected. In the afebrile patient, CSF examination has been advocated when no cause of delirium can be found, but the clinical yield is low (92).

The EEG appears to be useful in the diagnosis of delirium. In one study, the characteristic EEG findings had a false-positive rate of 17% and a false-negative rate of 22% in differentiating "delirious" and nondelirious subjects (93).

The role of brain imaging is uncertain. In one study, delirium patients who fell into a high-risk group (e.g., severe illness, dementia, fever, renal impairment, or psychoactive drug use) and who had no new focal neurologic signs, were unlikely to have important findings on brain computed tomography (CT) scans (94). In another study, patients with delirium had a high frequency of abnormalities judged not to contribute to the delirium (95).

Some investigators have advocated use of the physostigmine challenge test (96). Rapid improvement in mental status in response to a test dose of 1 mg to 2 mg of parenteral physostigmine is considered diagnostic of anticholinergic intoxication. However, the safety and validity of this procedure have not been evaluated in elderly patients, where the etiology of delirium is often multifactorial.

Finally, assessment should include a measure of delirium symptom severity in order to monitor course and outcome. Five reliable and valid measures include: the Delirium Assessment Scale (97), the Memorial Delirium Assessment Scale (98), the Confusional State Evaluation (99), the Delirium Rating Scale–Revised-98 (31), and the Delirium Index (100).

TREATMENT

The treatment of delirium is based on clinical experience, case reports, review articles, and clinical practice guidelines (101, 102). There are surprisingly few original studies. The mainstay of treatment remains the diagnosis and treatment of the conditions predisposing to, precipitating, or perpetuating the delirium. Medications, particularly psychotropic, narcotic, and anticholinergic medications, should be reduced or discontinued whenever possible. Physical illnesses should be treated promptly. Also, supportive care and certain pharmacologic and nonpharmacologic measures may be useful.

SUPPORTIVE CARE

Supportive care is necessary while diagnosis and treatment of the putative cause(s) takes place. This care includes attention to oral intake, mobility, and psychosocial needs, and prevention of aspiration, falls, and decubitus ulcers. It is important to remember that delirium can be a distressing experience for both patients and caregivers (103).

Table 3. Putative Causes of Delirium

- Medications
  - Psychotropics (anxiolytics, sedative-hypnotics, barbiturates, antidepressants, antipsychotics, lithium)
  - Anticonvulsants
  - Analgesics
  - Anticholinergics (antihistamines, antispasmodics, antiparkinsonian agents)
  - Antiarrhythmics
  - Antihypertensives
  - Aminoglycoside antibiotics
  - Miscellaneous (cimetidine, steroids, nonsteroidal anti-inflammatory drugs, salicylates)
- Drugs of abuse (phencyclidine and hallucinogenic agents)
- Alcohol
- Poisons (heavy metals, organic solvents, methyl alcohol, ethylene glycol, insecticides, carbon monoxide)
- Withdrawal syndromes
  - Alcohol
  - Sedatives and hypnotics
- Cardiovascular
  - Congestive heart failure
  - Cardiac arrhythmia
  - Myocardial infarction
- Neurologic
  - Head trauma
  - Space-occupying lesions: tumor, subdural hematoma, abscess, aneurysm
  - Cerebrovascular diseases: thrombosis, embolism, arteritis, hemorrhage, hypertensive encephalopathy
  - Degenerative disorders: Alzheimer disease, multiple sclerosis
  - Epilepsy
- Infection
  - Intracranial: encephalitis and meningitis (viral, bacterial, fungal, protozoal)
  - Systemic: pneumonia, septicemia, subacute bacterial endocarditis, influenza, typhoid, typhus, infectious mononucleosis, infectious hepatitis, acute rheumatic fever, malaria, mumps, diphtheria, AIDS
- Metabolic
  - Hypoxia
  - Hypoglycemia
  - Acid-base imbalance: acidosis, alkalosis
  - Electrolyte imbalance: elevated or decreased sodium, potassium, calcium, magnesium
  - Water imbalance: inappropriate antidiuretic hormone, water intoxication, dehydration
  - Failure of vital organs: liver, kidney, lung
  - Inborn errors of metabolism: porphyria, Wilson disease, carcinoid syndrome
  - Remote effects of carcinoma
  - Vitamin deficiency: thiamine (Wernicke encephalopathy), nicotinic acid, folate, cyanocobalamin
- Endocrine
  - Thyroid: thyrotoxicosis, myxedema
  - Parathyroid: hypo- and hyperparathyroidism
  - Adrenal: Addison disease, Cushing syndrome
  - Pancreas: hyperinsulinism, diabetes
  - Pituitary hypofunction
- Hematologic
  - Pernicious anemia
  - Bleeding diatheses
  - Polycythemia
- Hypersensitivity
  - Serum sickness
  - Food allergy
- Physical injury
  - Heat: hyperthermia, hypothermia
  - Electrocution
  - Burns

PHARMACOLOGIC MEASURES

Occasionally, the delirium patient is so symptomatic that prompt pharmacologic control is vital. Antipsychotic drugs should be given in the lowest possible doses for the shortest possible time. Because many delirium patients are critically ill, these agents should be available in a parenteral form and have few cardiorespiratory effects.

There is little evidence that one antipsychotic is more effective than another, but high-potency agents such as haloperidol are useful because they have less sedative, anticholinergic, and hypotensive effects (107). An initial dose of 0.5 mg may be adequate. Onset of action occurs in 10–30 minutes, so doses should be given at intervals of no less than 20 or 30 minutes. Occasionally, rapid loading may be needed, involving doubling each successive dose at 30-minute intervals until agitation is controlled.

The use of CNS-depressant drugs (e.g., benzodiazepines, barbiturates) to control symptoms should be avoided because they may worsen delirium. However, in alcohol- and sedative hypnotic-withdrawal delirium, tapering doses of chlordiazepoxide 25 mg–50 mg every 6 hours or diazepam 2 mg–5 mg every 12 hours (with or without haloperidol) are frequently used to control symptoms and prevent seizures.

NONPHARMACOLOGIC MEASURES

There is limited evidence that nonpharmacologic measures (interpersonal contact, environmental manipulations) reduce symptoms. Nonetheless, nursing interventions (e.g., reducing noise; providing soft lighting, clocks, and calendars; orienting the patient to time and place; correcting sensory deficits with eyeglasses and hearing aids; increasing the patient's sense of control) may reduce symptoms (101, 102, 104, 105). Eye contact, frequent touching, and verbal orientation from family members may lessen behavioral disturbances (101, 102, 106). Room changes should be minimized.

Restraints are often used for agitated patients despite their potential to cause harm. A useful alternative may be constant observation by sitters or family members.

SYSTEMATIC DETECTION AND TREATMENT

Systematic detection and treatment of delirium in hospital settings may improve outcomes. The results of the nine studies discussed are summarized in Table 4 (91, 105, 108–114). Most of the interventions evaluated the effectiveness of the early detection and management of putative causal fac-

tors (by geriatric or geriatric psychiatry consultation, education of house staff, monitoring of postoperative patients, or post-discharge rehabilitation and follow-up) and/or special nursing care to increase stimulation, reorientation, and recovery of function. The interventions appeared to have a beneficial effect on the cognitive and functional status of older surgical patients but little effect on older medical patients. The larger effect among surgical patients may have been related to putative causes that were more specific (e.g., postoperative hypoxia) and more readily treatable (e.g., with supplemental oxygen).

PREVENTION

Many cases of delirium occur after admission to hospital (5), when there is a confluence of factors (e.g., drug intoxication, infections, unfamiliar environment) believed to predispose to, precipitate, and perpetuate delirium. The results of 13 trials of preventive interventions are summarized in Table 5 (104, 106, 108, 109, 115–123). The evidence suggests that a broad spectrum of interventions (education, support, re-orientation, anxiety-reduction, pre-operative medical assessment) may be modestly effective in preventing delirium among surgical patients. The absolute risk-reductions among surgical patients ranged from –13% to 19% (median: 13%). Interventions by nurses alone were as effective as interventions involving physicians. Notably, patient-controlled analgesia seems to have virtually eliminated the occurrence of delirium in a frail surgical population (117).

Although two studies of older medical patients reported little benefit (109, 123), a recent trial offers hope of preventing delirium in this population (120). This trial involved identification of patients with at least one of six targeted risk factors (dementia, immobility, dehydration, vision problems, hearing impairments, sleep deprivation) and implementation of intervention protocols for each of the risk factors present. The intervention attenuated the risk factors and reduced the incidence of delirium by 40%. The program was cost-effective for intermediate- but not high-risk patients (18).

SUBSYNDROMAL DELIRIUM

DSM-IV delirium requires the coexistence of symptoms from multiple domains. However, it is common for elderly patients to display one or more symptoms without having the full syndrome. Such symptoms may precede or follow an episode of delirium or may never progress to delirium. The latter condition is known as subsyndromal delirium (SSD). In one study (124), the frequencies of risk factors for delirium in a group with SSD were either similar to those of a delirium group or intermediate between those of delirium and normal groups. Upon discharge, 44% of patients with delirium were institutionalized, versus 10% of patients with SSD and none of the normal subjects.

A recent study (125) reported that prevalent SSD was associated with more symptoms of delirium, a lower cognitive and functional level, increased length of acute-care hospital stay, and decreased post-discharge survival at 12 months. Most of the findings for incident SSD were similar but not statistically significant. Moreover, patients with prevalent or incident SSD had the same set of risk factors that predict the likelihood of developing DSM-defined delirium: older age, dementia, and greater physiologic severity of illness. In three related studies (9, 14, 15), most of the baseline measures and outcomes of patients with SSD were intermediate between those of patients with no SSD and patients with DSM-defined delirium.

These findings support the notion of a spectrum of acute neurocognitive disorder quantitatively related to adverse outcomes. Therefore, the presence of even one or two symptoms of delirium appears to identify patients who warrant clinical attention.

CLINICAL RESEARCH

There are many areas for clinical research. Three will be discussed briefly: validation of diagnostic criteria, determination of delirium subgroups, and improvement of treatments.

VALIDATION OF DIAGNOSTIC CRITERIA

The development of diagnostic criteria has been an evolving process. The current criteria, from DSM-IV, are useful but based only on expert opinion (3, 4). There is still disagreement on the clinical features essential to the diagnosis and those that are merely supportive of the diagnosis. Only prospective studies that examine symptoms of delirium in relation to core syndrome features (e.g., fluctuation, reversibility) will establish the diagnostic criteria.

DETERMINATION OF DELIRIUM SUBGROUPS

Delirium is probably a heterogeneous condition related to the type of patient and the setting in which it occurs. Delirium subgroups may be asso-

ciated with specific etiologic factors and neurotransmitter pathways. Hence, exploration of subgroups may provide clues to pathophysiology and treatment. New clinical studies (or even the reanalysis of data from previous studies) should try to define subgroups in terms of symptoms, epidemiology, risk factors, pathogenetic mechanisms, course, outcome, and response to treatments. One subgroup may include patients in whom delirium is a terminal event (126).

IMPROVEMENT OF TREATMENTS

Three areas of research may lead to better treatments of delirium (127). The first area could involve the development of drugs that target the neurochemical disturbances of delirium. There are several lines of investigation, even if the evidence is weak. Elevated serum anticholinergic activity in patients with delirium (54, 56) suggests that drugs with cholinergic activity (physostigmine, donepezil) may be useful in the treatment of delirium. Temporary remission of symptoms after injection of flumazenil (128, 129), a short-acting benzodiazepine receptor antagonist, suggests that longer-acting benzodiazepine-receptor antagonists may be useful. Finally, the apparent success of mianserin in treating delirium suggests that 5HT receptorantagonists may be useful (130).

The second area involves efforts to reduce serum anticholinergic activity. In addition to traditional anticholinergic medications, there is some evidence that many drugs used to treat common medical conditions (e.g., digoxin, furosemide, theophylline, prednisone, cimetidine) have anticholinergic activity (at least in vitro) (90). Determining which of these drugs have central anticholinergic activity and reducing their use could improve outcomes.

The third area for research involves a paradigm shift in our thinking about the nature of delirium. Recently, delirium was reported to predict lower cognitive and functional status, an increased rate of institutionalization, and increased mortality up to 12 months later (9, 15). As part of these studies, a research assistant assessed the frequency of symptoms of delirium at enrollment, then 2, 6, and 12 months later. The frequency of symptoms was greatest at enrollment, but many symptoms persisted up to 12 months later among patients with or without dementia (89). These findings suggest that, in many elderly medical inpatients, delirium may be a chronic rather than an acute disorder—a chronic disorder (like depression or chronic obstructive pulmonary disease) that has a chronic course, with periods of acute exacerbation that we label as episodes of delirium. Delirium in many elderly medical inpatients may be closely related to dementia. Dementia is a risk factor for delirium (52); delirium is a risk factor for dementia (16); both delirium and dementia may have a similar pathogenesis (131). Within this paradigm, important new approaches to the management of delirium in this population could involve continuous monitoring for symptoms of delirium and appropriate adjustments in the treatment of medical conditions and medication use or the use of cognition-enhancing drugs (e.g., donepezil).

CONCLUSION

Delirium is a frequent and serious mental disorder in elderly patients. It is often not diagnosed, even though there are potential strategies (e.g., screening by nurses, risk-factor assessment) and instruments that can improve detection and diagnosis. Although there has been limited progress in understanding the etiology, pathogenesis, assessment, and specific treatment of delirium, systematic detection and treatment programs appear to be beneficial for elderly surgical patients, as are preventive programs for elderly medical and surgical patients. Even now, there is probably enough evidence to recommend implementation of these two types of programs in acute-care hospitals.

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Table 4. Summary of Studies Assessing Effectiveness of Systematic Detection and Treatment for Delirium

Author/Year	Intervention(s)	Inpatient Population	Design	Number of Patients	Length of Follow-Up, Days	Outcome Measures	Results
Surgical patients							
Budd and Brown, 1974[105]	Screening for post-op confusion, then reorientation	Cardiac surgery	NR	16	5	Incidence of delirium and post-op complications	Large ↓ in intervention group
Gustafson et al., 1991[108]	Careful monitoring and intervention in post-op patients	Elderly orthopedic	NR	214	7	Incidence of severe confusion Length of stay	Large ↓ in severe confusion and length of stay
Aakerlund and Rosenberg, 1994[111]	Screening for hypoxia and supplementary oxygen for hypoxic patients	Chest surgery	C	24	8	Delirium symptoms	All cases of delirium improved
Medical-surgical patients							
Cole et al., 1991	Geriatric psychiatry consultation	Elderly medical-surgical	R	80	56	Length of stay Cognition Anxiety Depression Functioning	Small effect overall, but cases of delirium and depression improved most often
Medical patients							
Wanich et al., 1992[109]	Special nursing care	Elderly medical patients	NR	235	35	Delirium mortality Disposition Length of stay Functioning	Small ↑ in functional status in intervention group
Cole et al., 1994[91]	Screening, geriatric consultation, and follow-up by liaison nurse	Elderly medical patients	R	88	56	Cognition Functioning Length of stay Mortality	Small ↑ in cognition and functioning in intervention group
Rockwood et al., 1994[112]	Education of house staff in diagnosing and managing delirium	Elderly medical patients	NR	434	N/A	Diagnosis of delirium (or equivalent) Length of stay Mortality Disposition Cognition Functioning	After intervention, ↑ rate of diagnosis (9% versus 3%) and ↓ length of stay (10 versus 15 days)
Rahkonen et al., 2001[113]	Continuous counseling, rehabilitation periods	Elderly medical patients	NR	102	587	Mortality Disposition	↓ institutionalization in intervention group
Cole et al., 2002[114]	Screening, geriatric consultation and follow-up by liaison nurse	Elderly medical patients	R	227	56	Cognition Functioning Length of stay Mortality Disposition	No significant benefit

R=randomized trial; NR=non-randomized trial; C=cohort

Table 5. Summary of Trials Assessing Effectiveness of Systematic Interventions to Prevent Delirium in Hospitalized Medical and Surgical Patients

Patient Category; Trial	Interventions	Intervention Personnel	Timing of Intervention	Inpatient Population	Design	Number of Patients		Incidence of Delirium, Percent		Absolute Risk Reduction, Percent
						Treatment	Control	Treatment	Control	
Surgical patients										
Lazarus and Hagens, 1968[118]	Psychiatric assessment and support, re-orientation	Physician/ Nurse	Pre-op+ Post-op	Cardiac	NR	21	33	14	33	19
Layne and Yudofsky, 1971[119]	Psychiatric interview	Physician	Pre-op	Cardiac	NR	42	19	10	22	12
Chatham, 1978[106]	Education of spouse	Nurse	Post-op	Cardiac	R	10	10	Q[a]	—	—
Owens and Hutelmyer, 1982[115]	Education of patient	Nurse	Pre-op	Cardiac	R	32	32	59	78	19
Williams et al, 1985[104]	Special nursing care	Nurse	Pre-op+ Post-op	Elderly orthopedic	NR	57	170	44	52	8
Schindler et al., 1989[116]	Psychiatric assessment	Physician	Pre-op+ Post-op	Cardiac	R	16	17	13	0	–13
Egbert et al., 1990[117]	Patient-controlled analgesia	N/ A	Post-op	Elderly surgical	R	43	40	2	18	16
Gustafson et al., 1991[108]	Special medical and surgical care	Physician	Pre-op+ Post-op	Elderly orthopedic	NR	103	111	48	61	13
Marcantonio et al., 2001[121]	Proactive geriatric consultation	Physician	Post-op	Elderly orthopedic	R	62	64	32	50	18
Milisen et al., 2001[122]	Screening, nurse specialist; pain protocol	Nurse	Post-op	Elderly orthopedic	NR	60	60	20	23	3
Medical patients										
Nagley, 1986[123]	Special nursing care	Nurse	—	Elderly medical	NR	30	30	3	0	–3
Wanich et al., 1992[109]	Special nursing care	Nurse	—	Elderly medical	NR	135	100	19	22	3
Inouye et al., 1999[120]	Risk factor abatement	Nurses	—	Elderly medical	NR	426	426	9.9	15	5.1

NR=nonrandomized; R=randomized
a quantitative symptom measures only

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