patient's treating physician. In moderate-to-later stages of the disease course, patients will become dependent for basic daily activities such as eating, bathing, and grooming, and may also display challenging behaviors like wandering or agitation. Maintaining a regular, predictable schedule that includes some form of activity, ensuring good nighttime sleep, and assessing for other causes of agitation (eg, infection; pain) can be helpful in these situations. Occasionally, medications can be prescribed to combat agitation or aggression, though certain types of medications (eg, antipsychotics, sedatives) often have unwanted side effects in older adults or those with dementia, so these decisions need to be made judiciously. Patients with late-stage disease often experience difficulties with swallowing, communication, and/or bladder and bowel control and need round-the-clock-care. In moderate to late stage disease, many families find they need to rely on hired caregivers or consider an assisted living facility for assistance in managing their loved ones' needs. Caregiver support and education is essential at all stages of the disease.

Lewy Body Disorders

Lewy body dementia (LBD) encompasses both DLB and PDD. The primary neuropathologic feature in both diseases is the accumulation of cortical Lewy bodies, resulting from abnormal aggregation of α-synuclein. However, additional pathologic features, including accumulation of tau protein, concurrent vascular and/or AD pathology, neurotransmitter abnormalities, and frontostriatal projections that have been disrupted by loss of dopaminergic neurons, can all contribute to the cognitive decline associated with these diseases.

Although PD and DLB have historically been considered related but separate clinical entities, many of the neuropathologic, clinical, cognitive, and psychiatric characteristics of the two diseases have considerable overlap. Both are associated with cognitive fluctuations, visual hallucinations, psychiatric symptoms, and REM sleep behavior disorder in the context of PD motor symptoms, and thus recent debates have examined whether PD, PDD, and DLB should be placed along a clinical continuum representing the same underlying pathology. Currently, the differential diagnosis is based on the timing of the onset of the cognitive symptoms. A patient with PD who develops dementia after 1 year of well-established motor symptoms is classified as "PDD," while a patient with motor

symptoms occurring after the onset of dementia (or within one year of motor symptom onset) is classified as "DLB."

Parkinson disease Diagnosis of PD according to the United Kingdom Parkinson Disease Society Brain Bank clinical diagnostic criteria requires specific motor symptoms, including bradykinesia and at least one of the following: muscular rigidity, rest tremor, and/or postural instability. Although motor symptoms have long been considered the defining feature of PD, a wide range of associated nonmotor symptoms, such as impaired sleep patterns, psychiatric symptoms, gastrointestinal dysfunction, and cognitive impairment, are increasingly recognized as having substantial impact on functional abilities and quality of life for these patients. Of these nonmotor symptoms, cognitive dysfunction is a substantial concern, with upwards of 80% of patients who live for 20 years or more with PD expected to develop PDD over the course of the disease. Current Movement Disorder Society task force recommended consensus diagnostic criteria for PDD include (1) a diagnosis of PD, (2) PD symptoms developed prior to the onset of dementia, (3) impaired global cognition (eg, on MMSE or MoCA), (4) cognitive impairment severe enough to impair activities of daily living, and (5) impairments in more than one cognitive domain on detailed neurocognitive testing. Additional supportive symptoms may include psychiatric symptoms (eg, depression, apathy, delusions) or impaired sleep. Even among patients without dementia, however, the rate of concurrent cognitive impairment can be quite high. PD-mild cognitive impairment (PD-MCI), similar to MCI due to AD, is characterized by subjective cognitive decline (noted by the patient, collateral, or clinician), objective impairments on neuropsychological assessment, and absence of functional impairment sufficient to significantly interfere with functional independence in the presence of clinically verified PD. PD-MCI is common, with overall prevalence estimates approximately 30% to 40%. Cognitive deficits often emerge early during the course of the disease, with 10% to 30% of newly diagnosed patients with PD identified with cognitive impairment. However, there is substantial variability in the nature and course of cognitive symptoms in PD, with many patients maintaining a stable or fluctuating course and others demonstrating more rapid decline (**Figure 57-3**). Several variables associated with more rapid cognitive decline have been identified, including age, disease duration, sex, and specific genetic mutations.

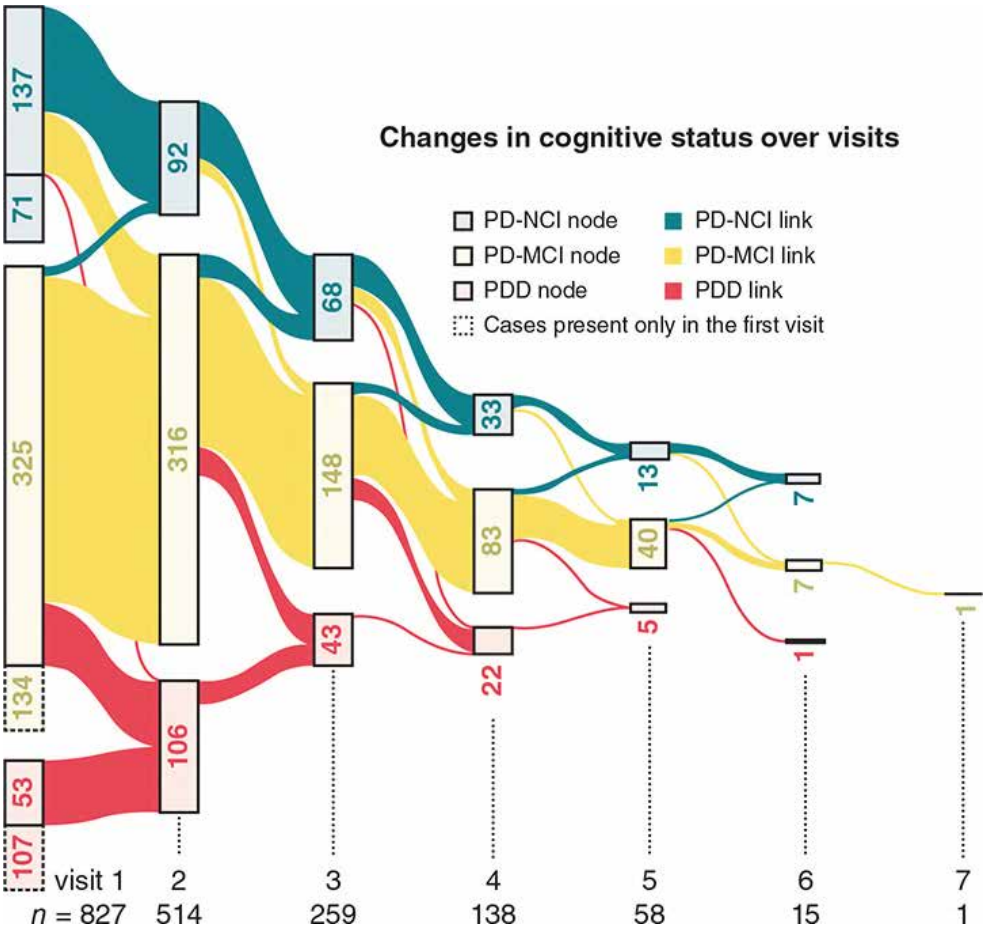

FIGURE 57-3. Change in cognitive diagnostic status over time in a multi-site Parkinson disease (PD) cohort. The number inside each node represents the number of people with the corresponding cognitive status indicated by its color. The nodes with dashed lines represent people with only data from the first visit. The links represent the group participants who continued to the next visit. PDD, PD with dementia; PD-MCI, PD with mild cognitive impairment; PD-NCI, PD with no cognitive impairment. (Reproduced with permission from Phongpreecha T, Cholerton B, Mata IF, et al. Multivariate prediction of dementia in Parkinson's disease. *NPJ Parkinsons Dis*. 2020;6:20.)

Most patients with PD exhibit at least some decline in attention, working memory, processing speed, or other executive functions, although the nature and degree of impairments across other domains are variable. PDD is often characterized by worsening visuospatial deficits, impaired verbal fluency, difficulty planning or shifting to a new stimulus, slowed information processing speed, and impaired memory. Memory impairment is most frequently attributable to a retrieval deficit since recognition is often intact. Procedural learning may be impaired, a pattern atypical in normal aging or in AD. Some language skills are intact, such as vocabulary, while others that

tap additional cognitive domains, such as verbal fluency, may be impaired. Mechanical aspects of speech are often impaired as well. Although PDD has been previously characterized as a "subcortical" dementia to distinguish it from cortical dementias such as AD, this characterization has been criticized more recently and may serve simply as a gross depiction of the cognitive profile. Indeed, recent research suggests that while initial mild cognitive deficits in PD likely result from depleted dopamine in the midbrain and resulting defects in the frontostriatal loop, cortical pathology is required for progression to dementia.

Dementia with Lewy bodies Current consensus criteria for probable DLB include (1) a diagnosis of dementia (defined as cognitive impairment sufficient to impair functional abilities) and (2) two or more core clinical features (fluctuating cognition, well-formed visual hallucinations, rapid eye movement [REM] sleep behavior disorder, and/or one or more cardinal motor symptoms of PD), or one core clinical features in the presence of one or more indicative biomarkers (eg, reduced dopamine uptake on SPECT or PET scan, REM sleep disorder diagnosed by polysomnography). As discussed above, DLB and PDD share many of the same features, including cognitive fluctuations, neuropsychiatric features, and motor symptoms. However, the timing and severity of these symptoms may differ. Visual hallucinations often occur earlier in DLB, delusions may be more common, and a differential response to antiparkinsonian medications has been reported. In terms of cognition, prominent visuospatial and executive impairments are noted, similar to PDD. Memory impairments, although not necessary for diagnosis, tend to be more prominent in DLB. It is thus unsurprising that among patients with DLB, there tends to be a likelihood of concurrent AD pathology.

Given the overlap in symptoms and pathology, differential diagnosis between DLB and AD can thus also be difficult. The presence of visual hallucinations in patients with MMSE scores greater than 20 is highly suggestive of DLB. Neuropsychological studies have identified typical cognitive profiles that may aid in diagnosis. In DLB, patients have more difficulty than AD patients in copying complex designs, assembling pieces of an object, or completing other tasks requiring visuospatial skills. In contrast, AD subjects generally show significantly more impairment on delayed recall tasks than patients with DLB. DLB patients have attentional skills that are generally equivalent to those of AD patients; however, patients with DLB

exhibit significant attentional fluctuations. As a result, evaluating attention over time is more helpful than the overall severity of attention problems in the differential diagnosis. Finally, these cognitive profiles are most evident early in the course of the diseases. As the diseases progress, all cognitive functions become impaired and neuropsychological testing is less helpful for diagnosis.

Palliative care concerns specific to PD and DLB There is increasing recognition that appropriate palliative care that addresses cognitive changes in PD and DLB is both vital and underutilized. Given the range of symptoms in PD and associated caregiver and patient burden, an early focus on nonmotor symptom control, adjustment to cognitive changes, and advance care planning is strongly recommended in addition to routine care that has historically focused nearly solely on motor symptom management. To address the problems associated with increasing cognitive decline, occupational therapy, integrated care models, and psychoeducational programs for patients and family members may be helpful tools. In general, however, both patients and caregivers report that they are not provided with enough information about the nature and prognosis of the diagnosis, and thus lack the tools necessary to address end-of-life care issues and mitigate problems associated with advancing cognitive disease, such as medication reconciliation and home safety issues. DLB is associated with specific difficulties in accessing palliative care, largely due to lack of knowledge about the diagnosis in the general medical community and related difficulty in adequately diagnosing DLB. Further, patients with DLB often present with behavioral problems that may result in difficulty accessing resources. As a result, patients are often not appropriately medicated and physicians rarely discuss what to expect as the disease progresses. Assessment resources such as the Palliative Care Outcome Scale or the Edmonton Symptom Assessment System may be helpful to identify care needs in patients. However, provider education is a vital initial step to providing adequate community palliative care for PD/DLB.

Vascular Cognitive Impairment

VCI is an umbrella term that includes both mild VCI and major VCI (VaD) in the context of imaging evidence for cerebrovascular disease. A diagnosis of mild VCI requires impairment in at least one cognitive domain with mild or no impairment in activities of daily living that are independent from any motor or sensory impairments caused by the vascular event. A diagnosis of

major VCI (or VaD) requires significant deficits in at least one cognitive domain along with correlated impairment in daily functional activities (again that are independent of any motor or sensory sequelae associated with the vascular event). VaD subtypes include poststroke dementia (the only subtype that requires a clear temporal relationship between vascular event and cognitive decline), subcortical ischemic VaD, multi-infarct dementia, or mixed dementia (representing combined suspected vascular disease and other neurodegenerative diseases including AD and LBD).

Cognitive profiles of patients with VCI, especially in mild or early forms, can be quite variable given the underlying neuropathologic heterogeneity associated with the diagnosis. Executive function deficits, reduced verbal fluency, and slow processing speed are common. Depression, irritability, and lack of initiative are also frequently seen in patients with VCI. Contrary to long-standing clinical lore, VCI does not necessarily present primarily with a clear temporal relationship to a known vascular event nor to stepwise deterioration in cognition. Rather, continuous small vessel insults can lead to slowly progressive decline in cognitive abilities. Thus, it can be difficult to differentiate VaD from AD on the basis of the clinical course of symptoms. Detailed review of cardiovascular risk factors and cognitive profile may provide better differentiation. A review of studies examining early-stage AD and VaD found that the latter group had more pronounced deficits in executive function on tests such as the Wisconsin Card Sorting Test and the executive function scale of the Mattis Dementia Rating Scale than did adults with AD. Interestingly, performance between the two groups was similar on tests of selective attention and working memory such as the Trail-Making Test and Stroop Color Word Interference Test. In contrast, VaD patients had better performance than AD patients on tests of verbal learning and story recall, such as the California Verbal Learning Test and the Logical Memory subtest of the Wechsler Memory Scale-Revised (WMS-R), with fewer intrusions. However, VCI can impact the structure and function of the hippocampus, thus leading to more notable memory deficits in some patients, although these impairments may not occur until later in the disease process. Because memory impairment is most often the reason patients seek evaluation, adults with VaD may have more progressed dementia and greater cognitive impairment at the time of diagnosis. It is important to note that as both VaD and AD progress, the cognitive profiles become more similar, so that differentiating mid-stage disease is very

difficult. In addition, neuropathologic studies have shown that many patients previously diagnosed with VaD due to presence of vascular risk factors such as diabetes, hypertension, and radiologic evidence of ischemia have prominent AD pathology as well. Prevalence estimates of the co-occurrence of AD and VaD range from 20% to 40% of patients with dementia. Few studies have attempted to differentiate between mixed AD/VaD and either form of dementia on a neuropsychological basis, although it has been suggested that mixed dementia most closely resembles VaD from a cognitive perspective. Vascular pathology increases the likelihood that patients with neuropathologic AD will show significant cognitive impairment.

Palliative care concerns specific to VCI Given the variable (and often unknown) progression of cognitive symptoms in VCI, palliative care concerns are likely to be patient-specific, and may include lifestyle interventions aimed at maximizing retained cognitive abilities, quality of life, and overall physical health. Occupational therapy, psychoeducation, managing comorbid depression, and training and support for caregivers may all be helpful interventions. In advanced major VCI, palliative care interventions and end-of-life planning and preparation similar to those used most frequently in AD are recommended.

Frontotemporal Lobar Degeneration

Frontotemporal lobar degeneration (FTLD) is caused by a range of underlying neuropathologic conditions (including intracellular inclusions of tau or transactive response DNA-binding protein [TDP-43], among others). FTLD onset occurs at slightly younger ages than other conditions such as AD, with onset occurring most commonly in the late 50s-to-early 60s. It is thought to be the second most common form of dementia in individuals under the age of 65. Roughly 30% to 40% of FTLD cases are linked to genetic mutations, including granulin (GRN) and microtubule-associated protein tau (MAPT) mutations, and patients with some types of genetic mutations may develop symptoms at even earlier ages. As with AD, FTLD patients show insidious onset of symptoms with a gradual progression. Various clinical presentations can be caused by FTLD, primarily resulting in gradually progressive disturbances in language and/or behavior. Although comparisons of AD and FTLD groups do not always reveal significantly different cognitive profiles, in general, FTLD patients show relatively spared memory performance in comparison to their executive and language functioning, especially when

memory cues are provided. Apraxia is also more common in FTLD than in AD. Often a multidisciplinary approach may be most helpful in the differential diagnosis since studies indicate that up to 75% of pathologically confirmed FTLD patients also appear to meet clinical criteria for probable AD, and certain subtypes of FTLD are often misdiagnosed as a primary psychiatric disorder early on. The following diagnostic variants are currently recognized as most likely resulting from FTLD, although the extent to which these conditions may have shared pathology with other diseases, and the likelihood that these represent distinct disorders is not currently well defined.

Behavioral variant FTLD This diagnostic category (bvFTD) accounts for nearly 50% to 60% of all FTLD diagnoses. This variant most often presents initially with a prominent decline in social cognition and behavior and/or executive dysfunction, with relative sparing of other cognitive functions, and includes at least three of the following: (a) disinhibition, (b) apathy, (c) diminished empathy/sympathy, (d) perseverative, stereotyped, or compulsive behaviors, and/or (e) hyperorality/dietary changes. These behavioral and/or executive symptoms are the source of impairment in daily activities. While these criteria are sufficient for a diagnosis of "possible" bvFTD, a diagnosis of "probable" bvFTD requires neuroimaging findings of disproportionate frontal or temporal lobe involvement, or a pathogenic mutation. Early in the disease process, performances on formal neuropsychological testing may be remarkably well preserved, underscoring the importance of a thorough diagnostic interview and history with the patient and an informant; however, many individuals do display impaired selective and divided attention, difficulty shifting mental set, poor abstraction and reasoning, impaired verbal fluency, and perseverations. Unfortunately, cognitive screeners such as the MMSE are not very helpful in screening for early bvFTD since many patients score within normal limits early in the disease.

Primary progressive aphasia PPA typically occurs in the fifth or sixth decade of life, and its rate of progression varies greatly. The diagnosis of PPA requires initial prominent language dysfunction with relative sparing of other cognitive domains early on, and the absence of radiologic evidence of cerebrovascular or other neurologic injury that would account for the aphasia. Because anomia and other language deficits may occur in a number of neurodegenerative conditions, the differential diagnosis of PPA rests on the clear demonstration that nonlinguistic cognitive and behavioral functions

are intact during the initial stages of the disease. The clinician must carefully determine whether poor performance on memory and other nonlanguage tests is due to language deficits such as impaired comprehension of instructions. Differential diagnosis is also complicated by the heterogenous etiologies of PPA demonstrated by the different subtypes. Although not consistent across all cases, agrammatic PPA is often associated with tau pathology, logopenic PPA with AD pathology (although not always in brain regions typically associated with AD), and semantic PPA with TDP-43 pathology. PPA variants include (1) agrammatic/nonfluent aphasia and (2) semantic variant PPA (sometimes called semantic dementia [SD]). As noted, a third variant, LPA, is often included under the larger umbrella of PPA; however, neuropathologically, LPA is primarily attributed to AD-type pathology, so it is often considered a language-variant of AD.

Progressive Nonfluent/Agrammatic Aphasia Progressive nonfluent/agrammatic aphasia (PNFA) is characterized by labored articulation and/or agrammatism, frequently occurring alongside apraxia of speech. Patients with PNFA also typically have intact comprehension for simple speech and phrases but impaired comprehension for complex or syntactically irregular phrases. Semantic knowledge is also well preserved.

Semantic Dementia SD, on the other hand, involves a loss of ability to understand words (semantic knowledge of words and objects), which is accompanied by marked deficits in confrontational naming. Other deficits include difficulty with visual recognition of objects, dyslexia, and dysgraphia. Patients with semantic dementia may display prominent visual agnosias and may not be able to demonstrate object use accurately. In contrast to PNFA, speech production remains intact in early disease as does repetition.

Logopenic Aphasia LPA is the most recently characterized PPA variant. LPA presents with impaired word retrieval in spontaneous speech and difficulty with naming, in addition to impaired sentence repetition, and in some instances, sentence comprehension. The hypothesized mechanism behind some of the language deficits in LPA, especially impaired sentence repetition, is a deficiency in short-term working memory, and hence, single-word repetition, which requires minimal working memory, is well preserved. The naming deficit in LPA is not as dramatic as in SD, and these patients also have preserved object knowledge. While patients with LPA

demonstrate effortful word retrieval, this again is less severe than in PNFA and their speech is usually grammatically accurate and free from motor speech abnormalities, which marks another useful distinction between LPA and other PPA subtypes.

FTLD movement disorders Certain movement disorders, which may also include behavioral and/or language disturbance, may be caused by or associated with FTLD.

FTLD-Motor Neuron Disease Frontotemporal dementia with motor neuron disease (FTD-MND) tends to be a rapidly progressive condition, with death typically occurring 3 to 5 years after symptom onset. Age of onset is more variable and can range from 35 to 75, on average. The FTD-MND syndrome is typically characterized by gradual onset of both cognitive and psychiatric symptoms, in addition to, though not necessarily simultaneously to, development of classic upper and/or lower motor neuron dysfunction, such as muscle wasting, paraparesis, fasciculations, or abnormal reflexes. Early bulbar involvement can also lead to symptoms of dysphagia and pseudobulbar affect, or uncontrollable episodes of laughing or tearfulness. Behaviorally, these patients may display similar symptoms to patients with bvFTD. Cognitive symptoms can include variable language and executive dysfunction.

Progressive Supranuclear Palsy Although Lewy bodies are found in only the minority of progressive supranuclear palsy (PSP) cases, PSP is frequently misdiagnosed as PD. A core feature of the disorder is vertical supranuclear gaze palsy, although this symptom may not present early in the course of the disease. Patients also present with postural instability, and falls are often seen shortly after onset. Cognition is characterized by mental and psychomotor slowing and notable executive dysfunction, often fairly early in the disease course. Memory impairments are observed, but they are not as severe as in AD. Language functions resemble those seen in PD. Visual spatial deficits and increased apathy are also observed.

Corticobasal Syndrome Corticobasal syndrome (CBS) is the primary clinical phenotype of corticobasal degeneration, which is characterized by abnormal tau deposition, and relatively focal and asymmetric cortical atrophy in frontal and parietal brain regions on imaging. The mean age of onset for CBS is in the early 60s. CBS is characterized by progressive, asymmetric motor symptoms such as tremor, loss of coordination, rigidity, and myoclonus, and a

higher prevalence of alien limb syndrome. Unilateral apraxia (most commonly ideomotor) is common. A range of language abnormalities including slowed verbal fluency, and/or executive dysfunction may also be seen in CBS. In contrast to AD, memory is typically well preserved early on, but may worsen with disease progression and may even become prominent in some patients. Neuropsychiatric and behavioral symptoms are common and can include apathy, personality change, disinhibition, and irritability.

Palliative care concerns specific to FTLD Given the heterogeneity in FTLD phenotypes, care recommendations vary by subtype. Many of the core symptoms of bvFTD and related subtypes, including impulsivity, poor judgment, and disinhibition, can be distressing for family members, so education about bvFTD and early support for family and caregivers is essential. Education about possible environment and behavioral modifications is recommended and typically focuses on mitigating safety risks (eg, driving impulsively, poor management of money, falling victim to scams, etc) given reductions in insight and self-awareness are quite common in bvFTD. Early consultation with a psychiatrist is often helpful as well; there is some evidence that treatment with selective serotonin reuptake inhibitors may be helpful in managing unwanted behavioral symptoms. Patients with either primary (PPA subtypes) or secondary language dysfunction (PSP; CBS; FTD-MND) may benefit from consultation with a speech-language pathologist (SLP) early on in the course of their disease, who may be able to provide useful strategies. Augmentative and alternative communication devices can also be employed as the condition progresses. SLPs may also be of benefit as part of a multidisciplinary team as some of these patients may have, or go on to develop, dysarthria and/or dysphagia. Physical therapy can also be a valuable tool to assist with early motor dysfunction in FTD-MND, PSP, and CBS. Like most neurodegenerative conditions, motor and/or sensory dysfunction can occur in other FTLD subtypes as well as the disease progresses to moderate or severe stages.

Dementia Due to Suspected Non-Alzheimer Disease Pathophysiology

Dementia due to suspected non-Alzheimer disease pathophysiology (SNAP) is a relatively new biomarker-based term that is used to describe individuals who have evidence of neurodegeneration on neuroimaging, but who lack biomarkers classic to AD—specifically, amyloid. SNAP is more prevalent with increasing age. While there is little evidence of SNAP in persons

younger than 50, prevalence increases with increasing age after the age of 60. Most commonly, the term SNAP has been used to describe individuals with either normal cognition or MCI who lack evidence of clinically significant amyloid but have evidence of neurodegenerative changes in the brain. Neurodegeneration characteristic of SNAP is also observed in individuals with clinical dementia; however, these individuals' condition is usually attributed to a non-AD etiology based on clinical presentation (eg PPA, DLB), and it is hypothesized that TDP-43, hippocampal sclerosis, vascular disease, and/or other pathophysiological processes may be the causative factor. No definitive cognitive phenotype has been identified in individuals with SNAP who are deemed clinically normal, though SNAP does appear to confer risk for subsequent cognitive decline. Not surprisingly, those with SNAP and MCI have greater likelihood of progression to dementia than those with SNAP and no evidence of MCI. Further, those with SNAP, regardless of cognitive status, have a greater risk of decline compared to those without SNAP. The data is mixed on the risk of decline in SNAP compared to those without SNAP but who are amyloid and/or tau positive, though it is generally accepted that the presence of neurodegeneration, amyloid, and tau combined confers the greatest risk for accelerated cognitive decline.

Limbic-Predominant Age-Related TDP-43 Encephalopathy

Limbic-predominant age-related TDP-43 encephalopathy (LATE) is a common, but relatively recently described finding in those in their eighth or ninth decade of life. Estimates vary, but recent autopsy studies of individuals aged 80 and older have identified evidence of LATE in 5% to 50% of their samples. This proteinopathy was first discovered in autopsies of individuals with cognitive impairment that mimicked AD; that is, these individuals had an amnestic cognitive syndrome similar to AD. Like AD, LATE can also evolve to include multiple cognitive domains but the clinical presentation remains distinct from other TDP-related conditions such as FTLD-TDP. Given the occurrence in very late life, it is unsurprising that the pathological changes of LATE often co-occur with those of AD, LBD, and/or VCI. While data on this entity is still in its infancy, there is some indication cognitive changes progress more slowly in those who only have evidence of LATE compared to those with evidence of multiple pathologies.

Alcohol-Related Dementia

Contradictory evidence exists as to the role of mild-to-moderate alcohol and risk for developing certain dementias, including AD and VaD. Chronic and profound alcohol use, however, can have a negative effect on cognition and may exacerbate the cognitive symptoms of other dementias and brain injuries. Poor nutrition (thiamine deficiency in particular) resulting from alcohol abuse is a primary contributor to the onset of cognitive problems. In addition, liver disease can interfere with thiamine regulation in the brain and may be a factor in the multiple cognitive and motor impairments associated with long-term alcohol use.

Persistent alcohol dementia Alcohol dementia involves impairment in more than one area of cognitive function that persists after the patient stops drinking for a period of time. Visuospatial problem-solving deficits and executive problems, including apathy, decreased judgment, and reduced interest in self-care, are prominent in these patients. Memory problems, in particular anterograde amnesia, are also common, but are generally not more impaired than other cognitive domains, and recognition is often intact. Typical neuropsychological sequelae include impairments on tasks requiring visual scanning, visuospatial organization, perceptual-motor speed, sustained attention, abstraction, and mental flexibility, while language functions are generally preserved. Perseveration and confabulation are common indicators of impaired executive function in the responses of patients with chronic alcohol use. It is also noteworthy that chronic alcohol use may potentiate the onset of AD, and produce a clinical picture of conjoint cognitive deficits.

Wernicke–Korsakoff syndrome The most severe neurologic outcome of heavy and prolonged alcohol use, and the result of critical malnutrition, is Wernicke–Korsakoff syndrome. In contrast to patients with persistent alcohol dementia, Wernicke–Korsakoff patients exhibit an acute symptom onset, often beginning with a grave confusional state, nystagmus, and significant ataxia. During this phase, symptoms progressively and rapidly worsen if treatment (immediate thiamine replacement) is not applied. This phase is almost always followed by a chronic and progressive stage that is associated primarily with impaired frontal and cerebellar functions. Unlike persistent alcohol dementia, Korsakoff patients have significant impairments in memory relative to other cognitive effects, and memory impairment includes both retrograde and anterograde amnesia for episodic events, frequently with prominent confabulation. In contrast to AD, semantic memory is relatively spared in the Korsakoff patient. Patients show a characteristic gradient of remote memory

impairment, with better recall for remote events and progressively reduced recall of recent events. As with persistent alcohol dementia, executive dysfunction and visuospatial impairments are also significant symptoms of the syndrome. Cerebellar atrophy and peripheral nerve damage lead to impaired gait, decreased or abnormal reflexes, and other movement abnormalities in these patients.

Palliative care concerns specific to alcohol-related dementias Alcohol-related dementias, unlike progressive dementias such as AD and DLB, may be amenable to interventions if made in a timely manner (such as drinking cessation and nutritional supplementation), which may improve cognitive symptoms or stall further cognitive decline. Once these important interventions have been put in place, encouraging skill maintenance, providing adequate scaffolding for cognitive skills, maintaining daily structure and routine, and help with general self-care may be useful for maintaining maximal cognitive function.

Prion Diseases

The prion diseases are a group of rare fatal spongiform encephalopathies that result from mutations and polymorphisms in the prion protein gene (*PrP*), causing rapid neurodegeneration. These diseases, of which Creutzfeldt–Jakob is the most well-known, produce a profound and quickly progressive dementia, and may be sporadic, familial, or infectious. Sporadic cases are the most common, and are generally diagnosed in people in their 60s, with a typical age range between 40 and 80. Early cognitive signs of the prion diseases are usually vague and nonspecific, such as poor memory, concentration, and problem solving. Initially, there are also often psychiatric symptoms, including apathy, emotional lability, impaired sleep, and appetite loss. Early frank neurologic symptoms are not common, but as the disease progresses, hyperreflexia, impaired coordination, changes in saccadic eye movements, and incontinence may occur. Given the early vague symptoms and dearth of neurologic symptoms, patients are not likely to present for evaluation until they are in the more moderate-to-advanced stages, which can occur in a matter of months. Diagnosis typically involves measuring electroencephalographic changes, hyperintensities on MRI, and abnormal 14-3-3 protein deposits in the CSF. The most common differential diagnoses include depression, AD, and LBD. Given the generally rapid course of disease in combination with diagnosis that typically occurs in the later stages

of disease, palliative care often consists largely of hospice care, social work interventions to address disability and making end-of-life decisions, and bereavement resources and interventions for caregivers.

Normal Pressure Hydrocephalus

NPH is a potentially reversible dementia that makes up about 6% of dementia cases. Abnormalities in the production, absorption, or flow of CSF result in ventricular dilatation. Patients may present with a triad of clinical symptoms that include gait or balance disturbance, urinary incontinence, and cognitive deficits. Unlike most other dementias, cognitive symptoms often present later in the course. This can make early clinical diagnosis difficult since gait abnormalities and incontinence have a variety of etiologies in geriatric populations. Radiographic evidence and intraventricular pressure measurement aid in the diagnosis. When cognitive deficits are present, they are most frequently observed in executive functioning. Although many subjects may have subjective memory complaints, memory deficits are not a prominent early symptom, and some memory declines are attributable to attention problems, which are more common. However, many of these patients may have concurrent underlying neurodegenerative disease, and thus may present with varied cognitive profiles.

When treated, a ventriculoperitoneal shunt is usually used to divert CSF for better absorption. However, surgery in geriatric populations always involves added risks, and the benefits of shunt surgery remain unclear. A wide variety of success rates have been reported, with better outcomes often reported after shorter follow-up periods. Patients with the full triad of symptoms appear to respond best to shunt surgery. Gait problems show the most frequent improvement, while cognitive function improves in the fewest patients. Recently, findings from a 5-year follow-up of NPH patients with and without shunt surgery showed that at the 6-month assessment, 83% of the shunt cases improved in gait and 46% improved in memory. Of surviving shunt cases 5 years after surgery, 39% remained improved in gait, and fewer than 10% continued to show improvements on cognitive tests. Results suggested that outcomes may be improved in younger patients. Palliative care may involve inpatient and outpatient rehabilitation, physical therapy, occupational therapy, and other interventions aimed at maximizing retained cognitive functions.

HIV-Associated Neurocognitive Disorder

Although there is often the perception that geriatric patients are not at risk for human immunodeficiency virus (HIV) infection, the Centers for Disease Control and Prevention reported that 10% of all HIV cases in the United States are in patients of 50 years or older, and these numbers are expected to grow. With the use of combination antiretroviral therapies, progression to HIV-associated dementia is rare (2–3%). However, the prevalence of milder cognitive deficits is more frequent, with prevalence estimates ranging from 50% to 60%. Commonly affected areas of cognition are speed of information processing, attention, and motor speed, although it is increasingly recognized that impairments in broader executive functions, learning, and prospective memory are prevalent. As a result, differentiating these symptoms from early AD can be difficult clinically and may require more careful evaluation of both AD- and HIV-related CSF and imaging biomarkers. Palliative care depends upon severity of disease but should focus on managing potential multiple medical and psychosocial comorbidities and end-of-life planning as appropriate.

Neurosyphilis

Despite successes in treatment and education, syphilis cases have continually increased since 2000. Neurosyphilis can occur any time during the disease; however, syphilitic dementia may occur as the disease advances (generally 5–25 years after initial infection) that may present with hallucinations, delusions, mood disturbance, personality change, strokes, ataxia, or cognitive decline. Deficits are observed in short-term memory and mental status with progressive cognitive decline in all areas of functioning. Although neurosyphilis is often classified as a reversible dementia, there is only limited evidence to support cognitive benefits with penicillin treatment. Thus, following treatment with penicillin, palliative care may include occupational therapy or cognitive rehabilitation to help maximize remaining cognitive function. Neurosyphilis is more likely to occur in patients with comorbid HIV, and thus both should be considered during differential diagnosis. Neurosyphilis should further be considered in a differential diagnosis of dementia of unclear etiology in geriatric patients.

CONCLUSION

We have greatly furthered our understanding that age-related medical conditions not considered classically neurologic in nature can nevertheless impact the central nervous system and thereby affect cognition. This knowledge has led to the realization that many of the changes in cognition previously thought to be unavoidable concomitants of normal aging are in fact preventable and in some cases even reversible. The deleterious consequences of not treating such disorders have become evident, given that many common diseases such as T2DM and hypertension appear to be risk factors for dementia. In turn, early identification of dementia or the prodromal condition MCI will become critical as therapeutic options for delaying disease progression proliferate. Careful characterization of cognitive status through neuropsychological assessment can provide the clinician with essential information to determine whether the patient is experiencing symptoms that warrant concern or further treatment. As the field of geriatrics approaches the goal of controlling or even preventing endemic late-life chronic diseases, it will become increasingly clear that deleterious cognitive changes that occur with healthy aging are fewer and more subtle than we thought, and that they are accompanied by age-related strengths in experience and knowledge that will enable us to lead vital, productive lives well into our 80s and beyond.

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Chapter

58

Delirium

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Delirium, an acute disorder of attention and global cognitive function, is a common, serious, and potentially preventable source of morbidity and mortality for hospitalized older persons. Delirium affects as many as half of all people age 65 and older who are hospitalized. With the aging of the US population, delirium has assumed heightened importance because persons aged 65 and older presently account for nearly 40% of all days of hospital care. Total costs attributable to delirium spanning the hospital and posthospital period exceed $60,000 per patient; annually over $183 billion (in 2018 US dollars) of US health care costs are attributable to delirium. Importantly, delirium is preventable in up to 50% of cases. Substantial additional costs linked to delirium accrue after hospital discharge because of the increased need for institutionalization, rehabilitation services, closer medical follow-up, and home health care. Delirium often initiates a cascade of events in older persons, leading to a downward spiral of functional and cognitive decline, loss of independence, institutionalization, and ultimately, death. Delirium is a critical risk marker to identify patients at high risk for poor outcomes. Recently, this fact has been underscored in the care of patients affected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the COVID-19 pandemic, as those who present with delirium experience worse hospital outcomes compared to those who do not. With its common occurrence, its frequently iatrogenic nature, and its close linkage to the processes of care, incident delirium can serve as a marker for the quality of hospital care and provides an important opportunity for quality improvement.

DEFINITION

The definition of and diagnostic criteria for delirium continue to evolve. Standardized criteria for delirium in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5, 2013) represent the current diagnostic standard. These criteria are based on (A) a disturbance in attention and awareness; (B) an acute onset and fluctuating course; (C) an additional deficit in cognition (such as memory, orientation, language, or visuoperceptual ability); (D) impairments not better explained by dementia and do not occur in context of severely impaired level of consciousness or coma; and (E) evidence of an underlying medical etiology or multiple etiologies. Expert consensus was used to develop these criteria, however, and performance characteristics such as diagnostic sensitivity and specificity have not yet been reported for DSM-5 criteria. A standardized tool, the Confusion Assessment Method (CAM), provides a brief, validated diagnostic algorithm that is currently in widespread use for identification of delirium. The CAM algorithm relies on the presence of acute onset and fluctuating course, inattention, and either disorganized thinking or altered level of consciousness. The algorithm has a sensitivity of 94% to 100%, specificity of 90% to 95%, and high interrater reliability. Given the uncertainty of diagnostic criteria for delirium, a critical area for future investigation is to establish more definitive criteria, including epidemiologic and phenomenologic evaluations assisted by advances in neuroimaging and other potential diagnostic marker tests.

Learning Objectives

- Learn the epidemiology, pathophysiology, clinical presentations, evaluation, and management of delirium in older adults.
- Understand the role of various predisposing and precipitating factors in increasing risk of older persons to delirium and associated prognosis and mortality.
- Learn the special relationship between dementia and delirium and the role of certain medications in predisposing older adults to delirium.
- Recognize that delirium is preventable in up to 50% of cases with proven effective nonpharmacologic approaches.
- Gain a clear understanding of the specific indications and efficacy of various treatments, including pharmacologic and nonpharmacologic strategies commonly used to manage delirium.

- Understand the latest concepts about special issues related to delirium, including the COVID-19 pandemic, patient preferences and decision making, nursing home care, and palliative and end-of-life care.

Key Clinical Points

1. **Delirium is commonly encountered in older adults in various clinical settings and associated with significant morbidity and mortality, especially in intensive care units, inpatient settings, nursing homes, and following major medical illnesses or surgery.**
2. **Delirium is unrecognized in up to 70% of older patients and can lead to long-term functional and cognitive deficits.**
3. **The pathophysiology of delirium is currently unclear but posited to be the end result of multiple pathogenic pathways eventually culminating in the dysfunction of various neurotransmitters and major brain networks.**
4. **Delirium is commonly due to multiple causes and is preventable in up to 50% of cases through addressing as many predisposing and precipitating factors as possible.**
5. **Among the precipitating factors, decreased mobility is strongly associated with delirium, and medical equipment and devices may further contribute to immobilization.**
6. **Dementia is the underlying risk factor in up to two-thirds of cases of delirium and must be suspected in patients with slowly progressive cognitive and functional deficits.**
7. **Acute onset, varying levels of alertness, and inattention are cardinal features of delirium, and obtaining historical details from a close family member or friend is critical in making a correct diagnosis of delirium.**
8. **Nonpharmacologic strategies are the preferred treatment for delirium in older patients, and medications are reserved for more severe symptoms that affect either medical management or patient safety.**

EPIDEMIOLOGY

Most of the epidemiologic studies of delirium involve hospitalized older patients, in whom the highest rates of delirium occur. Reported rates vary based on the subgroup of patients studied and the setting of care. Previous studies estimated the prevalence of delirium (present at the time of hospital admission) at 7% to 80% and the incidence of delirium (new cases arising during hospitalization) at 8% to 82%. The highest prevalence and incidence rates occur among ventilated intensive care unit patients. The incidence rates of delirium in high-risk hospital venues, such as the intensive care unit and surgical settings, range from 16% to 82% and 8% to 58%, respectively. Delirium occurs in up to 48% of patients in nursing homes or postacute settings, and in up to 83% of all patients at the end of life. The rates of delirium in all older persons presenting to the emergency department in several studies have ranged from 8% to 27%. While less frequent in the community setting, delirium is an important presenting symptom to outpatient clinics and often heralds serious underlying disease. Delirium is often unrecognized. Previous studies have documented that clinicians fail to detect up to 70% to 85% of affected patients across all of these settings. Furthermore, the presence of delirium portends a potentially poor prognosis. Delirium in the intensive care unit is associated with a fourfold increased risk of in-hospital mortality and a sixfold increased risk of mortality at 6 months. In the emergency department, delirium is associated with a sevenfold increased risk of mortality at 6 months. Longer lengths of stay, cognitive and functional sequelae lasting up to 1 year postoperatively, and institutionalization are also consequences of delirium.

PATHOPHYSIOLOGY

The fundamental pathophysiologic mechanisms of delirium remain unclear. Delirium is thought to represent a functional rather than structural lesion. The characteristic electroencephalographic (EEG) findings demonstrate global functional derangements and generalized slowing of cortical background (alpha) activity. It has been hypothesized that delirium is mediated via a final common pathway of different but interacting pathogenic mechanisms leading to dysfunction of multiple brain regions and neurotransmitter systems and

culminating in disruption of large-scale networks. Evidence for a single pathway is lacking, and it remains difficult to ascribe delirium to a distinct neurobiological mechanism. Another hypothesis which has gained favor is that delirium occurs in the setting of an acute stressor, such as surgery or sepsis, superimposed on an underlying brain vulnerability, such as cognitive impairment or frailty. This model suggests that as vulnerability increases, delirium can be triggered by relatively minor acute stressors. Numerous contributions to brain vulnerability have been suggested, such as structural lesions, vascular changes, alterations in brain connectivity, neuroinflammation, or neurodegeneration, and other age-related changes. Evidence from EEG, evoked-potential studies, and neuroimaging studies in delirium suggest focal dysfunction localized to the prefrontal cortex, thalamus, basal ganglia, temporoparietal cortex, fusiform, and lingual gyri of the nondominant cortex. Studies using computed tomography (CT) or magnetic resonance imaging (MRI) have found lesions or structural abnormalities in the brains of patients with delirium. Single-photon emission computed tomography (SPECT) studies have shown that delirium is mostly associated with decreased cerebral blood flow, but these results have been variable.

Associated neurotransmitter abnormalities involve elevated brain dopaminergic function, reduced cholinergic function, or a relative imbalance of these systems. Serotonergic activity may interact to regulate or alter activity of these other two systems, and serotonin levels may be either increased or decreased. Extensive evidence supports the role of cholinergic deficiency. Acetylcholine plays a key role in consciousness and attentional processes. Given that delirium manifests as an acute confusional state often with alterations of consciousness, it is likely to have a cholinergic basis. Anticholinergic drugs can induce delirium in humans and animals, and serum anticholinergic activity is increased in patients with delirium. Physostigmine can reverse delirium associated with anticholinergic drugs, and cholinesterase inhibitors appear to have some benefit even in cases of delirium that are not induced by drugs. Neurotransmitter systems can also be affected indirectly. For instance, in sepsis, the systemic inflammatory response triggers a cascade of local (brain) neuroinflammation, leading to endothelial activation, impaired blood flow, neuronal apoptosis, and neurotransmitter dysfunction. Neuroinflammation can lead to microglial overactivation, resulting in a neurotoxic response with further neuronal

injury. Animal studies have found that neurodegeneration causes priming of astrocytes and microglia, resulting in a greater neuroinflammatory response, as well as alterations in vasculature, including the blood-brain barrier, which may render the brain more vulnerable to circulating inflammatory molecules. The stress response associated with severe medical illness or surgery involves sympathetic and immune system activation, including increased activity of the hypothalamic-pituitary-adrenal axis with hypercortisolism, and release of cerebral cytokines that alter neurotransmitter systems, the thyroid axis, and modification of blood-brain barrier permeability. Age-related changes in central neurotransmission, stress management, hormonal regulation, and immune response may contribute to the increased vulnerability of older persons to delirium. The description of delirium as "acute brain failure"—involving multiple neural circuits, neurotransmitters, and brain regions—suggests that understanding delirium may help to elucidate the underlying mechanisms of brain functioning.

ETIOLOGY

The etiology of delirium is usually multifactorial. Among older persons, delirium results from the interrelationship between patient vulnerability (ie, predisposing factors) and the occurrence of noxious insults (ie, precipitating factors). For example, patients who are highly vulnerable to delirium at baseline (eg, such as patients with dementia or serious illness) can experience delirium after exposure to otherwise mild insults, such as a single dose of a sedative medication. Older patients with few predisposing factors (low baseline vulnerability) are relatively resistant, with precipitation of delirium only after exposure to multiple potentially noxious insults, such as general anesthesia, major surgery, multiple psychoactive medications, immobilization, and infection (**Figure 58-1**). Based on validated predictive models for delirium, the effects of multiple risk factors appear to be cumulative. Clinically, the importance of the multifactorial nature of delirium is that removal or treatment of one risk factor alone often fails to resolve delirium. Instead, addressing many or all of the predisposing and precipitating factors for delirium is often required before the delirium symptoms will improve.

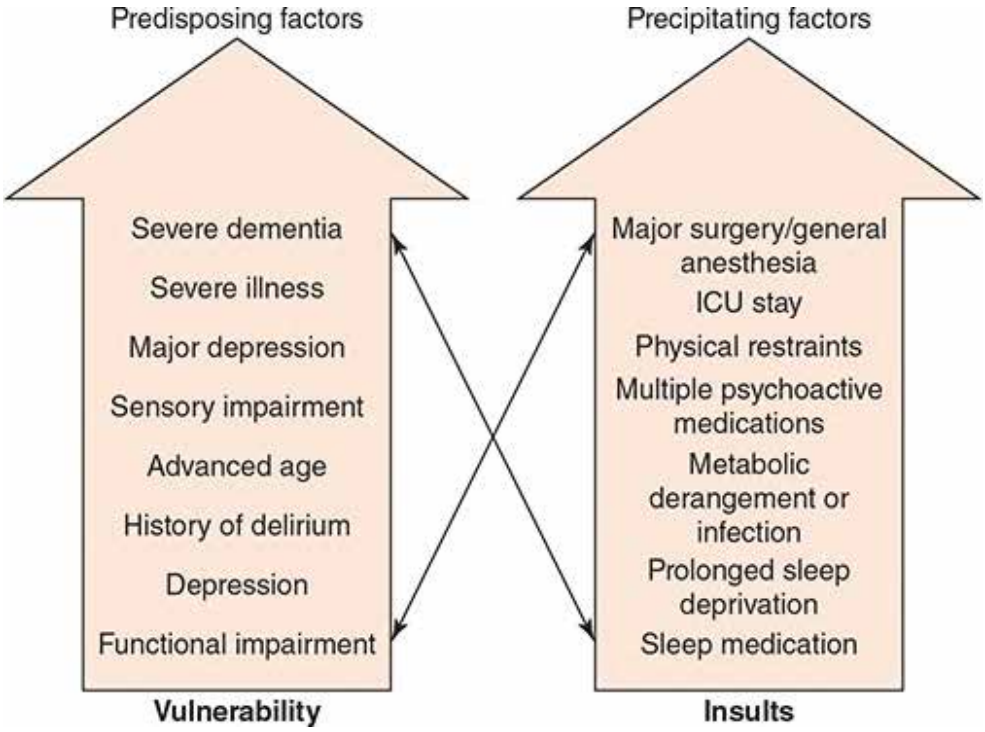

FIGURE 58-1. Multifactorial model for delirium. The etiology of delirium involves a complex interrelationship between the patient's underlying vulnerability or predisposing factors (*left axis*) and precipitating factors or noxious insults (*right axis*). For example, a patient with high vulnerability, such as with severe dementia, underlying severe illness, or hearing or vision impairment, might develop delirium with exposure to only one dose of a sleeping medication. Conversely, a patient with low vulnerability would develop delirium only with exposure to many noxious insults, such as general anesthesia and major surgery, intensive care unit (ICU) stay, multiple psychoactive medications, and prolonged sleep deprivation.

Predisposing Factors

Predisposing factors for delirium include preexisting cognitive impairment or dementia, a history of delirium, advanced age (> 70 years), severe underlying illness and multimorbidity, functional impairment, depression, alcohol abuse, a history of stroke, hypertension or transient ischemic attack, carotid artery disease and sensory impairments (vision or hearing) (**Table 58-1**). Preexisting cognitive impairment, including dementia, is one of the most powerful and consistent risk factors for delirium demonstrated across multiple studies in various settings, with patients with dementia having a two- to fivefold increased risk for delirium. Up to two thirds of delirious patients have underlying dementia. Nearly any chronic medical condition can predispose a patient to delirium, ranging from diseases involving the central nervous system to diseases outside the central nervous system, including

infectious, metabolic, cardiac, pulmonary, endocrine, or neoplastic etiologies. Predictive risk models that identify predisposing factors in populations, such as general medicine, intensive care, surgical patients (cardiac and noncardiac), cancer patients, and nursing home residents, can help identify patients at an increased risk of delirium.

TABLE 58-1 ■ PREDISPOSING AND PRECIPITATING FACTORS FOR DELIRIUM FROM VALIDATED PREDICTIVE MODELS

Predisposing factors

- Dementia or cognitive impairment
- Comorbidity/severity of illness
- Depression
- Vision and/or hearing impairment
- Functional impairment
- History of transient ischemia or stroke
- History of alcohol abuse
- History of hypertension
- Carotid artery disease
- History of delirium
- Age > 70

Precipitating factors

- Drugs (polypharmacy, psychoactive medications, sedatives, hypnotics)
- Use of physical restraints
- Indwelling bladder catheter
- Physiologic
  - Elevated BUN/creatinine ratio
  - Elevated serum urea
  - Abnormal serum albumin
  - Abnormal sodium, glucose or potassium
  - Metabolic acidosis
- Infection
- Iatrogenic complications
- Major surgical procedure (eg, aortic aneurysm repair, non-cardiac thoracic surgery, and neurosurgery)
- Trauma admission
- Urgent admission
- Coma
- ICU stay > 10 days

Precipitating Factors

Major precipitating factors identified in validated predictive models include medication use (see section on "Drug Use and Delirium"), which are associated with up to a fivefold increased risk of delirium, use of indwelling bladder catheters, use of physical restraints, dehydration, malnutrition, iatrogenic events, infections, metabolic and electrolyte derangements, surgery, admissions that are urgent or involve trauma, extended ICU stays (> 10 days), and coma (see **Table 58-1**). Decreased mobility is strongly associated with delirium and concomitant functional decline. The use of medical equipment and devices (eg, indwelling bladder catheters and physical restraints) may further contribute to immobilization. Major iatrogenic events occur in up to 40% of older hospitalized adults (three to five times the risk when compared with adults younger than 65 years) and double the risk for development of delirium. Examples include complications related to diagnostic or therapeutic procedures, allergic reactions, and bleeding caused by over-anticoagulation. Disorders of any major organ system, particularly renal or hepatic failure, can precipitate delirium. Occult respiratory failure has emerged as an increasing problem in older patients, who often lack the typical signs and symptoms of dyspnea and tachypnea. In older adults, acute myocardial infarction and congestive heart failure may present with delirium or "failure to thrive" as the cardinal feature, and minimal symptoms of angina or dyspnea. Occult infection is a particularly noteworthy cause of delirium because older patients may not present with leukocytosis or a typical febrile response. Metabolic and endocrinologic disorders, such as hyper- or hyponatremia, hypercalcemia, acid-base disorders, hypo- and hyperglycemia, and thyroid or adrenal disorders, may also contribute to delirium. Precipitating factors for delirium in hospitalized older patients that have been validated include use of physical restraints, malnutrition, more than three medications added during the previous day (> 70% of these were psychoactive drugs), indwelling bladder catheter, and any iatrogenic event. The presence of each of these independent factors confers a two- to fourfold increased risk of delirium. The presence of multiple factors has a cumulative effect, yet each risk factor is potentially modifiable.

Drug Use and Delirium

In 30% or more of delirium cases, use of one or more specific medications contributes to its development. While medications often incite delirium, they

are also the most common remediable cause of delirium. The most common culprit medications have psychoactive effects, such as sedative hypnotics, anxiolytics, narcotics, and medications with anticholinergic activity (**Table 58-2**). In previous studies, use of any psychoactive medication was associated with a fourfold increased risk of delirium; use of two or more psychoactive medications was associated with a fivefold increased risk. Sedative-hypnotic drugs are associated with a 3- to 12-fold increased risk of delirium; narcotics with a threefold risk; and anticholinergic drugs with a 5- to 12-fold risk. The incidence of delirium, similar to other adverse drug events, increases in direct proportion to the number of medications prescribed because of the effects of the medications themselves and the increased risk of drug–drug and drug–disease interactions. Suboptimal medication management, ranging from inappropriate use to overuse of psychoactive medications, occurs commonly in older adults, suggesting that many cases of delirium and related adverse drug events may be preventable.

TABLE 58-2 ■ MEDICATIONS ASSOCIATED WITH INDUCING OR WORSENING OF DELIRIUM (AMERICAN GERIATRICS SOCIETY BEERS CRITERIA, 2019)

- Anticholinergics (including antihistamines, antiparkinsonian agents, skeletal muscle relaxants, tricyclic antidepressants and paroxetine, antimuscarinics, antispasmodics, antiemetics including prochlorperazine and promethazine)
- Antipsychotics (chronic and as-needed use)
- Benzodiazepines
- Corticosteroids (oral and parenteral)
- H2-receptor antagonists (cimetidine, famotidine, nizatidine, and ranitidine)
- Meperidine
- Nonbenzodiazepine benzodiazepine receptor agonist hypnotics, including zolpidem, eszopiclone, and zaleplon
- Tricyclic antidepressants

Data from 2019 American Geriatrics Society Beers Criteria® Update Expert Panel. American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults, J Am Geriatr Soc. 2019;67(4):674–694.