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NEUROLOGIC DISORDERS IN THE OLDER PATIENT:

A PRIMER ON DIAGNOSIS AND MANAGEMENT FOR PRIMARY CARE

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Neurologic Disorders in the Older Patient: A Primer on Diagnosis and Management for Primary Care

Supplement 3 to Volume 72, October 2005

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Preface:
Internists and the older patient with neurologic illness

Internists are treating a growing number of elderly patients who have neurologic diseases. Often these patients seek diagnosis and medical care chiefly from their primary care physician rather than from a specialist in another field. Among the most common neurologic diseases in the elderly are dementia, movement disorders, seizure disorders, and the depression that often accompanies neurologic impairment. In addition, stroke prevention has increasingly come within the purview of primary care physicians.

Advances in the diagnosis and treatment of these conditions enable most older patients to be evaluated and treated effectively by their primary care physician. For this reason, we believe this collection of review articles on recognizing and managing these common conditions in the elderly is a timely update for practicing internists.

Adam Rosenblatt leads off the supplement with a comprehensive and up-to-date review of dementia. He appropriately emphasizes that dementia is a pathologic process, not a normal and acceptable accompaniment of aging. His article explores the differential diagnosis of dementia and considers the relationship between dementia and depression (see also the review by Carson and Margolin). The benefits and limitations of current treatments for the cognitive and behavioral aspects of dementia are also lucidly discussed.

Within the broad field of cerebrovascular disease in the elderly, Geoffrey Ling and Shari Ling have focused on ischemic stroke and strategies for reducing its risks with advancing age. They explore various risk factors, emphasizing aspects common to both cerebrovascular and cardiovascular disease. Preventive approaches, including modification of predisposing disorders such as hypertension, diabetes, and atrial fibrillation, are reviewed. These authors also evaluate data forming the basis for a rational approach to medical and surgical therapies to minimize the impact of the inevitable effects of aging on cerebrovascular function.

Internists may be less comfortable treating seizure disorders. To this end, Elizabeth Waterhouse and Alan Towne provide a useful summary of the types of seizure disorders, the differential diagnosis of "spells," and approaches to the diagnosis and treatment of both epilepsy and status epilepticus in older patients. Internists and geriatricians will find the clear discussion of side effects, special dosing considerations, and comparative characteristics of the newer and traditional antiepileptic drugs particularly helpful.

After Alzheimer disease, Parkinson disease is the most common neurodegenerative disorder in the elderly. Mark Baron's timely and practical review of movement disorders in the older patient helps internists navigate the differential diagnosis of Parkinson disease and other disorders that share features of parkinsonism. Among the other disorders covered are multiple system atrophy (in its major forms), progressive supranuclear palsy, dementia with Lewy bodies, essential tremor, and restless legs syndrome.

Depression is often difficult to diagnose accurately in the older patient, especially in the setting of a coexisting neurologic illness. The review by Alan Carson and Richard Margolin helpfully illuminates the subtleties of depression diagnosis and management in this population, offering advice on recognizing its manifestations in a variety of neurologic conditions and on the treatment modifications that may be required.

We hope you find these articles practical and relevant, and that they will collectively help internists provide optimal care to their older patients with neurologic disease.

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The art of managing dementia in the elderly

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ABSTRACT

Dementia presents unique challenges for physicians, patients, and families, but it also offers a singular opportunity to practice the essence of the art of medicine. Elderly patients' complaints about cognition require evaluation and should never be written off as a "normal" part of aging. Dementia should be distinguished from conditions such as delirium and depression, and the type of dementia should be identified, since this will determine treatment. Treatments seek to alter the fundamental course of the disorder, to ameliorate symptoms, or to manage concomitant psychiatric and behavioral problems. Even when treatments prove ineffective, providing information and support is of great value to patients and their families and caregivers.

KEY POINTS

Dementia in the elderly is underdiagnosed, so even though the US Preventive Services Task Force does not recommend formal dementia screening in asymptomatic elderly patients, it is nevertheless worth asking about cognitive complaints during routine office visits.

Despite misconceptions that there is a "normal," aging-associated kind of dementia, any cognitive changes that result in frank disorientation or significant impairment in daily function should never be considered normal.

Reversible, treatable cognitive impairment needs to be ruled out early, often with laboratory studies. Causative conditions may include normal-pressure hydrocephalus, hypothyroidism, vitamin deficiencies, vasculitis, and neurosyphilis.

Studies suggest that cognitive stimulation helps preserve cognition. Intellectual stimulation and mental exercise also may improve quality of life in patients with preexisting dementia.

Treatments include attempts to alter the fundamental course of the condition, to temporarily improve cognitive function, or to manage behavioral problems and functional deficiencies associated with dementia.

Dementia presents unique challenges for physicians, patients, and families. Yet for physicians it also offers a unique opportunity to practice the true art of medicine. Although dementia may evoke feelings of helplessness, its more common forms can be readily diagnosed, and many of its symptoms respond to treatment, as do associated psychiatric syndromes and behavioral disturbances. The main goal for clinicians is to remain hopeful and to communicate that hopefulness to patients and their families, keeping in mind that sometimes dementia is curable and that "incurable" does not mean untreatable. Even when treatments are ineffective, patients and their families greatly appreciate the physician's support.

This article reviews key aspects of dementia management from a primary care perspective, including the evaluation and differential diagnosis of dementia, the various types of dementia, and available therapies and management strategies.

THE SCOPE OF THE PROBLEM

Dementia may be defined as a global decline in cognitive function, including impairment of memory, that is due to an abnormal change in the structure or function of the brain and is sufficient to interfere with day-to-day function.

Dementia, including Alzheimer disease or Alzheimer dementia (AD), is one of the most common neurologic disorders of the elderly, affecting approximately 8% to 10% of people older than 65 years and perhaps as many as 40% of those older than

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TABLE 1
Conditions resembling dementia in the elderly

Condition	Description	Ways to distinguish from dementia	Potential course of action
Age-related cognitive changes	Decline in cognitive performance in the elderly (typically memory lapses) that is normal for age and education	Within norms for age and education No impairment of day-to-day function	Reassure patient that changes are normal
Mild cognitive impairment	Cognitive decline with performance below normal for age and education, not causing significant functional impairment	Not severe enough to impair day-to-day function	Follow closely, consider presumptive treatment
Delirium	Reversible impairment of attention and consciousness caused by intervening medical condition	Acute onset Condition fluctuates from one exam to another Impaired consciousness	Identify and address underlying medical cause
Depression	Mood disorder that may present with cognitive complaints, paucity of speech, or functional difficulties	Depressive symptoms Subacute onset Prior history	Antidepressants and/or psychotherapy

85 years.[1] It has enormous associated costs of as much as $80 to $100 billion per year,[2] leads to psychiatric symptoms of "burnout" in caregivers,[3] and is a common cause of institutionalization of elderly persons.[4,5]

The prevalence of dementia in nursing home populations has been estimated at 25% to 74%.[6,7] The Maryland Assisted Living Study, the first large-scale study to perform comprehensive evaluations for dementia on a population sample in this setting, indicated a rate of 68%, with another 7% suffering from other forms of cognitive impairment.[8] This finding suggests that lower estimates may have been, in part, due to cursory examination or the use of proxies to estimate the prevalence of dementia.

DETECTING DEMENTIA IN THE ELDERLY

Dementia is underdiagnosed in clinical settings.[9,10] The US Preventive Services Task Force did not find sufficient evidence to recommend formal dementia screening in asymptomatic elderly persons,[11] but clinicians should ask about cognitive complaints during routine visits. Suspicion of dementia is warranted whenever an elderly patient presents with a memory complaint, difficulties with activities of daily living, personality change, or a new behavioral problem. Obtaining a baseline cognitive score may assist with diagnosis if a patient develops a progressive decline or becomes acutely delirious, much as baseline electrocardiography may help in the assessment of chest pain.

In addition to the Mini-Mental State Examination (MMSE),[12] tests that have been advocated for screening of dementia include the General Practitioner Assessment of Cognition (GPCOG),[13] the Abbreviated Mental Test (AMT),[14] the clock-drawing test,[15] and the Mini-cog, a clock-drawing test in combination with a three-word recall.[16] The MMSE has the advantages of being widely known and easy to score and of assessing various cognitive domains. Truncating the MMSE to its orientation questions, or describing a patient as "alert and oriented ×3," is insensitive, is not comparable to the findings of other clinicians, and will tend to miss non-Alzheimer dementias.

EVALUATING FOR DEMENTIA

The first task of the clinician evaluating a patient with a cognitive complaint is to decide whether an objective problem exists at all.

Age-related cognitive changes

The patient may be complaining of normal age-related cognitive changes (Table 1), particularly in the area of memory.[17] The instruments used for cognitive assessment, such as the MMSE, have norms based on age and educational level,[18] but the distinction can be difficult in mild cases and in the very old, in whom dementia is common and norms have not

been well established.

A widely held misconception about dementia is that there is a "normal" kind of dementia, associated with the aging process, that is different from AD and other named conditions. Age-related cognitive changes should not result in frank disorientation or significant impairment in daily function. It is common for families to bring a loved one to the clinic hoping to hear that the changes are simply due to "old age." The clinician must explain that, while common in the elderly, dementia is a disease process amenable to assessment and treatment and no more "normal" than other diseases of the elderly, such as macular degeneration or osteoporosis.

Mild cognitive impairment

Another condition to consider is mild cognitive impairment (MCI) (Table 1). Defined relatively recently, MCI is a decline in cognitive function that becomes a focus of clinical attention but is not severe enough to merit the diagnosis of dementia. Recent studies indicate a 10% to 15% annual progression to AD.[19]

Some very educated or intelligent patients may report a decline in their previously very high level of cognitive functioning but, in the absence of baseline testing or because of ceiling effects, may show test performance within norms for their age and educational level. Other explanations of the cognitive complaint, such as depression, should be ruled out, and such patients should be reevaluated periodically to determine whether a dementia has manifested itself and to look for evidence of progression.

There is recent evidence that progression of MCI to dementia may be delayed by some of the medications indicated for the treatment of AD,[20] but there is as yet no professional consensus on the treatment of MCI. Clinicians may consider empiric pharmacotherapy, particularly if there is a family history of dementia.

Cognitive changes that are not dementia

When a patient with a definitive cognitive change has been identified, various nondementia conditions must also be considered (Table 1). Chief among these are delirium and depression.

Delirium may be distinguished from dementia by its more acute onset, a disturbed or fluctuating level of consciousness, and the presence of an acute or chronic medical problem commonly associated with delirium, such as hypoxia, sepsis, renal failure, or polypharmacy. Studies suggest that delirium occurs in 14% to 56% of hospitalized elderly patients, among whom it is associated with death rates of 10% to 65%.[21] The condition is also frequently observed in ambulatory patients.

It is possible for delirium and dementia to coexist. In fact, demented persons are especially vulnerable to delirium.[22] Sometimes a patient with dementia may present with delirium. In other instances, preexisting dementia may obscure the diagnosis of delirium, with grave consequences if the cause is not addressed.

Dementia of depression. Elderly patients with depression may present with cognitive complaints, paucity of speech, or functional difficulties that suggest a dementing process. They may have subjective cognitive complaints[23] or show objective cognitive impairment on the MMSE or on more comprehensive testing.[24] The common term for this condition is "pseudodementia," although a more accurate term is "the dementia of depression."[25] The dementia of depression may be compared to other reversible dementias found in conjunction with other severe medical problems such as beriberi or myxedema.

Depression may be distinguished from dementia on the basis of family history, history of depression, subacute onset, presence of overt depressive symptoms, and results of neuropsychological testing, on which it tends to show a more subcortical pattern.[26] Depression can coexist with dementia, leading to a bleaker cognitive picture and making it hard to ascertain the true severity of the dementia. In such cases it is best to withhold prognostic judgment until the depression has been treated.

DETERMINING THE TYPE OF DEMENTIA

Evaluation of dementia

Once the clinician is convinced that a patient has dementia, the next step is to identify the type (Table 2). The evaluation of dementia begins with a comprehensive history, often obtained from a family member, paying special attention to whether the onset of the condition was insidious and difficult to pinpoint in time or more subacute, whether the progression (if any) was gradual or stepwise, and specific neurologic and psychiatric symptoms encountered since the onset of the illness.

The history is the most informative part of the evaluation, and clinicians will usually have a strong suspicion as to the type of dementia on the basis of the history alone. The diagnosis will then be refined on the basis of the neurologic and mental status examinations, the results of neuropsychological testing, and imaging and laboratory studies. The neurologic examination is useful in detecting focal changes, evidence of extrapyramidal syndromes such as parkinsonism, and frontal release signs.

Formal neuropsychological testing is not always

TABLE 2
Dementias of the elderly

Type of dementia	Frequency	Distinguishing features	Supportive tests
Alzheimer dementia	55%–75% of dementia cases	Insidious onset Progressive worsening Clear consciousness Nonfocal exam	CT or MRI Functional imaging *ApoE ε4* allele
Vascular dementia	13%–16% of cases	Focal neurologic exam Stepwise progression	CT or MRI
Dementia with Lewy bodies	15%–35% of cases	Fluctuating cognition Visual hallucinations Parkinsonism	Functional imaging Neuropsychological testing
Frontotemporal dementia	Uncommon	Insidious onset Gradual progression Impaired personal conduct Emotional blunting Weight loss	Functional imaging Neuropsychological testing

available, but it can help describe the pattern of cognitive deficits. For example, it may help make the distinction between cortical and subcortical dementia. Cortical dementias such as AD are typically characterized by amnesia, disorientation, and relatively preserved personality.[27] Patients with subcortical dementias, such as those associated with HIV infection, Parkinson disease, Huntington disease, and some vascular dementias,[28] tend to show relatively preserved memory but have difficulties in executive function, attention, and concentration. They also generally show a greater degree of personality erosion and psychiatric symptoms such as apathy, irritability, disinhibition, and perseveration.[29] Finally, testing may also be important therapeutically by helping to delineate the patient's strengths and weaknesses and thus to identify likely areas of trouble, to suggest compensation strategies, and to aid in behavioral management.

Alzheimer dementia

AD is the most common type of dementia, accounting for approximately 55% to 75% of cases on the basis of autopsy studies.[30,31]

According to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA), the criteria for probable AD include a course characterized by gradual-onset and continuing cognitive decline and the following:

(1) Dementia established by examination and objective testing
(2) Deficits in two or more cognitive areas
(3) Progressive worsening of memory and other cognitive functions
(4) No disturbance in consciousness
(5) Onset between 40 and 90 years of age
(6) Exclusion of systemic disorders and other brain diseases that could account for the cognitive and memory deficits.[32]

AD is often spoken of as a diagnosis of exclusion, but this may lead some clinicians to avoid making an explicit diagnosis even in straightforward cases. Although microscopic examination of the brain is the only way to be 100% certain, the clinical diagnosis of AD is approximately 90% accurate as shown by autopsy confirmation.[33]

Other tests to confirm the diagnosis of Alzheimer dementia. In addition to the clinical evaluation, a number of tests may serve to confirm or strengthen the diagnosis in patients with an unusual presentation, in patients who are unusually young, or even when the patient or family are having difficulty accepting the diagnosis. These may include functional neuroimaging such as positron-emission tomography and single-photon-emission computed tomography, and genetic tests such as for the *ApoE ε4* allele, a risk gene that is associated with the common late-onset variety of AD[34] and that may support the diagnosis of AD in a patient with a likely clinical presen-

tation. However, being homozygous for the *ApoE ε4* allele does not guarantee that the dementia is AD, and having no *ApoE ε4* allele does not exclude it.

Commercial testing is also available for presenilin 1[35] and the much less common presenilin 2.[36] These are causative mutations associated with a familial early-onset form of AD, and testing should be reserved for unusual cases.[37] More widespread use of genetic testing for AD is controversial and, because of ethical considerations, should generally be limited to research studies.

Withholding the diagnosis of Alzheimer dementia. Reluctance to tell patients and families of the diagnosis of AD may stem more from a lack of comfort in discussing dementia than from genuine uncertainty. At least in the United States, it is no longer considered ethical to deliberately withhold a diagnosis from a patient except in the most extreme circumstances. Clinicians sometimes worry that telling a patient that he or she is suffering from AD will precipitate depression or otherwise reduce the person's quality of life. There is no evidence to support this idea. In fact, explaining the diagnosis and prognosis to patients and families in a supportive way, emphasizing how common the problem is, that progression is slow, that treatments are available, and that it is still possible to enjoy life, will enable the patient to make appropriate plans for the future, abstain from dangerous or especially frustrating activities, and take advantage of available therapies and support services and organizations.

Vascular dementia

Vascular or multi-infarct dementia is probably the second most common form of dementia and accounts for approximately 13% to 16% of cases.[30,31]

The clinical diagnosis of vascular dementia is not as accurate as that of AD, with AD and mixed pathology often found at autopsy.[38] Published criteria[39] define it as a cognitive disorder resulting from ischemic or hemorrhagic stroke or from ischemic-hypoxic brain lesions as evidenced by the following:

(1) A diagnosis of dementia
(2) Cerebrovascular disease defined by the presence of focal signs on neurologic examination and evidence on brain imaging
(3) A relationship between criteria 1 and 2 implied by onset of dementia within 3 months after a stroke, with abrupt deterioration in cognitive function or fluctuating, stepwise progression of cognitive deficits.

Criterion 2 is particularly important, as vascular dementia should not be diagnosed in the absence of focal findings, solely on the basis of vascular risk factors such as hypertension or diabetes. To do so might yield the wrong prognosis and would deprive patients of available therapies indicated for AD.

Dementia with Lewy bodies

Dementia with Lewy bodies (DLB) is a third type of dementia, with its own characteristic neuropathologic findings, ie, the presence of cytoplasmic inclusions, which are found in the substantia nigra of patients with idiopathic Parkinson disease but in DLB are distributed widely throughout the cortex.[40]

Clinically, as in most dementias, the central feature is progressive cognitive decline interfering with normal functioning. However, prominent or persistent memory impairment is not necessarily present in the early stages, whereas deficits on tests of attention and frontal-subcortical skills may be prominent. The core clinical features are fluctuating cognition; recurrent visual hallucinations, typically of a well-formed and detailed sort; and parkinsonism. One of these features is required for a diagnosis of possible DLB and two for probable DLB. Features considered supportive of the diagnosis are repeated falls, syncope, transient loss of consciousness, neuroleptic sensitivity, systematized delusions, and hallucinations in other modalities.[41] Functional neuroimaging may also be helpful in identifying likely cases.

Estimates of the prevalence of DLB are somewhat controversial. Autopsy studies have demonstrated the presence of Lewy bodies in approximately 15% to 35% of demented autopsy subjects, which would make DLB the second most common type of dementia.[42] However, many of these subjects never manifested the expected syndrome while living.

The precise relationship of DLB to both AD and Parkinson disease is not fully understood. As with vascular dementia, the diagnosis of DLB should not be made in patients who do not meet any of the core criteria, ie, only on the basis of supportive findings such as psychosis or adverse response to a neuroleptic drug.

Frontotemporal dementia

Finally, there are several subtypes of frontotemporal dementia.[43] The consensus criteria include insidious onset and gradual progression, with early decline in social conduct, impaired regulation of personal conduct, emotional blunting, and loss of weight. Supportive features include a behavior disorder characterized by decline in personal hygiene, mental rigidity, distractibility, hyperorality and dietary changes, perseveration and stereotyped behavior, and utilization behavior (ie, unrestrained exploration of objects

TABLE 3
Commonly prescribed agents for Alzheimer dementia (AD)

Drug	Indication	Starting dose	Effective dose	Maximum dose	Side effects
Donepezil	Mild-moderate AD	5 mg once daily	5 mg once daily	10 mg once daily	Nausea, vomiting, diarrhea
Rivastigmine	Mild-moderate AD	1.5 mg twice daily	3 mg twice daily	6 mg twice daily	Nausea, vomiting, anorexia, dizziness
Galantamine (extended-release)	Mild-moderate AD	8 mg once daily	16 mg once daily	24 mg once daily	Nausea, vomiting, anorexia, dizziness, syncope
Memantine	Moderate-severe AD	5 mg once daily	10 mg twice daily	10 mg twice daily	Dizziness, headache, confusion, constipation

in the environment). Speech and language abnormalities are often present, characterized by altered speech output, stereotypy, echolalia, perseveration, and mutism. Physical signs can include primitive reflexes, incontinence, akinesia, rigidity and tremor, and low or labile blood pressure.[44] Dementias due to other neurologic disorders such as Parkinson disease, Huntington disease, or hydrocephalus can presumably be recognized by the features of these conditions.

Conditions to rule out

A number of reversible, or at least treatable, forms of cognitive impairment need to be ruled out early in the process, often by means of laboratory studies. These include conditions such as normal-pressure hydrocephalus, hypothyroidism, vitamin deficiencies, vasculitis, and neurosyphilis. The usual panel of tests consists of an interview to rule out depression, an imaging study, if not previously performed, vitamin B_{12}, and thyroid-function screening. Rapid plasma reagin, erythrocyte sedimentation rate, and other tests such as HIV antibody or toxicology screening may be dictated by specific elements of the history or presentation.[45] Although these conditions rarely account for the entire presentation, they are easily ruled out by simple tests and may result in permanent or fatal complications if left untreated.

TREATMENT OF DEMENTIA

Treatment of dementia has many different meanings. It can refer to treatments that seek to alter the fundamental course of the condition, symptomatic treatments that temporarily improve cognitive function, or strategies that help to manage some of the comorbidities of dementia, such as behavioral problems and functional deficiencies.

No treatments have been definitively shown to alter the histopathologic progression of AD. In the case of vascular dementia, plausible treatments include an attempt to mitigate the progressive course through aggressive management of vascular risk factors, such as hypertension, hypercholesterolemia, or diabetes. Aspirin and other anticoagulants are commonly used for secondary prevention of further cerebrovascular accidents but have not been definitively established as useful for vascular dementia. Vascular dementia may respond symptomatically to some of the medications used for AD.[46]

Cognitive stimulation

Patients' families often ask whether some form of mental exercise will help maintain cognitive function in persons suffering from dementia. Some studies suggest a protective effect of cognitive stimulation.[47] Intellectual stimulation and mental exercise may also improve quality of life in persons who already have dementia—for example, by helping them maintain an appropriate sleep-wake cycle. This is a particular focus of 2005 Alzheimer's Association chapter educational programs. The practice, however, should not be taken to extremes, putting patients at odds with their families or doctors over exercises and challenges that are beyond their desire and capabilities.

Drugs approved for Alzheimer dementia

Five drugs have been approved by the US Food and Drug Administration for the treatment of AD, and four are commonly prescribed (Table 3). All are intended to target symptoms, although there have been suggestions[48] that they could also affect underlying pathologic changes.

The life expectancy of the typical AD patient is

approximately 4 to 6 years.[49] The use of these agents is therefore justified by the fact that they can provide symptomatic improvement for most of that time, as controlled and uncontrolled studies suggest.[50,51]

The acetylcholinesterase inhibitors (ACIs) tacrine, donepezil, rivastigmine, and galantamine have all been shown in controlled studies to improve measures of cognitive function such as the MMSE or AD Assessment Scale cognitive subscale (ADAS-cog), measures of functional abilities,[52,53] and measures of behavioral disturbance such as the Neuropsychiatric Inventory (NPI).[54–56] Tacrine is rarely used any more because of its hepatic side effects and complicated dosing regimen. Despite pharmacologic speculations to the contrary, the remaining three agents appear to be about equally efficacious.[57,58] Donepezil is the most widely used and seems to be the most easily tolerated.[59] Patients can be switched from one agent to another in the case of inefficacy or intolerability but should first receive an adequate trial.

The effects of the ACIs can be subtle and must be observed against a background of expected cognitive decline. A reasonably sensitive quantitative instrument such as the MMSE is important for detecting initial improvement, demonstrating treatment effects to the patient and family, and following the patient longitudinally.

Educating patients and families is also paramount. Patients and families should understand that improvements will usually be mild and that the patient's condition will continue to decline but, it is hoped, not to the same point as would be reached without treatment. Families tend to lose heart when the patient who showed a response to an ACI crosses the initial baseline, and they sometimes conclude that the drug has "stopped working." However, sudden discontinuation at this point deprives the patient of ongoing benefit from the drug and sometimes leads to a sharp decline in function.

How long to continue these agents is currently a matter of individual clinical judgment, but an ACI need not be discontinued at some arbitrary point if it is well tolerated and the patient clearly showed an initial response.

The ACIs are approved only for the treatment of patients with mild to moderate AD, which might correspond to an MMSE score of 10 or above. Recent studies suggest a possible role for these medications in patients with moderate to severe AD[60] and vascular dementia.[61]

Memantine is an *N*-methyl-D-aspartate receptor antagonist approved in the United States for the treatment of moderate to severe AD. Controlled studies have shown that it improves cognition and function[62] compared with placebo, with an effect size similar to that of the ACIs. The role of memantine in vascular dementia is unclear, with some data to suggest an improvement in cognition but not in global function.[63]

Memantine is the only agent approved for use in patients with severe AD (MMSE ≤ 10, approximately), but is not currently approved for mild cases (MMSE > 17, approximately), but the range of indications for all these agents will probably expand.

Since memantine belongs to a different class than the ACIs, combination therapy may be possible. There is already evidence that the addition of memantine can further improve the cognitive function of responders to donepezil.[64]

Do current drugs improve long-term outcomes?

A controversial topic is whether the ACIs produce long-term benefits that might improve mortality or institutionalization rates. Some observational studies seem to demonstrate better long-term outcomes for AD patients who continue to take ACIs.[65] Unpublished data from the Maryland Assisted Living Study suggest that ACI use has a significant effect on retention of AD patients in assisted living centers, at least until the 6-month mark. On the other hand, in a recently published controlled study of community-dwelling AD patients in the United Kingdom, donepezil produced improvements in cognition and function compared with placebo but did not improve institutionalization rates.[66] The study population was much smaller than intended because of recruitment problems. On the basis of these findings the authors concluded that ACIs are "not cost-efficient."

Based on controlled clinical trials, ACIs improve the cognition, function, and quality of life of AD patients, and these effects are detectable and clinically significant. These studies support the routine use of such medications in patients with mild to moderately severe AD. Issues of cost and long-term outcomes are still unresolved but should not prevent clinicians from attempting to provide symptom relief. Even small gains in function can be very important to patients and their families when the baseline is already so impaired.

Proposed therapies with little supportive evidence

Vitamin E. In AD, retrospective studies have seemed to show prophylactic effects for vitamins E and C.[67] These results have led to trials in the symptomatic population. A randomized clinical trial compared

vitamin E and the antiparkinson drug selegiline, alone and in combination, with placebo in 341 patients with AD.[68] In the first analysis, there were no significant differences between any of the groups in the primary outcome measure, time to death or institutionalization. When a statistical correction was performed to account for the MMSE score at baseline, a significant effect emerged for both agents. This led some physicians to treat AD patients with 1,000 units of vitamin E twice a day. However, recent concerns about all-cause mortality in relation to vitamin E doses of 400 units or higher has caused most clinicians to stop recommending the use of vitamin E.[69] There has been no similar trend toward the use of selegiline.

A recent trial of vitamin E in MCI has thus far yielded negative results.[20]

To date there is no direct evidence that vitamin supplements prevent AD.

Hormone therapy and NSAIDs. Like vitamin therapy, the use of nonsteroidal anti-inflammatory drugs (NSAIDs) has appeared to show a protective effect against AD in retrospective studies.[70,71] Additionally, hormone replacement therapy in women has been associated with a lower risk of developing AD in a prospective study,[72] although estrogen-progestin combination therapy actually appeared to increase the risk of AD in another prospective trial.[73] Among patients already symptomatic for AD, estrogen replacement proved ineffective against AD in one study,[74] as did NSAIDs in another.[75] The Alzheimer Disease Anti-inflammatory Prevention Trial, a large-scale study of the prophylactic effect of the NSAIDs naproxen and celecoxib vs placebo in subjects at risk for AD by virtue of age and family history, has been suspended because of safety concerns.[76]

Treatment of behavioral problems in dementia

Behavioral symptoms are extremely common in persons with dementia,[77] are frequently serious,[78] and can lead to caregiver burnout, institutionalization, and higher costs.[79] Even if the dementia does not respond to treatment of cognitive dysfunction, successful treatment of psychiatric and behavioral problems may produce a substantial difference in outcome.

Depression. The reported prevalence of major depression in patients with dementia is high—approximately 20%.[80,81] Depression should not be dismissed as simply the patient's reaction to having dementia. It may have an atypical presentation in this population because of impaired communication. The patient may present with such problems as anorexia, social withdrawal, insomnia, or increased agitation. Purely symptomatic treatments such as benzodiazepines may make matters worse. In ambiguous cases, presumptive treatment for depression may be considered.

Depressed persons with dementia are not amenable to most forms of psychotherapy but can be supported and reassured. A wide range of antidepressant drugs may be useful, although there are few published efficacy trials such as the Depression in Alzheimer's Disease Study (DIADS).[82,83] This population is very sensitive to side effects and delirium, so clinicians should be cognizant of polypharmacy issues, including the half-lives, potential interactions, and anticholinergic properties of the drugs in question. Selective serotonin reuptake inhibitors (SSRIs) are probably the most common first choice. The drug selected must be given in an appropriate geriatric dose for an appropriate duration (generally 8 to 12 weeks) in the initial trial, and the patient must be evaluated at intervals to see if the treatment is helping.

Psychosis. Psychosis, the presence of delusions and hallucinations, is not uncommon in demented patients.[77] It can be a primary feature of the dementia itself or an aspect of other conditions such as delirium or, in the case of visual hallucinations, eye disease.[84] Apparent psychosis in patients with dementia does not always require drug treatment—or any intervention, for that matter. For example, demented patients frequently confabulate, but this is unlikely to respond to neuroleptics and differs from delusions in that the erroneous beliefs are not fixed. When confabulating patients report impossible events such as visits by deceased relatives, families often tell the clinician, incorrectly, that the patient is hallucinating.

Visual agnosias and misinterpretations such as being unable to recognize one's own reflection may also be misinterpreted as hallucinations. When the presence of delusions or hallucinations is confirmed, the clinician must rule out reversible causes and consider how much harm the symptom is actually producing and whether the benefits of drug therapy are likely to outweigh the risks. A delusion that a caregiver is actually the patient's daughter, for example, might be handled with humor and gentle reminders or may not need to be confronted at all. Families should be instructed to "pick their battles" and not to argue unnecessarily in an attempt to counter false beliefs.

When pharmacotherapy is attempted, the newer antipsychotic agents such as risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole are generally better tolerated by elderly patients. Among the older drugs, high-potency agents such as haloperidol have

fewer anticholinergic effects. It is also possible that ACIs alone may mitigate psychosis.[54–56]

Executive dysfunction. Patients with every sort of dementia, but particularly the so-called subcortical varieties such as the dementia of Parkinson disease, Huntington disease, or HIV infection, may show a constellation of symptoms described by the pseudoanatomical term "frontal." This may be described more accurately as the executive dysfunction syndrome.[85] Typical symptoms include apathy, disinhibition, perseveration, and irritability. Common problem behaviors include wandering, calling out, rooting, and explosive outbursts. Some of these behaviors may be managed by close observation and control of the environment. Very scant treatment data are available, and there are no established or approved therapies, but medications that have been tried include ACIs, SSRIs, amphetamines, and dopaminergic agents such as amantadine.[86]

Agitation. Agitation is a term that conveys little useful information. It is not a diagnosis, and there are no specific treatments for it. Caregivers and staff members should be trained by the clinician to describe the actual problem behavior, whether it is calling out, hitting, wandering, being uncooperative with personal care, or some other issue. The clinician's task is to determine the nature and pattern of the problem behavior, to uncover precipitants and mitigating factors, and to make specific diagnoses where possible. For example, an elderly patient with dementia may be constantly irritable and combative, as in a condition such as mania; may be combative only during short, predictable intervals, such as during personal hygiene; or may display a truly random pattern. The first problem would require a specific treatment. The second might be managed environmentally with extra supervision, a gentle manner, and possibly very time-limited use of physical restraints. Only the final scenario might require "something for agitation."

In cases of explosive, violent, or obnoxious behavior that seems to arise directly out of the dementia and is not amenable to behavioral treatment or environmental interventions, the possible range of medications includes antidepressants, neuroleptics, anticonvulsants, benzodiazepines, beta-blockers,[87] amphetamines, and dopaminergic agents.[86] Deliberate sedation is a last resort, since the goal is to treat the behavioral syndrome while preserving the patient's ability to participate in activities that contribute to quality of life.

SUMMARY AND SYNTHESIS

Dementia is a common, serious, yet treatable condition in the elderly. Although many clinicians do not have a high level of comfort in screening for, diagnosing, and treating dementia, the most common forms of dementia can be readily diagnosed, largely on the basis of the history. Many symptomatic treatments exist, and the outlook is even more favorable for treatment of associated psychiatric syndromes and behavioral disturbances.

Clinicians can offer the best care by striving to remain hopeful and to communicate hopefulness to patients and their families, keeping in mind that sometimes dementia is curable, necessitating a comprehensive initial evaluation and a search for reversible causes; that "incurable" does not mean untreatable; and that even when dementia does not respond to direct treatment, it may have treatable consequences, such as depression.

The management of the patient with dementia, including the provision of diagnosis, prognosis, and support, even when other treatments prove ineffective, is greatly appreciated by patients and their families. The clinician need not feel helpless and should take comfort in knowing that the services he or she is providing represent the very essence of the physician's art.

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Preventing ischemic stroke in the older adult

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ABSTRACT

Stroke is a deadly and disabling disease that preferentially afflicts older adults. It shares common risk factors with myocardial infarction (MI), such as hypertension, diabetes, and hyperlipidemia. Blood pressure control, cholesterol reduction with statins, and glucose control reduce the risk for both stroke and MI. Additionally, management of atrial fibrillation with warfarin reduces stroke risk. Beyond risk factor reduction, antiplatelet therapy is an effective option for lowering the likelihood of stroke in at-risk patients. Among antiplatelet agents, aspirin has been shown effective for secondary stroke prevention as well as primary and secondary MI prevention; clopidogrel for secondary stroke and MI prevention; and both ticlodipine and dipyridamole for secondary stroke prevention. Combining antiplatelet agents is rational. Carotid endarterectomy should be considered for stroke prevention in patients with ischemic symptoms; for patients with asymptomatic stenosis, potential benefit must be balanced against surgical risk.

KEY POINTS

In older patients, stroke and myocardial infarction (MI) are causally linked and treatments that effectively reduce risk for one also reduce risk for the other.

Prior stroke increases the risk of MI threefold, and prior MI increases the risk of stroke threefold. Death in stroke patients is due largely to the coexisting relationship of stroke with heart failure.

Hypertension increases the risk of stroke sevenfold. Reducing blood pressure lowers the risk for first stroke by 30% to 45%, and perhaps by 55% to 60% if normotension is attained.

In elderly patients, blood pressure reduction must be gradual to maintain normalized cerebral blood flow and reduce the risk of ischemic injury.

Although antiplatelet therapy substantially lowers the incidence of stroke and MI in at-risk patients, fewer than 50% of patients who stand to benefit from antiplatelet therapy receive it.

The utility of carotid endarterectomy for stroke prevention in at-risk patients is highly dependent on whether the patient has ischemic symptoms, the degree of stenosis, and the surgeon's perioperative complication rate.

Cerebral infarction (stroke) and myocardial infarction (MI) are critically important diseases. This is particularly true among the elderly. Alone, stroke is the third leading cause of death and disability among adults. The incidence of stroke has continued to increase since the mid-1960s, with up to 700,000 new cases reported in the United States each year.[1,2] Although significant advances have been made in our understanding and treatment of this disease, it remains a scourge. However, the close relationship of stroke and MI means that comprehensive risk factor management, proper antiplatelet therapy, and appropriate surgical intervention can greatly reduce the risk for both.

STROKE CLASSIFICATION AND PATHOGENESIS

There are two main stroke categories of etiologic importance: ischemic stroke, accounting for about 83% of cases, and hemorrhagic stroke.[3] The ischemic strokes are attributable to arterial thrombosis (20%), embolism (25%), small-vessel disease (25%), and cryptogenic causes (30%). Hemorrhagic strokes are further subcategorized as intraparenchymal (60%) or subarachnoid hemorrhage (40%). As ischemic stroke is the cause of significant morbidity and mortality in the elderly, its

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prevention will be the focus of this article.

In older adults, the predominant process leading to the development of stroke is progressive atherosclerosis (Figure 1).[4,5] Temporal arteritis and amyloid angiopathy, although infrequent, disproportionately afflict older adults and also result in stroke. Some recently identified diseases such as homocysteinemia may prove to increase the risk for stroke in the elderly, but their roles are uncertain, as are specific intervention strategies.

The sidebar on page S16 provides an overview of stroke pathogenesis.[4–7]

Similarities with ischemic heart disease

Ischemic brain disease and ischemic heart disease share pathogenesis and risk factors, and it is not surprising that these diseases often coexist. Nearly 60% of patients over age 60 presenting with ischemic stroke have evidence of coronary artery occlusion.[8] A review of leading secondary stroke prevention trials reveals that 30% to 35% of these patients also have significant coronary artery disease.[9–12] This pattern of coexistence is consistent across diverse ethnic backgrounds.[13] The high prevalence of acute coronary syndromes has stimulated extensive research on ameliorating this disease. Neurologists and neuro-interventionalists have adopted clinical strategies developed by cardiologists for managing heart disease. Antihypertensive and lipid-lowering agents, glucose management, antiplatelet therapy, surgical management, reperfusion treatments, and endovascular interventions are all being used.

SEQUELAE AND COMPLICATIONS OF STROKE

With a 5-year mortality of greater than 50%, stroke is a deadly disease that ranks with serious cancers such as hepatic carcinoma and invasive bladder cancer.

A 2003 analysis of the Perth Community Stroke Study database showed that 60% of stroke patients die within 5 years and 80% within 10 years.[14,15] The risk of death among 1-year survivors remains fairly consistent at 10% per year, and the annual case fatality rate is 5% per year.[14,15] A 2003 analysis of a Connecticut Medicare database likewise found that 60% of patients who suffer ischemic stroke die within 5 years.[16] Survival after transient ischemic attack (TIA) is also poor, with 49.6% mortality at 5 years.[16] Furthermore, patients who have survived one stroke are at nine times greater risk for subsequent stroke,[17] with incident stroke as the leading cause of death in the first 6 months following the index stroke.[18,19]

The coexistence of stroke and MI has profound prognostic significance. Patients who have had a stroke are at three times greater risk for MI compared with patients sharing a similar risk factor burden who have not had a stroke.[20] Conversely, patients who have had an MI are at three times greater risk for stroke than patients who have not had an MI. Any history of nonacute cardiac disease also dramatically increases the risk for stroke. History of congestive heart failure increases stroke risk fourfold, and this is further doubled if the patient has atrial fibrillation.[18]

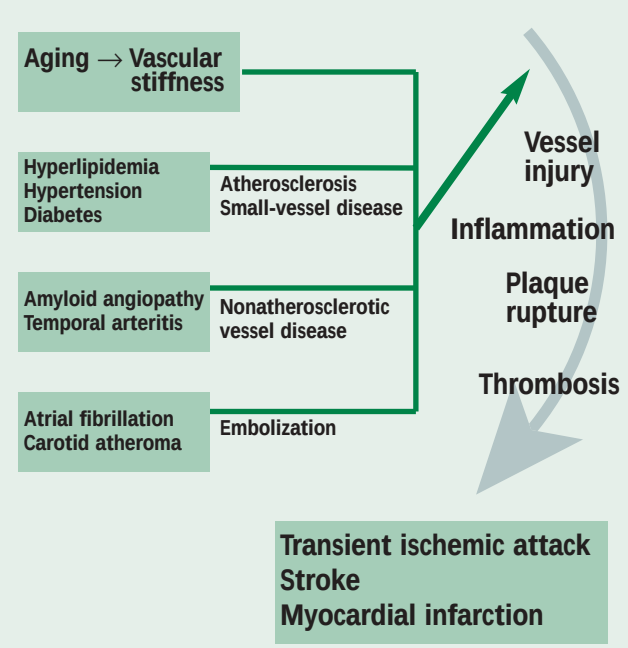

FIGURE 1. Schematic showing contributors to and progression toward stroke and myocardial infarction.

Coexisting heart disease is major driver of mortality

Death in stroke patients is due largely to the coexisting relationship with heart disease. A 1993 analysis from the Oxfordshire Community Stroke Project found that 35% of patients with stroke die from cardiovascular causes during the first 6 years after the initial event.[21] This is twice the number of deaths due to stroke (17%).[21] The Northern Manhattan Stroke Study confirmed these results in 2001, finding 29% of deaths to be attributable to cardiac events compared with 8% to incident stroke.[19] In 2003, the Perth Community Stroke Study yielded similar results, finding incident stroke to be the leading cause of death in the first 6 months after the index stroke, with death chiefly attributable to cardiac events thereafter.[15] During years 1 to 10 after the index stroke, cardiac events accounted for 41% of deaths and recurrent stroke for only 5% of deaths.[15]

Stroke pathogenesis at a glance

Stroke starts with endothelial damage to intracranial cerebrovasculature or extracranial conductive vessels to the brain (eg, the aortic arch, the carotid or vertebral arteries). In general, damage is induced by underlying conditions such as hypertension or diabetes. The ensuing lesion initiates an inflammatory response that is mediated by macrophages. In a hyperlipidemic state, macrophages filled with lipid are known as "foam cells." These foam cells respond to the injured endothelium and give rise to a connective tissue–protein matrix that becomes, in turn, the atheromatous plaque. Over time, the endothelium is reinjured and the cycle repeats.

As the plaque increases in size, the blood vessel lumen narrows, which eventually can compromise blood flow. If this process is not mitigated, lumen occlusion develops, resulting in ischemia "downstream" of the occlusion, particularly if the occlusion develops rapidly. This may be the case during plaque rupture. If a plaque fractures, platelets are recruited to stop the bleeding. Activated platelets form a fibrin clot that will stop the plaque bleeding. If there is significant vessel stenosis, the aggregation of platelets may be large enough to acutely occlude the blood vessel. The structures supplied by this vessel become ischemic. The clinical result is a stroke.[4,5] Gradual vessel occlusion may allow sufficient time for collateral blood flow to develop, in which case the consequences of vessel occlusion may be clinically insignificant.

The atheromatous plaques most prone to fracture and bleeding are unstable plaques. These are believed to pose a particularly high risk. Efforts are under way to elucidate the mechanisms leading to instability, as well as methods to identify those plaques that are most prone to fracture.[6,7]

The coexistence of cardiac disease also has functional significance for stroke survivors, as it further complicates rehabilitative management following stroke. Cardiac disease and stroke independently result in disability and together may broaden the functional limitations of either alone.

RISK FACTOR MODIFICATION

Over the past 2 decades, remarkable advances have been made in both preventing and treating stroke. Beginning in the 1960s, a number of epidemiologic studies have identified risk factors for stroke, some of which are now targets of medical intervention (Table 1). These include hypertension, nonrheumatic atrial fibrillation, hypercholesterolemia, diabetes, and cigarette smoking. Advanced age is the leading nonmodifiable risk factor. The risk factors associated with stroke are similar to those associated with coronary artery disease. Reducing risk factors for myocardial ischemia also reduces the risk of stroke.

Hypertension

Of the known risk factors for stroke, hypertension is the most significant, as it is associated with a sevenfold increase in stroke risk.[22]

Reducing blood pressure reduces the risk for first stroke by approximately 30% to 45%, and perhaps by as much as 55% to 60% if normotension is achieved.[23,24] The 1,627-patient Swedish Trial in Old Patients With Hypertension found that antihypertensive treatment with either beta-blockers or thiazide diuretics reduced systolic blood pressure (SBP) by 20 mm Hg, reduced diastolic blood pressure (DBP) by 5 mm Hg, and reduced stroke incidence by 45%.[25] In a meta-analysis of 14 antihypertensive trials encompassing 37,000 patients with a mean treatment duration of 5 years, Collins and colleagues[26] found that a DBP reduction of 5 mm Hg corresponded with a 42% reduction in risk for stroke. Risk for cardiovascular disease and vascular death were also reduced.[26] Similar findings were reported from the Systolic Hypertension in the Elderly Program (SHEP), a double-blind, randomized, placebo-controlled trial of chlorthalidone and atenolol in 4,736 patients age 60 or older (mean, 72 years).[27] After 5 years, a reduction in SBP of 10 mm Hg (to 143 mm Hg) was associated with a 36% improvement in stroke risk.[27]

More recently, the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) compared the thiazide diuretic chlorthalidone, the calcium channel blocker amlodipine, and the ACE inhibitor lisinopril in 33,357 patients with hypertension and multiple risk factors for coronary heart disease.[28] Whereas chlorthalidone and amlodipine comparably reduced the risk for MI, stroke, and death, lisinopril was less effective. However, the doses were not adjusted among the three drugs to produce the same blood pressure reduction, which may in part explain some of the differences observed.[28] The Losartan Intervention for Endpoint reduction in hypertension study (LIFE) compared the angiotensin receptor blocker losartan with the beta-blocker atenolol in 9,193 patients.[23] In addition to the study drugs, many patients were also taking other agents, such as the diuretic hydrochlorothiazide. Overall, the two agents provided similar blood pressure control, but

TABLE 1
Stroke risk factors and corresponding therapeutic interventions

Risk factor	Treatment	Relative risk reduction for stroke	References
Hypertension	Antihypertensive therapy to a goal SBP < 140 mm Hg and a goal DBP < 90 mm Hg	Primary prevention, 30%–45% Second prevention, 43%	24, 33
Hyperlipidemia	Cholesterol reduction to a goal LDL < 70–100 mg/dL	Primary prevention, 19%–26%	61, 62
Atrial fibrillation	*High risk*: warfarin *Moderate risk*: warfarin or aspirin (325 mg/day) *Low risk*: aspirin (325 mg/day)	Primary prevention, 80% Secondary prevention, 33% (warfarin) Secondary prevention, 25% (aspirin)	52, 53
Diabetes	Metformin, glucose control	Primary prevention, 40%	42

SBP = systolic blood pressure; DBP = diastolic blood pressure; LDL = low-density lipoprotein

losartan reduced stroke risk by 25% relative to atenolol, a statistically significant reduction. Losartan was also associated with better MI and survival outcomes. Interestingly, black patients responded better to atenolol.[23] Other data suggest that blacks may also benefit from ACE inhibitors (eg, ramipril).[29]

There is speculation that antihypertensive medications may impart other beneficial effects, such as vascular protection, arterial remodeling (ACE inhibitors, angiotensin receptor blockers, calcium channel blockers), or neuroprotection (calcium channel blockers, thiazide diuretics).[30,31] This has not been clearly proven. From a practical standpoint, however, it is more likely that specific antihypertensive agents are selected for use on the basis of coexisting conditions such as renal disease, diabetes, or congestive heart failure.

Antihypertensive therapy for secondary stroke prevention. Treatment of hypertension is also beneficial in patients who have already suffered a stroke. The Post-Stroke Antihypertension Treatment Study (PATS), a placebo-controlled trial of the diuretic indapamide in 5,665 stroke patients in China, found that indapamide use resulted in a 29% reduction in stroke rate at the end of 3 years.[32] In the Perindopril Protection Against Recurrence of Stroke Study (PROGRESS), 6,105 patients in Europe and Asia received the ACE inhibitor perindopril alone, perindopril combined with indapamide, or placebo.[33] After 4 years of treatment, the combination of perindopril–indapamide reduced blood pressure by 12/5 mm Hg and stroke risk by 43%. Perindopril alone was not effective in reducing stroke. Interestingly, benefits were achieved in both hypertensive and normotensive patients.[33] These studies demonstrate that blood pressure management after stroke, like that before stroke, is effective in reducing risk for subsequent stroke.

Caution needed when lowering blood pressure in the elderly. Although evidence clearly supports treatment of hypertension regardless of patient age,[34] blood pressure should be reduced cautiously in older adults.[35] Using data from the Rotterdam Study, Voko and colleagues[36] described a J-shaped relationship between blood pressure and stroke. Risk for stroke increased directly with increases in blood pressure in untreated patients, but risk also increased when SBP was less than 130 mm Hg and DBP was less than 65 mm Hg.[36] Similar observations were reported from the Cardiovascular Health Study.[37]

A shift in the cerebral autoregulatory curve, which describes the relation between cerebral perfusion pressure and cerebral blood flow, is thought to be the basis of this phenomenon. Cerebral perfusion pressures that are adequate in normotensive patients are inadequate in those with chronic hypertension. As a result, rapid reduction in blood pressure, even to a range normally tolerated by normotensive patients, may compromise cerebral blood flow and perfusion in a hypertensive patient, and ischemic injury may ensue. Thus, reduction of blood pressure to the normotensive range reduces stroke risk but must be gradual to allow normalization of cerebral autoregulation.[36]

Diabetes mellitus

Diabetes is a risk factor for both stroke and MI, increasing the risk of stroke threefold beyond that which can be accounted for by smoking, hypertension, and dyslipidemia.[38] The UK Prospective Diabetes Study (UKPDS) is a unique study comprising 5,102 patients with newly diagnosed type 2 diabetes mellitus who have been followed longitudinally for up to 17 years for vari-

ous macrovascular and microvascular outcomes, including stroke.[39] Among 3,776 patients in the UKPDS without known cardiovascular disease, 99 (2.6%) had a stroke over the initial 8 years of observation; significant risk factors for stroke were age greater than 60 years, male sex, and hypertension.[40] In the subset of 3,728 patients with electrocardiographic data at entry, atrial fibrillation increased the risk of stroke eightfold.[40]

Two parallel substudies of the UKPDS have examined the effect of intensive blood glucose control on cardiovascular complications. UKPDS 33, conducted in a subcohort of patients with ideal body weight, found that intensive blood glucose control with a sulphonylurea or insulin to a target fasting glucose level of less than 6 mmol/L (n = 2,729) reduced the rate of microvascular complications, but not of strokes, compared with conventional treatment (diet) to a target fasting glucose level of less than 15 mmol/L (n = 1,138).[41] UKPDS 34, conducted in a subcohort of 1,704 overweight patients, randomized patients to metformin (n = 342), diet therapy alone (n = 411), or intensive glucose control achieved by chlorpropamide, glibenclamide, or insulin (n = 951) after an initial 3 months of diet therapy.[42] In these overweight diet-treated patients, metformin significantly reduced the risk of diabetes-associated cardiovascular events, including stroke, compared with diet alone and compared with chlorpropamide, glibenclamide, or insulin.[42] However, because comparable benefits were not observed in nonoverweight metformin-treated patients,[41] it remains uncertain whether the benefits with metformin were attributable to tight glucose control, blood pressure reduction, or modification of some other risk factor.[43,44]

Another UKPDS substudy assessed the effectiveness of tight blood pressure control along with glucose control in a sample of 1,148 hypertensive patients with diabetes.[45] It found a highly significant 44% reduction in stroke risk in patients under tight blood pressure control (mean, 144/87 mm Hg) compared with those under less-tight control (mean, 154/87 mm Hg).

Nonvalvular atrial fibrillation

Atrial fibrillation increases stroke risk fivefold.[46] Treating atrial fibrillation with warfarin reduces stroke risk. The Stroke Prevention in Atrial Fibrillation (SPAF) trials showed that warfarin, dosed to achieve an international normalized ratio (INR) of 2 to 3, reduced the risk of first stroke by close to 80% and of subsequent stroke by 33%.[47–49] Aspirin (325 mg/day orally) is also effective and imparts a 25% relative risk reduction compared with placebo.[47–49] Hylek and colleagues[50,51] provided evidence that a target INR of 2 to 3 is optimal. Compared with an INR of 2, risk for stroke is two times higher with an INR of 1.7, three times higher with an INR of 1.5, and seven times higher with an INR of 1.3. No additional benefit is seen with INR levels above 3, even when extrapolated to an INR of 7, although bleeding risk increases dramatically with an INR above 4.[50,51]

Recently, Hart and colleagues from the SPAF investigators group further compared warfarin and aspirin in the context of a treatment algorithm for atrial fibrillation that incorporated comorbidities such as advanced age, heart disease, and hypertension.[52–55] For patients who have suffered a stroke or TIA, warfarin should be used with a target INR of 2 to 3. Patients age 75 or older who have multiple risk factors but have not yet suffered a stroke also should receive warfarin. Patients between ages 65 and 75 with a single risk factor (considered to be at moderate risk) may be treated with either aspirin (325 mg/day) or warfarin. Patients over age 55 with no risk factors (other than atrial fibrillation) are at low risk for stroke and may be treated with aspirin only.[52–55]

Unfortunately, warfarin and aspirin are underused in spite of the clear evidence of their effectiveness in reducing stroke in patients with atrial fibrillation. Only one third of patients who should be treated are receiving warfarin. Although there is a reasonable concern about the risk of bleeding, fewer than half of patients not receiving anticoagulant therapy are receiving antiplatelet medication. This is especially true among the elderly, who have the highest risk for stroke.[56–59]

Hyperlipidemia

Cholesterol-lowering therapy with statins (HMG-CoA reductase inhibitors) reduces risk for stroke. This was first demonstrated as a secondary outcome in the Cholesterol and Recurrent Events (CARE) trial, which found pravastatin to reduce stroke incidence by 31% relative to placebo over 5 years of follow-up among 4,159 patients with a previous MI.[60] This protective effect against stroke has been confirmed by subsequent meta-analyses of statin trials that included stroke as an outcome.[61,62] One such analysis, which included 28 statin trials encompassing more than 106,000 patients with coronary artery disease, including some with prior stroke or TIA, demonstrated a 19% reduction in stroke risk with statin therapy.[61] Another analysis, which comprised 38 studies with more than 81,000 patients, showed a 26% reduction in stroke risk with statin therapy.[62]

The recent PROVE IT–TIMI 22 study examined the effect of intensive vs moderate lowering of low-density lipoprotein (LDL) cholesterol in 4,162 patients with recent acute coronary syndromes.[63] It

found that, after 2 years, intensive reduction of LDL cholesterol (ie, to a mean of 62 mg/dL) was associated with a 16% reduction in the combined risk for MI, stroke, or vascular death compared with moderate LDL reduction (ie, to a mean of 95 mg/dL). This study suggests that more aggressive reduction of LDL cholesterol—ie, to less than 70 mg/dL rather than the usual target of less than 100 mg/dL—might provide additional benefit in patients at high risk for cardiovascular events, including stroke.[63]

Aging

Finally, advanced age has been a common element in all studies of stroke prevention. Age was an independent predictor of death in the Connecticut Medicare database analysis discussed above[16] and was the most robust predictor of death (even more robust than cardiac failure) in the Perth Community Stroke Study.[14] In the latter study, age was also a predictor of recurrent stroke and hemorrhagic stroke.[14] Age greater than 65 is a predictor of ischemic stroke and age older than 75 of hemorrhagic stroke.[64]

Although age itself is not a modifiable risk factor, studies are investigating the contributions of age-associated vascular stiffening and thickening of the intimal media to stroke and other cardiovascular events.

BEYOND RISK FACTORS: ANTIPLATELET THERAPY

In addition to reducing risk factors, clinicians may also consider antiplatelet therapy to reduce the chance of ischemic events in at-risk patients (Table 2).

Aspirin

Acetylsalicylic acid (aspirin) is the most widely used antiplatelet drug. It is an irreversible cyclo-oxygenase inhibitor that prevents thromboxane A_2 production, thereby inhibiting platelet aggregation. Precedence for aspirin therapy was first established in primary and secondary MI prevention studies, which showed nearly reductions of nearly 50% in ischemic cardiac events.[65–67] The American Heart Association recommends an aspirin dosage of at least 75 mg/day orally for these purposes.[68]

Aspirin has also been proved effective for secondary prevention of stroke in high-risk patients. The most recent work of the Antiplatelet Trialists Collaboration is a collaborative meta-analysis of 287 studies involving 212,000 patients, of whom 187,000 were enrolled in placebo-controlled trials.[69] This analysis showed that aspirin use reduced the risk of subsequent stroke by 25% and effectively reduced the risk of other serious vascular events, such as MI (by 34%) and vascular death.[69] Although there is no definitive evidence on the most effective dosage of aspirin for secondary stroke prevention, 75 to 150 mg/day is recommended by the Antiplatelet Trialists Collaboration and 75 mg/day or more by the American Heart Association.[68,69]

Thienopyridines

A new class of oral platelet inhibitors, the thienopyridines, was introduced in 1989.

Ticlopidine is the prototype of this class of agents, which prevent platelet aggregation by blocking the adenosine diphosphate site. Two large clinical trials showed the efficacy of ticlopidine for stroke prevention.[9,10] In one, ticlopidine reduced recurrent stroke risk by 33% relative to placebo.[9] In the other, ticlopidine reduced the risk of nonfatal stroke at 3 years by 12% relative to aspirin and reduced the risk of all strokes (fatal and nonfatal) by 22% vs aspirin.[10] However, because of a 2.4% incidence of neutropenia associated with ticlopidine use,[70] the US Food and Drug Administration requires monitoring of complete blood counts every other week for the first 3 months of therapy.

In a cohort of 1,809 black patients, ticlopidine (500 mg/day) was compared with aspirin (650 mg/day) for reducing recurrent stroke, MI, or vascular death.[71] There were trends favoring aspirin with respect to both efficacy and adverse effects (neutropenia and thrombotic thrombocytopenic purpura), but neither reached statistical significance. Thus, for blacks, the results suggest that high-dose aspirin imparts the same benefit as ticlopidine.

Other important side effects of ticlopidine are diarrhea, rash, and gastrointestinal distress. The incidence of thrombotic thrombocytopenic purpura with ticlopidine use is 1 case per 5,000 patients.[72]

Clopidogrel, another thienopyridine, was introduced in 1996. Clopidogrel was compared directly with aspirin in a randomized, double-blind trial in 19,185 patients with known symptomatic atherosclerotic disease, defined as a history of MI, stroke, or symptomatic peripheral vascular disease.[12] After 2 years of therapy with either aspirin (325 mg/day) or clopidogrel (75 mg/day), the rate of cardiovascular events (MI, stroke, or vascular death) was 8.7% lower in the clopidogrel group than in the aspirin group. For stroke alone, clopidogrel was associated with a 7.2% relative risk reduction compared with aspirin, but this difference was not statistically significant.

Dipyridamole

Dipyridamole, a phosphodiesterase inhibitor and nitric oxide carrier, represents another class of antiplatelet agent. This oral therapy has been studied as monotherapy in a large number of clinical trials,

TABLE 2
Interventions for stroke prevention: profiles of antiplatelet therapies and carotid endarterectomy

Intervention	Treatment/dosage	Relative risk reduction	References
Aspirin	75–325 mg/day	Secondary stroke prevention, 25% Primary MI prevention, 50% Secondary MI prevention, 34%	66, 67, 69
Ticlopidine	250 mg twice daily	Secondary stroke prevention, 33%*	9
Clopidogrel	75 mg/day	Secondary stroke prevention, 25%–30% Secondary MI prevention, 19%	12, 86
Dipyridamole-ER	200 mg/day	Secondary stroke prevention, 16% MI prevention, 0%†	11
Aspirin/dipyridamole-ER	30 mg/200 mg twice daily	Secondary stroke prevention, 36%	11
Aspirin/clopidogrel	75 mg/75 mg daily	Secondary stroke prevention, 25%–30%‡ Secondary MI prevention, 55%–70%	75, 84, 85, 113
CEA (symptomatic)	Lesion >70%: CEA + aspirin (325 mg/day)	Secondary stroke prevention, 70%	99
CEA (asymptomatic)	Lesion >60%: CEA + aspirin (325 mg/day)	Secondary stroke prevention, 53%§	102,103

* Not yet fully tested for secondary MI prevention.
† MI data are in stroke patients only; other MI data are in cardiac patients, but only for immediate-release preparation.
‡ In patients already taking aspirin when index event occurred.
§ Only if surgical risk is < 3%.
MI = myocardial infarction; ER = extended-release; CEA = carotid endarterectomy

most recently in the second European Stroke Prevention Study (ESPS-2).[11] Although treatment with dipyridamole reduces the stroke rate by approximately 16% when compared with placebo,[11] the protective effect is less than that with aspirin. Thus, dipyridamole is not recommended for use as a sole agent for preventing stroke.

Combination antiplatelet therapy

Combining drugs that exert the same effect by different mechanisms can result in "effect summation," ie, greater benefit with fewer side effects. This is the pharmacologic basis for the combinations of aspirin, dipyridamole, and clopidogrel that have been studied to date.

Aspirin plus dipyridamole. The ESPS-2 evaluated the combination of aspirin and extended-release dipyridamole (dipyridamole-ER) for secondary prevention of stroke.[11] It randomized 6,602 patients with recent stroke to either placebo, aspirin alone (25 mg twice daily), dipyridamole-ER alone (200 mg twice daily), or aspirin combined with dipyridamole-ER. Aspirin alone was 18% more effective at preventing a second stroke than placebo, dipyridamole-ER was 16% more effective, and aspirin plus dipyridamole-ER was 36% more effective.

Aspirin plus a thienopyridine. Combining aspirin with a thienopyridine should yield additive effects.[73] Used alone, ticlopidine has achieved a 33% reduction in stroke risk relative to placebo. Because placebo-controlled trials are unethical when a known effective therapy exists, no corresponding placebo-controlled data on stroke risk reduction are available for clopidogrel, but we can infer that clopidogrel lowers stroke risk by approximately 30% relative to placebo based on data from the aspirin-controlled Clopidogrel vs Aspirin in Patients at Risk of Ischemic Events study.[73,74] Thus, combining either ticlopidine or clopidogrel with aspirin should provide additive benefit. However, ticlopidine's unfavorable toxicity profile limits its usefulness.

The Management of Atherothrombosis with Clopidogrel in High-risk Patients (MATCH) trial evaluated the addition of aspirin to clopidogrel for reduction of secondary stroke risk in 7,599 patients who had suffered a stroke or TIA in the prior 3 months.[75] All patients were at high risk for further events, defined as having one or more risk factors such as diabetes or hypertension. Interestingly, 80% of patients were already taking aspirin at enrollment. All patients were treated with clopidogrel 75 mg/day, to which either aspirin 75 mg/day (n = 3,797) or placebo (n = 3,802) was added. After 18 months, the addition of aspirin to clopidogrel did not achieve greater reduction of stroke risk but did double the rate

of hemorrhagic complications (mostly in the gastrointestinal tract), to 2.6% from 1.3% with clopidogrel alone. The investigators attributed this disappointing finding to the high prevalence of diabetes (75%) or small-vessel disease.

Aspirin dosing in combination regimens. An alternative explanation for the disappointing result in the MATCH trial is aspirin resistance, which in prior studies was estimated to affect up to 40% of aspirin users.[76–78] For patients who suffer a stroke while taking aspirin, clinicians must question whether continued aspirin therapy will provide any protective benefit against stroke.[78]

The optimal aspirin dose for stroke prevention is highly controversial, and it is further complicated when combination therapy is considered. If a patient is taking 325 mg/day of aspirin and experiences a cerebrovascular event, is it prudent to reduce the dose when adding a second agent? This is a dilemma clinicians face regularly. In light of concerns over additional adverse effects, such as hemorrhage, decreasing the aspirin dose seems reasonable. However, higher doses could be more effective in some subsets of patients.[79–81] The technology of quantifying platelet aggregation is evolving[82] and may be useful as a pharmacodynamic response that could serve as a convenient surrogate for future cerebrovascular events.

It may simply be that continuation of aspirin in patients who suffer stroke despite adequate aspirin therapy would be rational only if there were another compelling reason, such as reducing MI risk.[76,77,83]

Combination therapy for MI prevention. Because MI is the leading cause of death in stroke survivors, optimizing MI prevention is important. Two clinical trials conducted in high-risk patients, the Clopidogrel for Reduction of Events (CURE) and Percutaneous Coronary Intervention from CURE (PCI-CURE) studies, showed an added benefit from combining aspirin with clopidogrel in reducing MI and death.[84,85] The incremental 21% benefit over aspirin alone compared favorably with the 19% benefit in the CAPRIE trial.[86] In the CURE and PCI-CURE trials, combination therapy with aspirin plus clopidogrel reduced the MI rate by approximately 55% to 70% relative to no therapy.[84,85]

Dipyridamole had not been previously shown to reduce acute coronary syndromes.[11,87–91] Thus, adding dipyridamole to aspirin would not be expected to impart additional protection against MI. The ESPS-2 trial showed a 13% reduction in MI incidence among patients with stroke, but only in its aspirin arm, with no additional protection against MI observed when aspirin was combined with dipyridamole.[11]

Drug interactions relevant to antiplatelet therapy

The interaction between aspirin and nonsteroidal anti-inflammatory drugs (NSAIDs),[92] such as ibuprofen, is clinically important in the context of stroke prevention, since many elderly patients suffer from arthritis and other painful conditions. For such patients, NSAIDs are critical in maintaining quality of life. The problem is that NSAIDs may interfere with aspirin's ability to protect against MI and stroke. Both classes of drugs act to inhibit cyclo-oxygenase; aspirin binds irreversibly, whereas ibuprofen attaches reversibly but at different sites that are in close proximity. If taken with aspirin, ibuprofen interferes with aspirin binding. Because aspirin is rapidly metabolized in blood, it will be degraded before it can attach and produce its beneficial effects. Since NSAIDs have not been shown to protect against MI (although naproxen may), patients may be left without protection against MI and stroke.[93,94] Some studies have suggested, however, that this effect may not be clinically relevant.[95,96]

A practical solution is to instruct patients to take aspirin 30 minutes or so before taking an NSAID.

NO ROLE FOR ANTICOAGULATION IN ABSENCE OF ATRIAL FIBRILLATION

Despite the protective effects observed in patients with nonvalvular atrial fibrillation, anticoagulation with warfarin to ameliorate secondary stroke risk has been disappointing. The Stroke Prevention in Reversible Ischemia Trial (SPIRIT), conducted in Europe, compared warfarin (INR 3 to 4.5) with aspirin (30 mg/day) in 1,316 patients.[97] The results favored aspirin, as the warfarin group suffered 37% more strokes, almost 2.5 times more deaths, and 100 times more bleeding episodes.[97] More recently, the Warfarin for Reduction of Recurrent Stroke (WARRS) trial compared aspirin (325 mg/day) with warfarin dosed to a lower INR goal (1.5 to 3) among 2,206 patients.[98] Warfarin provided no improvement over aspirin in stroke rate but imparted a 50% relative increase in minor bleeding.[98]

SURGICAL INTERVENTIONS FOR STROKE PREVENTION

Surgical intervention with carotid endarterectomy (CEA) is also an option for stroke prevention (Table 2).

Carotid endarterectomy in symptomatic patients

CEA is effective in patients with extracranial internal carotid artery stenosis of 70% or greater and ischemic symptoms referable to that stenosis.

The North American Symptomatic Carotid Endarterectomy Trial (NASCET), conducted in 659 patients who presented within 4 months of symptomatic carotid stenosis, demonstrated a 55% reduction in stroke risk following CEA plus aspirin therapy (325 mg/day) as opposed to aspirin therapy alone.[99] The surgical risk in this study was approximately 6.5%, which is comparable to the perioperative risk of CEA in similar trials.[99,100]

Tu and colleagues[101] reported an increase in CEA procedures following publication of the NASCET results. Many centers reported a 30-day death rate greater than 2%,[101] which is much higher than the 0.6% rate in NASCET and the 0.1% rate in the Asymptomatic Carotid Atherosclerosis Study (ACAS).[102] The perioperative complication rate of the surgeon performing the procedure must be comparable to or better than that of the study surgeons if an overall benefit is to be realized.

Carotid endarterectomy in asymptomatic patients

The role of CEA in asymptomatic patients is less certain.

The ACAS investigators randomized 1,662 asymptomatic patients to CEA plus aspirin (325 mg/day) or aspirin alone.[102] Subjects qualified if they had carotid stenosis of 60% or greater but had not yet suffered a cerebrovascular ischemic event. CEA imparted an overall 53% reduction in stroke risk relative to aspirin alone. Enrolled patients were highly selected, which might in part account for the good results.[103] Additionally, the surgeons in this study had overall perioperative morbidity and mortality rates of less than 3%. This is substantially less than the 6.5% rate for surgeons performing CEA in other trials[101]—an absolute difference of about 3.5 percentage points. When added to the absolute stroke rate of 5.8% in the group treated with CEA plus aspirin, the result is 9.3%. This is close to the absolute stroke rate of 11% in the group receiving aspirin alone. Thus, unless the surgeon has a perioperative complication rate of less than 3%, the benefit of undergoing this procedure will be negated by the surgical risk.

Notably, men were the primary beneficiaries of CEA in ACAS: within the CEA-treated group, men obtained a relative risk reduction of 69%, whereas the reduction was only 16% for women.[102]

In an analysis of patients with asymptomatic internal carotid artery stenosis from the NASCET database, Inzitari and colleagues[104] found that the 5-year risk for stroke from asymptomatic carotid lesions with stenosis of at least 60% was double that from lesions with stenosis of less than 60%. The risk for large-artery stroke was highest with the greatest stenosis (ie, 95% to 99% stenosis). Patients with asymptomatic carotid lesions with stenosis of at least 60% had a 5-year risk for stroke of 10%. These same patients also were at risk for stroke from other etiologies, including a 6% risk for lacunar stroke and a 2% risk for cardioembolic infarctions. Thus, close to half of the overall stroke risk in these patients could be attributed to lesions not associated with the carotid artery, for which CEA would not be ameliorative.[104]

Some experts believe that a more comprehensive evaluation should be done before surgery to determine the source of the greatest risk for stroke. If it is from the carotid lesion, surgical intervention should be considered if the patient is male and the surgeon has a perioperative complication rate below 3%. However, if there is other evidence of cardiac risk for stroke (eg, patent foramen ovale, atrial fibrillation), small-vessel disease, or intracranial carotid disease, CEA will probably not provide substantial benefit.[105] It must be emphasized that we have no evidence that such an evaluation strategy is effective.

Intra-arterial interventions

An evolving area of therapy is intra-arterial intervention. Stents and angioplasty have been used successfully in managing occlusive coronary disease. These technologies are now being applied to the management of cerebrovascular disease and stroke. The Stenting and Angioplasty With Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial was a randomized study that compared stenting with surgical CEA in 334 patients with carotid occlusive disease determined to be at high risk for complications from CEA.[106] The stenosis criteria were 50% if the patient was symptomatic and 80% if asymptomatic. The results showed no difference between the two procedures in stroke, death, or MI at 30 days or in stroke and death at 1 year. However, the long-term effectiveness of these procedures is still under investigation.[107–109]

BARRIERS TO EFFECTIVE STROKE PREVENTION

A frequently encountered barrier to effective stroke prevention is the persistent belief that stroke is either unpreventable or does not warrant aggressive management. Compared with the cost of cancer therapy, the penny-a-day cost of aspirin is an extraordinary bargain. In spite of this, there is evidence that fewer than 50% of patients needing antiplatelet therapy receive it.[110–112] It is even less commonly used among

the elderly, who are at the highest risk for stroke, MI, and vascular death.

The diagnosis and management of comorbid illnesses presents an additional management challenge in older patients. The overlap between two of the three deadliest diseases (ie, stroke and MI) cannot be ignored. Fortunately, these two diseases are etiologically linked and treatments that effectively reduce risk for one also reduce risk for the other. This is not the case with other comorbid illnesses that may require treatment with medications that either worsen stroke-risk profiles (drug-disease interaction) or interfere with drug efficacy or tolerability (drug-drug interaction).

CONCLUSIONS

Stroke remains a life-threatening disease that results in substantial disability in those who survive it. Risk factor modification can protect against initial and recurrent stroke, with additional roles for antiplatelet therapy and surgical interventions such as CEA. When applied appropriately, these strategies can greatly reduce stroke risk. Their implementation requires coordination between neurologists and primary care physicians, especially for older adult patients, who are at greatest risk for stroke and are likely to also have comorbidities that require management. Although current therapy simultaneously improves cerebrovascular and cardiovascular outcomes, it is important to remember the differences between the cerebrovascular and cardiovascular systems. Future research is likely to identify important differences between stroke and MI that will guide future brain-specific treatments.

Disclaimer

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Seizures in the elderly:
Nuances in presentation and treatment

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ABSTRACT

Acute symptomatic seizures and epilepsy are two of the most common neurologic complaints in the elderly. Stroke is the leading underlying etiology for both. Because clinical seizure manifestations in the elderly often differ from those in younger adults, they may be difficult to recognize or may be misdiagnosed. Interpretation of diagnostic tests in elderly patients with seizures is often complicated by comorbidities, and treatment decisions require careful consideration in the context of age-related physiologic changes, comorbidities, and the use of concomitant medications. Treatment of an acute seizure with a clear precipitating cause involves correcting the underlying etiology; antiepileptic drug (AED) therapy is generally reserved for patients with epilepsy (recurrent unprovoked seizures). The prognosis for elderly epilepsy patients treated with AEDs is generally good. Both older and newer AEDs are efficacious but have respective advantages and disadvantages; no ideal AED yet exists. Status epilepticus is a neurologic emergency that is particularly frequent in the elderly and associated with high mortality, although treatment can be effective.

KEY POINTS

The elderly have the highest incidence of seizures of any age group.

Nearly half of acute symptomatic seizures in the elderly and 30% to 50% of epilepsy cases in this age group are associated with stroke.

In the elderly, new onset of epilepsy is often associated with vague complaints such as confusion, altered mental status, or memory problems.

The differential diagnosis of seizures in the elderly should rule out spells due to other causes, such as syncope, transient ischemic attack, transient global amnesia, or episodic vertigo.

In treating epilepsy, the choice of antiepileptic drug (AED) is usually dictated by seizure type and tolerability and may be complicated by comorbidities or age-associated differences in AED pharmacokinetics.

Older and newer AEDs are both efficacious. Newer AEDs generally have better overall tolerability, fewer drug interactions, more predictable kinetics, and a broader spectrum of activity, but they also have slower titration schedules and cost considerably more than older AEDs.

The diagnosis and management of seizures and recurrent seizures (epilepsy) pose special challenges in the elderly. Seizures may present in elderly patients with nuances that are unique to this age group. Moreover, the treatment of seizures in the elderly is often complicated by concomitant medications and altered drug metabolism and excretion. Additionally, seizures threaten elderly patients' quality of life through potential injury and loss of independence, as well as through the side effects and costs of antiepileptic drugs (AEDs).

To explore these challenges and ways to address them, this article provides a general review of the diagnosis and management of seizures in patients aged 65 years or older, with a focus on the differential diagnosis

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of conditions with symptoms resembling seizures, the mechanism of seizures in older patients, the diagnostic work-up of elderly patients with suspected seizures, and the treatment of seizures in this population.

THE SCOPE OF THE CHALLENGE

The elderly are the fastest-growing segment of the general population. The US government predicts that by 2030 there will be 70 million adults over age 65 in the United States.[1] Whereas this segment made up 12.4% of the population in 2000, it will account for about 20% by 2030.[1] Figure 1 depicts the anticipated increased rate of growth of the elderly population.

The elderly have the highest incidence of seizures of any age group.[2] Older adults' increased risk for stroke, metabolic abnormalities, and comorbid conditions contributes to the frequency of seizures in this population. Thus, as the US population ages, physicians will increasingly face the challenge of diagnosing and effectively managing seizures in the elderly.

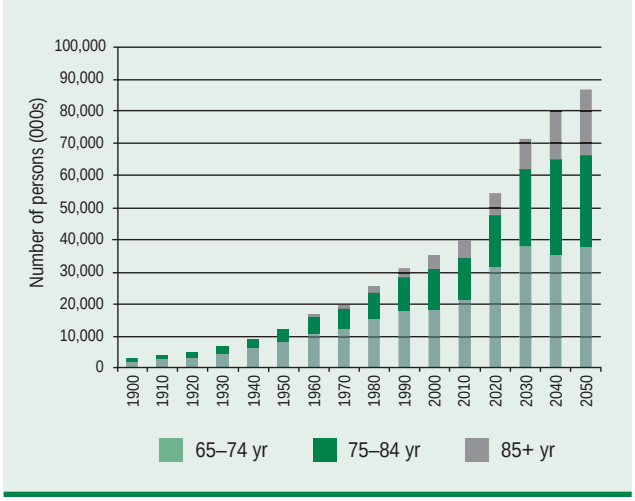

FIGURE 1. Older population of the United States by age, 1900 to 2050. US Bureau of the Census data (from reference 1).

DEFINITIONS: ACUTE SEIZURES VS EPILEPSY

Acute symptomatic seizures

Acute symptomatic seizures, or provoked seizures, occur in the context of an acute central nervous system (CNS) insult. The incidence of acute seizures in patients older than 60 years is approximately 100 per 100,000 population and increases with each decade of advancing age.[3–5]

Although drug withdrawal is the major cause of acute symptomatic seizures in adults aged 35 to 64 years, cerebrovascular disease is by far the most common cause of acute symptomatic seizures in the elderly, accounting for nearly half.[4] Most acute seizures occur within 24 hours of stroke onset.[6,7] Several studies of stroke patients have determined that 4% to 6% experience early seizures after a stroke.[7,8] Stroke type and location both play a role, with lobar location, hemorrhage, and anterior-hemisphere location associated with higher risk for early seizure.[7,8]

Other causes of acute symptomatic seizures in the elderly are trauma (responsible for 10.2% of cases), neoplasm (8.8%), and infection (2%).[3] Metabolic abnormalities, including hyponatremia, uremia, and hypocalcemia, are responsible for 10% to 15% of seizure cases in the elderly. Hyperglycemia or hypoglycemia related to insulin use can provoke seizures in elderly patients with diabetes.

Approximately 10% of seizures in the elderly are associated with alcohol or prescription drugs.[9] Commonly used drugs that are known to lower the seizure threshold include opioid analgesics (especially meperidine), beta-lactam and quinolone antibiotics, bupropion, theophylline, antipsychotic drugs (especially clozapine and phenothiazines), and isoniazid. Withdrawal from benzodiazepines or barbiturates can precipitate seizures.

Epilepsy

Epilepsy is defined as a condition of recurrent, unprovoked seizures. The incidence of epilepsy rises throughout adulthood. In adults older than 60 years, the annual incidence exceeds 100 per 100,000 population.[3] Begley et al[10] estimated that of the 2.3 million Americans with epilepsy, 24% (549,000) are older than 65 years and 11% live in nursing homes or assisted-living environments. New-onset epilepsy develops in an estimated 60,000 US adults over 65 each year, and 16,000 of them will continue to have seizures despite treatment.[10]

In about 50% of cases of epilepsy in the elderly, no cause is ascertained. For those in whom a cause is determined, the risk for epilepsy is highest in the first year or two after the insult.[3] As it is for acute symptomatic seizures, stroke is the most common cause of epilepsy in the elderly, accounting for 30% to 50% of cases in this age group.[3,11,12] Persons with cerebrovascular disease have a risk of epilepsy more than 20 times that of the general population.[13] The risk for developing seizures after a stroke ranges from 9% to 19%.[14]

Although most epilepsy in the elderly is idiopathic or a result of cerebrovascular disease, other causes have been identified. Degenerative disorders account for 11.7% of cases of epilepsy in the elderly.[3] Among elderly patients with dementia, 9% to 17% will develop epilepsy.[15] Neoplasms are associated with 4.5% to 10%

of cases, and trauma accounts for about 3%.[3,16,17]

PATHOPHYSIOLOGY OF SEIZURES IN THE ELDERLY

The potential mechanisms of epileptogenesis in the elderly are complex and incompletely understood. For example, the accumulation of comorbid conditions may lead to an increased occurrence of epilepsy in the elderly, or common age-related changes in the brain might cause altered neuronal response to insult, resulting in seizures. Various animal models have suggested an age-dependent susceptibility to seizures, but it is unclear whether humans have a similar susceptibility.[18–22]

Numerous changes in brain chemistry, neuronal function, and anatomy occur with human aging. These include neuronal dropout, synaptic loss and reorganization, and histologic abnormalities such as lipofuscin or amyloid deposition. These processes may alter the response of the aging brain to neurologic and systemic insults, thus contributing to the increased risk of epilepsy in the elderly.[23]

CLINICAL FEATURES

Seizures may have partial or generalized onset in the brain. Partial seizures involve a focal area of the brain, and their clinical manifestations vary according to the brain region involved. A partial seizure can spread to become a tonic-clonic seizure (secondary generalization). Generalized seizure types include absence, myoclonic, atonic, tonic, and tonic-clonic. Table 1 summarizes the most common seizure types and their typical clinical features.[24]

Manifestation differs between elderly and young

The manifestations of seizures in the elderly often differ from those in younger patients and may be challenging to diagnose. Vague presenting complaints such as confusion, altered mental status, or memory problems are common in the elderly with new onset of epilepsy. Focal clonic seizures, versive seizures, and bilateral asymmetric tonic seizures occur less frequently in elderly patients than in younger patients.[25]

The lack of typical clinical signs in the elderly may lead to delayed diagnosis and treatment. In the Veterans Affairs Cooperative Study of epilepsy in the elderly (also known as the VA Cooperative Study 428),[11] epilepsy was not considered in 26% of the initial medical evaluations of elderly patients who eventually were diagnosed with epilepsy.[26] Alternative diagnoses were altered mental status (41.8%), confusion (37.5%), blackout spells (29.3%), memory disturbance (17.2%), syncope (16.8%), dizziness (10.3%), and dementia (6.9%) (patients could have more than one initial diagnosis).[26]

Frequently, the symptoms of epilepsy in the elderly are attributed to other comorbid conditions. Postictal Todd's paralysis may be prolonged in the elderly, leading to the misdiagnosis of cerebrovascular disease rather than epilepsy.[27] In elderly patients with a history of transient ischemic attack (TIA) or stroke, the time to diagnosis of epilepsy was 1.7 years.[28]

Complex partial seizures (see Table 1) are the most common seizure type in the elderly, but certain features distinguish them from complex partial seizures in younger adults. While most complex partial seizures in the general population originate in the temporal lobe, in the elderly they are more likely to be extratemporal, usually frontal, coinciding with the areas of the brain that are frequently affected by stroke.[26] The elderly are less likely to experience the types of auras usually associated with temporal lobe epilepsy and instead report nonspecific symptoms, such as dizziness. Automatisms occur less frequently in complex partial seizures in the elderly, and postictal confusion may be prolonged.[26]

Video-electroencephalographic (EEG) monitoring has permitted accurate clinical characterization of paroxysmal events in the elderly. A recent study of video-EEG monitoring results in the elderly found that only about half had epileptic seizures, whereas psychogenic events were the most common type of nonepileptic spell.[29] The surprisingly high percentage of psychogenic events in this series emphasizes the need for definitive diagnosis of spells in the elderly.

DIFFERENTIAL DIAGNOSIS

Seizures must be differentiated from spells due to a variety of other causes, both neurologic and non-neurologic. Other common neurologic causes of such spells in the elderly include syncope, TIA, transient global amnesia, and episodic vertigo.[30] Cardiovascular disorders such as aortic stenosis, congestive heart failure, and arrhythmia can cause spells due to impaired cerebral blood flow. Antihypertensive or diuretic medications, as well as dehydration, can contribute to orthostatic hypotension. Less common causes of spells include migraine, sleep disorders, and psychogenic events. This broad differential diagnosis can be narrowed on the basis of the history, physical examination, and diagnostic tests.

A good history is critical in determining the diagnosis. The history should focus on a description of the event, any specific symptoms that preceded it, its duration, and any previous occurrence of spells. Patients are often unable to recall their spells or may be unaware of them, so it is helpful to interview caregivers for further details. The physician should also inquire about cardiac

TABLE 1
Clinical characteristics of seizure types

I. Partial seizures (seizures with focal onset)

A. Simple partial seizures

Consciousness is not impaired during simple partial seizures. The patient can respond appropriately to questions and commands and can remember events occurring during the seizure. The principal types are:

1. *Motor seizures*, which are characterized by localized stiffening or jerking of the face or extremity on the same side of the body.
2. *Somatosensory or special sensory seizures*, which can include any sensory modality including smell, taste (often unpleasant—eg, a metallic sensation), vision (such as flashing lights), hearing, or touch (such as paresthesias and electrical sensations).
3. *Autonomic seizures*, which are relatively common and may include changes in visceral sensation (eg, in abdomen or chest) and change in heart or breathing rates.
4. *Psychic seizures*, in which patients report feelings of fear, depression, or anxiety, or altered perceptions of time such as déjà vu and jamais vu.

B. Complex partial seizures

Complex partial seizures are characterized by impairment of consciousness. Frequently, the patient has automatisms, characterized by automatic movements such as lip-smacking, picking at bed sheets, grunting, or more complex acts. Complex partial seizures usually last no longer than 3 minutes, with postictal confusion lasting 15 minutes or less. These may begin as simple partial seizures and progress to impairment of consciousness, or there may be impairment of consciousness at the onset.

C. Secondarily generalized seizures

Partial seizures can secondarily generalize. Patients may describe an aura, which is a simple partial seizure preceding the loss of consciousness. Patients may also experience a complex partial seizure before the seizure becomes secondarily generalized.

II. Generalized seizures (seizures without focal onset)—the major types are absence, myoclonic, atonic, tonic, and tonic-clonic

A. Absence seizures

Absence seizures are usually classified as either true or typical absence (previously known as petit mal) or atypical absence.

1. *Typical absence seizures* are characterized by abrupt onset of impairment of awareness and responsiveness lasting 3 to 20 seconds. Return to awareness is immediate after the seizure ends. There is no warning before the seizure and no postictal confusion. The patient may report automatisms such as eye-blinking and lip-smacking. The EEG is important in making a diagnosis in this type of seizure and demonstrates a generalized 3-Hz spike-and-wave discharge.
2. *Atypical absence seizures* are usually seen in children with cognitive impairment as opposed to typical absence. They may be associated with atonic and tonic seizures. The EEG usually shows a generalized, slow, spike-and-wave complex (ie, < 2.5 Hz).

B. Myoclonic seizures

Myoclonic seizures are characterized by very brief bilateral synchronous jerks. Consciousness is usually not impaired unless there are successive myoclonic seizures. EEG generally demonstrates a polyspike-and-slow-wave discharge.

C. Atonic seizures

Atonic seizures are characterized by a sudden loss of postural tone with impairment of consciousness. These seizures rarely last more than 1 minute and generally last less than 5 seconds.

D. Tonic seizures

Tonic seizures are characterized by flexion or extension of both the upper and lower extremities. They generally last from 5 to 20 seconds and are common in patients with other neurologic abnormalities.

E. Tonic-clonic seizures

Primary generalized tonic-clonic seizures are not preceded by an aura and are characterized by an initial tonic phase of stiffening followed by a clonic phase of jerking of the extremities. The seizure lasts about 30 seconds to 2 minutes. It may be difficult to differentiate a primary generalized tonic-clonic seizure from a secondarily generalized seizure.

Adapted from reference 24.

risk factors and symptoms, medications, coexisting medical conditions, head trauma, and alcohol use. Table 2 lists factors to be considered in evaluating the patient who presents with a spell of unknown cause.[30,31]

DIAGNOSTIC EVALUATION

Routine investigations

Acute symptomatic seizures commonly have toxic and metabolic etiologies. Thus, patients who present with one or more acute seizures should be evaluated with a complete blood cell count, liver function tests, urinalysis, and measurement of electrolytes, calcium, and magnesium. Toxicology screening for drugs and alcohol should be considered. If the patient is febrile or immunosuppressed, a lumbar puncture is indicated. Oxygen saturation should be checked, and arterial

blood gases should be measured if respiratory compromise is suspected.

Electroencephalogram

Older patients with acute seizures may have a variety of EEG changes, only some of which are attributable to underlying pathology. EEGs of patients with encephalopathies often demonstrate diffuse slowing of the background activity or more specific waveforms, such as triphasic waves. Focal changes can occur if there is a structural CNS lesion. Although benign EEG variants with epileptiform morphology occur in all age groups, three that occur with a greater frequency in the older population are subclinical rhythmic electrical discharges of adulthood, wicket spikes, and small sharp spikes.[32] These patterns can potentially be misinterpreted as epileptiform abnormalities.

Interictal epileptiform activity occurs less frequently in older than in younger age groups.[33] Thus, elderly patients have a greater likelihood of nondiagnostic findings on a routine EEG. The VA Cooperative Study 428, conducted in elderly subjects, found interictal epileptiform activity in about one third of routine EEGs.[34] Prolonged EEG recording, ambulatory EEG, and inpatient video-EEG monitoring significantly increase the diagnostic yield.[29] Although elderly patients account for approximately 25% of newly diagnosed seizures in a general practice setting, they are relatively underrepresented in epilepsy-monitoring units.[25] Despite its usefulness in establishing a definitive epilepsy diagnosis in the elderly, long-term video-EEG monitoring remains underused.[29,35]

Neuroimaging

Neuroimaging is recommended as part of the initial evaluation of all older patients who present with a first seizure.[36] The underlying pathology, particularly strokes, can be identified in most elderly patients with seizures. The VA Cooperative Study 428 found that only 18% of elderly patients with epilepsy had normal findings on brain imaging (computed tomography [CT] or magnetic resonance imaging [MRI]).[26] Abnormal neuroradiology findings included cerebrovascular accidents (in 42.6% of patients), small-vessel disease (40.9%), encephalomalacia (9.1%), benign tumors (1.5%), and normal-pressure hydrocephalus (0.75%).[26] MRI is usually more sensitive than CT in detecting pathologic processes associated with seizures. CT is more widely available in emergency departments, however, and is appropriate when acute hemorrhage is suspected or MRI is contraindicated.

ANTIEPILEPTIC THERAPY

An acute symptomatic seizure with an obvious precipitating cause does not require AED therapy to prevent further seizures. Rectifying the underlying etiology is the appropriate management for such cases.

For older patients with an isolated idiopathic seizure, the question of therapy becomes more complex. Older persons who present with an initial seizure are more likely than younger individuals to have recurrent seizures.[37] The risk factors that are associated with an increased risk for seizure recurrence in younger patients—known symptomatic cause, partial seizures, a family history of epilepsy, epileptiform EEG, and abnormal neurologic findings—may predict seizure recurrence in the elderly as well.[38] At present, there are few studies to guide us in counseling older patients about future risk following an unprovoked seizure. AED therapy should be initiated for patients with epilepsy, and it should be considered for those with an unprovoked seizure and high risk of recurrence.

AED pharmacokinetics and the elderly

The pharmacokinetics of AEDs are more complex in the elderly than in younger patients because of lower protein binding, impaired hepatic metabolism, altered volume of distribution, decreased renal elimination, and decreased enzyme inducibility. Because polypharmacy is more prevalent in the elderly, AED therapy carries a greater risk of adverse effects (Table 3)[39,40] and drug interactions (Table 4) in elderly patients.

The optimal AED for use in this population would be fully absorbed and demonstrate linear pharmacokinetics, with clearance unaffected by renal impairment. It would neither induce nor inhibit hepatic enzymes. It would be inexpensive and well tolerated and would not interact with other medications. Unfortunately, there is no medication that completely fulfills these ideal characteristics.

AED use in the elderly is widespread

AEDs are widely prescribed for the elderly: 7.7% of nursing home residents are receiving AEDs upon admission to a nursing home, and AED therapy is initiated in another 2.7% within the first 3 months of nursing home admission.[41] AEDs account for almost 10% of adverse drug reactions in the elderly and are the fourth leading cause of adverse drug reactions in nursing home residents.[42]

Despite these statistics and the dramatic increase in treatment options for epilepsy over the past decade, few studies have specifically addressed the clinical use of AEDs in the elderly. Recent guidelines from the

TABLE 2
Variables that distinguish common causes of spells in the elderly

Variable	Seizure	Syncope	TIA	TGA	Metabolic	Psychiatric
Premonitory symptoms	None vs aura	None vs N/V, light-headedness, diaphoresis	None	None	None	None
Posture effect	None	Often erect	None	None	None	None
Onset	Acute	Variable	Acute	Acute	Acute	Variable
Bystander observations						
Duration	1–2 minutes	Seconds to minutes	Minutes to hours	Hours	Minutes to hours	Minutes to hours
Movements	Variable tonic-clonic movements	Loss of tone, clonic jerks	Deficits along vascular pattern	None	Variable, myoclonus, tonic-clonic	Variable, may have bizarre signs
Incontinence	Variable	None	None	None	None	None
Heart rate	Increased or decreased	Variable	Normal	Normal	Variable	Variable
EEG during ictus	Epileptiform pattern	Diffuse slowing	Focal slowing or normal	Rare slowing	Diffuse slowing	Normal
Trauma	Tongue laceration or ecchymoses	Ecchymoses or fracture	None	None	Rare	None
Postictal	Confusion, sleep	Alert or mild confusion	Alert	Alert	Alert when treated	Alert

Adapted, with permission, from reference 30.
TIA = transient ischemic attack; TGA = transient global amnesia; N/V = nausea and vomiting; EEG =electroencephalogram

American Academy of Neurology (AAN) and the American Epilepsy Society (AES)[43] address the use of second-generation AEDs to treat new-onset epilepsy in adults and children. These recommendations generally can be extrapolated to older patients, particularly with regard to safety and tolerability.

Older vs newer AEDs

The choice of an appropriate AED is initially dictated by the patient's seizure type. The older and newer generations of AEDs (Table 3) have efficacy for seizures with partial onset, including simple partial, complex partial, and secondarily generalized seizures. Traditionally, the older AEDs have been used as first-line agents, and the eight newer AEDs (all introduced to the US market from 1993 onward) have been used as adjunctive therapy (or, in the case of lamotrigine, conversion to monotherapy). Valproic acid is a broad-spectrum older AED that is effective for absence and myoclonic seizures, as well as seizures of partial onset. It is the first-line treatment for primary generalized tonic-clonic seizures, although newer AEDs such as lamotrigine, topiramate, and zonisamide also may be effective. Non-drug treatment options, such as vagus nerve stimulation and epilepsy surgery, are generally well tolerated by older adults but are reserved for medication-resistant epilepsy.[44–46]

After seizure type, a variety of factors affect the choice of AED, including potential side effects and cost. Older and newer AEDs are both efficacious, but the older drugs have a higher rate of drug-specific adverse effects, drug interactions, and nonlinear kinetics.[26] Phenobarbital and primidone, both old drugs, are not recommended for use in the elderly because of concern about cognitive impairment and other adverse effects. Total phenytoin concentrations in individual nursing home residents can vary two- to threefold, even when the dose is the same, putting this population at risk for seizures or toxicity.[47]

Despite the drawbacks of older AEDs, phenytoin is the AED most commonly prescribed for nursing home residents, and phenobarbital is the second most commonly prescribed adjunctive AED in this setting.[48] A recent retrospective study speaks directly to

TABLE 3
Comparative characteristics of older and newer antiepileptic drugs (AEDs)

Drug	Primary route of elimination	Advantages	Potential adverse effects	Idiosyncratic reactions	Representative maintenance dose	Cost*
Older AEDs						
Carbamazepine	Hepatic	Inexpensive	Ataxia, dizziness, drowsiness, diplopia, nausea	Rash, blood dyscrasia, SJS, hepatic failure, hyponatremia	400 mg twice daily	$15.30
Phenytoin	Hepatic	Inexpensive, once-daily dosing	Ataxia, gingival hyperplasia hirsutism, lymphadenopathy, nystagmus	Rash, hepatotoxicity, SJS, blood dyscrasias, aplastic anemia, neuropathy, lymphadenopathy, pancreatitis	200 mg once daily	$15.00
Valproic acid	Hepatic	Broad spectrum	Tremor, nausea, ataxia, somnolence	Rash, thrombocytopenia, blood dyscrasia, pancreatitis, SJS, hepatotoxicity	250 mg three times a day	$52.50
Phenobarbital	Hepatic	Inexpensive, once-daily dosing	Sedation, drowsiness, cognitive impairment	Hypersensitivity reactions, seizure exacerbation	90 mg once daily	$2.75
Newer AEDs						
Felbamate	Hepatic	Broad spectrum	Anorexia, nausea, weight loss, insomnia	Rash, aplastic anemia, SJS, hepatic failure, weight loss, anorexia, insomnia	400 mg three times daily (after meals)	$176.90
Gabapentin	Renal	No interactions with other AEDs	Somnolence, dizziness, fatigue, peripheral edema	Neutropenia	300 mg three times daily	$132.96
Lamotrigine	Hepatic	Broad spectrum	Rash, tremor, nausea, dizziness, headache	Rash, SJS, blood dyscrasia	150 mg twice daily	$231.00
Levetiracetam	Renal and hepatic	No drug interactions	Somnolence, dizziness, incoordination, agitation, psychosis	None reported	500 mg twice daily	$148.50
Oxcarbazepine	Hepatic	Better tolerated than carbamazepine†	Dizziness, nausea, diplopia, tremor	Rash, hyponatremia	600 mg twice daily	$231.60
Tiagabine	Hepatic	Clearly defined mechanism of action	Dizziness, sedation, confusion	Rash, paresthesias	32 mg/day (in three divided doses)	$231.30
Topiramate	Renal	Broad spectrum, weight loss	Cognitive impairment, dizziness, ataxia, tremor, fatigue, anorexia, weight loss, sedation, paresthesias	Nephrolithiasis, narrow-angle glaucoma	100 mg twice daily	$240.00
Zonisamide	Hepatic and renal	Once-daily dosing, broad spectrum	Somnolence, dizziness, ataxia, agitation,weight loss	Nephrolithiasis, rash, SJS, cross-allergy to sulfonamides, aplastic anemia	100 mg twice daily	$140.00

Adapted from references 39 and 40.

* Cost for 30-day supply with lowest given dosage of solid formulation, based on average wholesale price from *Drug Topics Red Book*, 2005 ed.

† Oxcarbazepine is an analog of carbamazepine.

SJS = Stevens-Johnson syndrome

TABLE 4
Drug-interaction profiles of the older and newer antiepileptic drugs (AEDs)

Drug	Drug interactions
Older AEDs	
Carbamazepine	Levels markedly raised by propoxyphene; decreases levels of calcium channel blockers (diltiazem, verapamil); its own levels are increased when taken with calcium channel blockers
Phenytoin	Carbamazepine and phenobarbital may reduce phenytoin serum levels; phenytoin serum levels may be increased by fluoxetine, H_2-antagonists, and valproate; phenytoin may impair efficacy of corticosteroids, warfarin, calcium channel blockers, oral contraceptives, and tricyclic antidepressants
Valproic acid	Can act as a metabolic inhibitor, increasing levels of lamotrigine, phenobarbital, and lorazepam; concomitant use may increase levels of phenytoin, diazepam, warfarin, amitriptyline; clearance of valproate may be increased with phenytoin, phenobarbital, primidone, and carbamazepine
Phenobarbital	Increased risk of acetaminophen toxicity; decreases levels of calcium channel blockers; decreases effect of warfarin
Newer AEDs	
Felbamate	May increase valproic acid and phenytoin levels; may decrease carbamazepine levels; may increase phenobarbital levels
Gabapentin	Does not reduce or inhibit any CYP-450 or UGT isoenzyme; does not interact with other hepatically metabolized drugs such as AEDs, warfarin, or theophylline; elimination is not impaired by other drugs
Lamotrigine	Metabolism significantly induced by phenytoin, carbamazepine, phenobarbital; metabolism significantly inhibited by valproic acid; no interaction with gabapentin, levetiracetam, topiramate, zonisamide
Levetiracetam	Does not induce or inhibit any CYP-450 or UGT isoenzyme; no known interactions with other AEDs; no effect on digoxin or warfarin
Oxcarbazepine	Inhibits CYP-2C19; induces CYP-450 3A4 and UGT isoenzymes; magnitude of interactions less than that of carbamazepine (of which oxcarbazepine is an analog); may increase phenytoin levels
Tiagabine	Does not induce or inhibit any CYP-450 or UGT isoenzyme
Topiramate	May increase serum phenytoin levels, presumably via inhibition of CYP-2C19; induces CYP-450 3A4 isoenzymes
Zonisamide	Does not inhibit the CYP-450 system; no effect on phenytoin, carbamazepine, valproic acid, or other drugs; half-life is reduced by phenytoin, carbamazepine, and valproic acid; metabolism is induced or inhibited by drugs that induce or inhibit CYP-450 3A4 isoenzymes

UGT = uridine diphosphate-glucuronosyltransferase

the issue of inappropriate AED prescribing for the elderly.[49] This analysis, which collected data from 21,435 elderly veterans with epilepsy, showed that most patients received potentially inappropriate AED therapy; phenytoin was prescribed for approximately 54% and phenobarbital for 17%.

Other recent studies have suggested that tolerability is a major limiting factor in the medical treatment of epilepsy in the elderly, particularly with older AEDs.[26] A multicenter, double-blind trial in elderly patients with newly diagnosed epilepsy showed a significantly greater dropout rate for subjects randomized to the older AED carbamazepine compared with the newer agent lamotrigine.[50] More recently, the VA Cooperative Study 428, an 18-center, parallel, double-blind trial, compared gabapentin, lamotrigine, and carbamazepine in patients aged 60 years or older with new-onset seizures.[11] Although seizure control in the three treatment groups was similar, there were significant differences favoring the newer agents gabapentin and lamotrigine over carbamazepine in measures of tolerability.[11] Using retrospective data, two reports suggest that the newer AED levetiracetam is effective and well tolerated in the elderly,[51,52] but larger, prospective studies are needed to substantiate these findings.

Although a detailed review of clinical trials of the new AEDs is beyond the scope of this article, readers are referred to the 2004 report by LaRoche and Helmers[53] for such a review. After conducting a systematic literature search and analysis of all randomized controlled trials (n = 55) of the eight newer AEDs in adults, these authors reported that no ran-

domized trials at that time had compared the new AEDs with each other or against the older AEDs. They concluded, however, that several studies suggested that the newer agents have a broader spectrum of antiseizure activity than the older AEDs, fewer drug interactions, and better overall tolerability.

Thus, the newer AEDs offer some advantages over the older AEDs, as detailed in Tables 3 and 4. However, the newer AEDs also have their own drawbacks. These include drug-specific side effects, slower titration schedules, and a lack of intravenous formulations. In addition, all the newer AEDs are significantly more expensive than their older-generation counterparts (Table 3). Further clinical trials clearly are needed to assess the efficacy and safety of the newer AEDs as adjunctive treatment and as monotherapy in the elderly.

Dosing in patients with renal or hepatic dysfunction

Renal function plays an important role in the excretion of AEDs. Glomerular filtration and creatinine clearance decrease by about 1% per year after age 40.[16] In elderly patients with renal insufficiency, dose reductions of AEDs with significant renal excretion are necessary to avoid intoxication. Dose adjustments should be made for gabapentin, topiramate, zonisamide, oxcarbazepine, lamotrigine, levetiracetam, phenobarbital, and primidone.[54] In AEDs with high protein binding, such as phenytoin, uremia is associated with decreased binding. In these instances, monitoring of the free (unbound) fraction is appropriate.[54]

Hepatic metabolism also slows with aging. While concentrations of liver enzymes do not change,[16] cytochrome P-450 microsomal concentrations can be altered by disease, concomitant medications, and nutritional disorders. Several categories of liver disease affect drug metabolism and elimination, including acute hepatitis, cholestasis, chronic liver disease, drug-induced hepatotoxicity, and neoplastic disease. In elderly patients with hepatic disease, phenytoin, valproic acid, phenobarbital, carbamazepine, benzodiazepines, lamotrigine, and tiagabine pose a risk for intoxication, requiring dose reduction and monitoring.[54]

Prognosis with AED therapy

The prognosis for elderly patients with epilepsy treated with AEDs is generally good. In the VA Cooperative Study 428, when seizures occurring during the titration phase were excluded, 63% of elderly patients who continued AED treatment were seizure-free at 1 year.[11] In a Canadian study of elderly subjects with new onset of seizures, 89% of the patients available for follow-up were taking AEDs, and seizure control was usually successful. Predictors of persistent seizures were having more than three seizures by the time of presentation, interictal epileptiform activity on EEG, and discontinuation of AEDs because of lack of efficacy.[55]

STATUS EPILEPTICUS IN THE ELDERLY

About 30% of acute seizures in the elderly present as status epilepticus (SE), a neurologic emergency associated with high mortality.[56] The incidence of SE in the elderly, 86 cases annually per 100,000 population, is almost twice that in the general population.[57] A European study of SE found more than a tenfold increase in the incidence of SE in the elderly compared with adults younger than age 60.[58] The "very old" elderly, those older than 80 years, have an SE incidence of 100 per 100,000 population per year.[59] In the general population, about 4 in 1,000 people who live to age 75 will have had an episode of SE.[60]

Etiologies in the elderly

As is the case with epilepsy, SE in the elderly is most often attributable to acute or remote stroke.[59,61–64] Other common causes include low AED level, hypoxia, and metabolic disturbances, as well as alcohol-related causes. Tumor, infection, anoxia, hemorrhage, CNS infection, and trauma each cause 10% or less of SE cases.[59]

Seizure type

The most common seizure type in elderly patients with SE is partial with secondary generalization (45%), followed by partial (29%) and generalized tonic-clonic.[59] Generalized tonic-clonic SE has a very high mortality, 49%, but even SE with partial seizures has a mortality of 30% in the elderly.

Nonconvulsive status epilepticus

Nonconvulsive SE (NCSE) in the elderly is challenging to diagnose. In the outpatient setting, it may present as waxing and waning confusion.[65] This type of NCSE generally responds well to an initial intravenous dose of a benzodiazepine. In hospitalized elderly patients, NCSE should be considered when a decreased level of consciousness is unexplained or prolonged. Suspected NCSE should be evaluated with EEG. NCSE has a worse prognosis in the elderly than in younger patients because of the severity of comorbidities in the elderly, including hospital-acquired infections.[66] NCSE mortality was 52% in a study of 25 critically ill elderly patients, and death was correlated with the number of acute life-threatening medical problems on presentation.[67] In this critically ill cohort, treatment of NCSE with benzodiazepines increased the risk of death, and aggressive anticonvulsant therapy did not improve outcome.

Treatment of status epilepticus

The treatment of SE in the elderly has been reviewed in detail elsewhere.[62] The initial recommended treatment consists of intravenous diazepam or lorazepam. If seizures persist, a loading dose of phenytoin or fosphenytoin is subsequently given. Blood pressure and cardiac rhythm must be monitored continuously during a rapid infusion, and if adverse effects occur, the infusion rate should be slowed. SE that is refractory to these therapies is usually treated with general anesthetic agents, and patients require intubation, mechanical ventilation, and careful hemodynamic monitoring in an intensive care unit. EEG monitoring is also recommended to document that electrographic seizures have stopped.

Mortality is linked to etiology

SE is associated with a 38% mortality in the elderly and with an even higher mortality, 50%, among patients older than 80 years.[57,68] Mortality in this population is related to the etiology of SE. Elderly patients who develop SE de novo during a hospitalization have a poor prognosis, which is usually related to underlying conditions.[69] Relatively favorable survival rates (mortality < 6%) are associated with SE resulting from low AED levels, alcohol withdrawal, and idiopathic etiologies.[59]

SPECIAL CONSIDERATIONS

AEDs and bone health in the elderly

Until recently, the risk of osteopenia and osteoporosis in patients taking AEDs was not widely appreciated.[70] AED-associated abnormalities in bone metabolism include hypocalcemia, hypophosphatemia, decreased levels of active vitamin D metabolites, and hyperparathyroidism.[71] Decreased bone mineral density and higher rates of osteopenia and osteoporosis have been documented by dual-energy x-ray absorptiometry (DXA) in adults taking AEDs.[72–76] AED use is a risk factor for bone fracture.[77] The risk of brittle bones and potential fracture is particularly relevant to the elderly, who may already be vulnerable to falls because of seizures or medical problems that impair gait, such as arthritis or neuropathy.

Most studies of AEDs and bone health involve older AEDs, especially phenytoin, phenobarbital, and primidone. AEDs that induce the hepatic cytochrome P-450 system are associated with altered bone metabolism and decreased bone density.[73,78–80] On the basis of animal and human studies, various mechanisms for these alterations have been proposed.[71] Accumulated evidence suggests that phenytoin, phenobarbital, and primidone present risks to bone health; the situation is less clear for other AEDs. There are conflicting study results regarding the effects on bone health of other older drugs, including valproic acid, an inhibitor of the cytochrome P-450 system, and carbamazepine, an inducer.[71] Although there is hope that newer AEDs are less deleterious to bone health than the older AEDs, few studies have systematically examined this issue.[81,82]

The elderly patient with epilepsy should be monitored for abnormalities in bone mineral density. In elderly men and women who have been taking older AEDs for many years, bone mineral density should be evaluated by DXA. Patients should also be advised to get adequate exposure to sunlight, a source of vitamin D.

Quality of life

Although tolerability is a key factor in AED selection for the elderly, few randomized clinical trials of AEDs have specifically reported on quality-of-life issues in this age group. The AAN-AES guidelines,[43] though not specifically geared toward elderly patients, offer recommendations for the treatment of new-onset epilepsy based on quality-of-life issues such as adverse effects. In general, however, rates of early study withdrawal for patients over age 60 are substantial, and adverse effects are common.[83]

Although adverse effects from AEDs are common at any age, elderly adults experience different adverse effects from those in younger adults. A community-based survey of 669 adults, including 155 elderly men and women, found that unsteadiness, upset stomach, dizziness, and disturbed sleep were reported more often by elderly patients than by younger patients, whereas younger patients reported more sleepiness, aggression, and skin problems.[84] Memory problems were frequent in both groups. Fractures were the only injury that was more common in older than in younger adults, reported by 9.3% of elderly patients. Interestingly, elderly patients with epilepsy diagnosed earlier in life reported more injuries than those whose epilepsy was diagnosed later in life. This study found no evidence of increased psychological dysfunction in elderly patients with epilepsy. However, elderly patients with late-onset epilepsy were more likely to report anxiety and depression and rated their overall quality of life less positively than did those whose epilepsy had been diagnosed at an earlier age.

Other quality-of-life issues have significant impact on the elderly. Loss of a driver's license because of seizures threatens the independence of elderly adults, especially those living alone. Older adults on a fixed income may experience financial hardship in paying for health care expenses. In one US cost analysis, the

average direct medical cost per person in the 6 years after an epilepsy diagnosis was $10,612 for elderly patients vs $6,429 for younger patients.[10] Unlike younger employed individuals, whose health insurance often includes prescription drug coverage, elderly patients often pay out of pocket for their medications, making cost an important factor in AED selection.

CONCLUSIONS

Seizures are common neurologic events in the elderly that may present with nuances unique to this population. Physicians who develop expertise in recognizing these nuances will make more timely diagnoses and be less likely to miss the diagnosis. In treating epilepsy, the choice of AED is usually dictated by seizure type and tolerability and may be complicated by issues of comorbidity or age-associated effects on AED pharmacokinetics. Appropriate adjustments in AED prescribing for the elderly include a lower initial dose, slower titration, and a lower target dose than for younger adults. Seizures and epilepsy have important implications for the independence, safety, and quality of life of elderly persons.

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Movement disorders in the older patient:
Differential diagnosis and general management

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ABSTRACT

Movement disorders are especially prevalent in the elderly, and some are highly treatable. Because reduced agility and slowing of gait are associated with numerous movement disorders as well as with the normal aging process, the differential diagnosis of movement disorders in the elderly can be challenging. Many of these disorders share features of parkinsonism—hypokinesia, tremor, and muscular rigidity. This article reviews common and less common movement disorders in the elderly from a primary care perspective, with an emphasis on the presenting features and the differential diagnosis. It also provides general management recommendations with advice for tailoring treatment to elderly patients.

KEY POINTS

A number of movement disorders—Parkinson disease (PD), essential tremor, dementia with Lewy bodies, small-vessel ischemic disease, and restless legs syndrome—are common in the elderly, with prevalences of more than 1% in this population.

Most medications for treating movement disorders should be titrated more slowly in elderly patients than is recommended by the manufacturers.

PD is defined by the presence of two of three cardinal motor signs—tremor, rigidity, and bradykinesia—in the absence of other causes for parkinsonism.

Early mobility problems in PD are usually treated with levodopa or dopamine agonists. Levodopa is more effective, better tolerated, easier to titrate, and less costly, but it may accelerate the onset of motor fluctuations.

Dopamine agonists should be avoided in elderly PD patients with confusion or hallucinations, as they are more apt than levodopa to cause or exacerbate these problems.

Parkinsonism can have many causes other than PD, including certain medications, multiple system atrophy, progressive supranuclear palsy, dementia with Lewy bodies, and other neurologic conditions.

Movement disorders are especially prevalent in the elderly, and both the large number of these disorders and their similarities can make differential diagnosis a challenge. Many of these disorders share the hallmark features of parkinsonism—hypokinesia, tremor, and muscular rigidity. Moreover, some of the symptoms of movement disorders can resemble the slowing of gait and reduced agility that accompany the normal aging process, in which the spine degenerates, joints become more lax and deteriorate, and peripheral sensorineural receptors degenerate.

This article provides a concise review for primary care physicians of key diagnostic features of common movement disorders in the elderly and less common conditions that mimic these disorders. It also provides an overview of recommended treatment strategies. Specific treatment algorithms will not be presented; instead, recommendations are offered for tailoring to individual elderly patients. With the principal exception of most medications used to treat Parkinson disease (PD), most of the recommendations include off-label uses for medications approved by the US Food and Drug Administration for other indications. Most

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of these recommendations are supported by good clinical studies and are widely followed by clinicians caring for these patients.

Because of the prevalence of PD and the complexity of its treatment, emphasis will be given to this disorder. Because other conditions in the elderly can be difficult to distinguish from PD (Table 1), the differential diagnosis of parkinsonism will also be a focus.

PARKINSON DISEASE

PD is a primary degenerative disease characterized by the loss of the neurotransmitter dopamine from the substantia nigra. It is increasingly common with advancing age, with a prevalence approaching 1% by age 65 and 2% at age 80.[1,2]

Patients with PD can normally remain independent and ambulatory (albeit slower) for a very long time. In a large series of patients with pathologically confirmed parkinsonian disorders reported in 2000,[3] no patients with PD progressed from initial symptom onset to stage III on the Hoehn and Yahr Scale of disability (ie, gait unsteadiness or imbalance, with or without falls) within 1 year of the onset of motor symptoms, whereas 72% of patients with atypical parkinsonism (multiple system atrophy, progressive supranuclear palsy, dementia with Lewy bodies, or corticobasal degeneration) did. The median time to progression to Hoehn and Yahr stage IV (severe disability, but still able to walk or stand unassisted) was approximately 14 years for those with PD vs less than 5 years for those with atypical parkinsonism. The advent of new medications and surgical interventions promises even a better prognosis for PD patients in the future.

Diagnosis

Although consensus criteria are lacking, movement disorder specialists often define PD by the presence of two of the following three cardinal motor signs in the absence of other apparent causes for parkinsonism:

- Tremor
- Rigidity
- Bradykinesia.

Drug-induced parkinsonism due to the use of dopamine-blocking agents (eg, neuroleptics, metoclopramide) should be especially excluded. Asymmetric tremor is the most common early sympom of PD encountered by primary care physicians and should always raise the possibility of PD. However, the absence of tremor should not exclude consideration of the possibility of PD. In fact, tremor is also the only cardinal feature that may never occur.

Stricter criteria for a diagnosis of PD require an unequivocal response to a dopaminergic medication (at least 1,000 mg/day of levodopa), but this requirement is limiting in that many patients with early symptoms are not treated.[4] Also, some patients with other forms of parkinsonism may respond to medications, at least initially. Additionally, rest tremor can be medication-resistant, although such an occurrence should always prompt review of the diagnosis. For patients with features typical of PD who respond predictably to antiparkinsonian medications, imaging studies are generally not necessary.

Postural instability is often considered a fourth cardinal feature of parkinsonism but is not generally considered in the diagnosis of PD because of its frequent presence in other parkinsonian syndromes. Moreover, if a patient exhibits postural instability (ie, stage III on the 5-stage Hoehn and Yahr Scale) within 1 year of the onset of motor symptoms or is wheelchair-dependent (Hoehn and Yahr stage V) within 7 or 8 years of disease onset, an alternative diagnosis is almost certain.[5] On occasion, uncertainty about responsiveness to a dopaminergic medication can be settled by gradually withdrawing the medication. See Table 1 for a summary of differentiating features of parkinsonian conditions in the elderly, most of which are described in detail in the text below.

General treatment considerations

A number of medications across several drug classes are commonly used to treat PD (Table 2). These include the mainstay therapy levodopa (the levorotatory form of dopa, the precursor of dopamine) as well as dopamine antagonists, catechol-*O*-methyltransferase (COMT) inhibitors, and anticholinergic agents. The focus here is on general pharmacologic treatment considerations, since neurology consultation is warranted with complicated drug regimens or advanced stages of PD and since most patients with complicated courses of PD are co-managed by neurologists in addition to their primary care physicians. It is also worth noting that most drugs that affect the central nervous system (whether for PD or other movement disorders discussed below) should be titrated more slowly in the elderly than is normally recommended by the manufacturers (see titration recommendations in Table 2).

Protective therapy

To date, no medications have convincingly been shown to delay the progression of PD. Epidemiologic studies suggest that caffeine,[6–8] tobacco,[9] and nonsteroidal anti-inflammatory drugs[10] may reduce the risk for PD, but it would be difficult to advocate the regular use of these agents.

TABLE 1
Differential diagnosis of parkinsonism in the elderly

Disorder	Differentiating clinical features
Parkinson disease (PD)	• Usually presents with asymmetric parkinsonian symptoms • Falling is rare early in course • Patient is ambulatory for >10 yr from onset • Highly responsive to dopaminergic drugs
Drug-induced parkinsonism	• Most often due to neuroleptics or metoclopramide • If parkinsonian symptoms are asymmetric, the offending drug is probably unmasking or exacerbating underlying PD
Multiple system atrophy	• Symmetric presentation • Autonomic dysfunction frequent (not universal) • Parkinsonism or cerebellar ataxia may predominate • Cognition is preserved • Medication-resistant • Patient wheelchair-dependent within 5 yr
Progressive supranuclear palsy	• Symmetric presentation • Prominent midline involvement • Falling from outset • Vertical gaze palsy (not universal) • Neuropsychiatric features • Medication-resistant • Patient wheelchair-dependent within 5 yr
Dementia with Lewy bodies	• Clinically resembles PD, but with progressive and prominent dementia beginning within 1 yr of onset of motor features • Variable medication response with poor tolerance due to hallucinations
Small-vessel arteriopathy	• Usually history of hypertension, often of transient ischmic attacks/strokes • Clinically: dementia, diffuse hyperreflexia, Babinski signs, disproportionate involvement of legs/gait and often relatively preserved finger-tapping • Medication-resistant
Normal-pressure hydrocephalus	• Triad of gait ataxia, dementia, urinary incontinence • MRI: ventricular enlargement disproportionate to cortical atrophy and small-vessel ischemic changes • Confirmed by beneficial response to large-volume tap (30–50 mL)

Treatment of mobility problems in PD

Levodopa vs dopamine agonists. Because of experimental[11] and clinical[12] evidence suggesting that treatment with levodopa, but not with dopamine agonists, accelerates the onset of motor fluctuations, dopamine agonists are commonly considered the preferred first-line agents for treating early mobility problems. On the other hand, levodopa is more effective, better tolerated, easier and quicker to titrate, and considerably less expensive. For older patients, these factors may favor the choice to initiate therapy with levodopa, but this decision should be based on the patient's overall health and cognition and not solely on chronological age. Also, even though dopaminergic medication–induced involuntary movements (dyskinesias) develop in approximately 40% of treated PD patients, motor complications are less prevalent in patients who are elderly.[13]

Levodopa. Levodopa is given with carbidopa, a peripheral dopa decarboxylase inhibitor, to reduce the systemic breakdown of levodopa. Without carbidopa, nearly all patients would experience intolerable side effects, mainly nausea and vomiting. Regular carbidopa/levodopa may be a good first choice in the elderly and is less expensive than sustained-release formulations (see Table 2 for recommended dosages). Although pulsatile exposure of dopamine receptors to levodopa is purported to accelerate motor fluctuations, a head-to-head study did not show any benefit of sustained-release vs regular carbidopa/levodopa in time to onset of motor fluctuations.[14] The convenience of a sustained-release formulation should be weighed against the additional cost.

Options among dopamine agonists. Bromocriptine was the first dopamine agonist approved in the United States but has been shown to be relatively less effective than the newer agents in this class.[15–19] Pergolide, like bromocriptine, is an ergot-derived dopamine agonist, but it has fallen into disfavor because of an associated risk for inducing valvular and pulmonary fibrosis.[20] If either of these agents is used, patients should undergo yearly echocardiogram studies and be monitored for pulmonary involvement.

Pramipexole and ropinirole are the newest dopamine agonists approved in the United States. Both are administered orally, and they have comparable efficacy and side-effect profiles (Table 2). Although patients can occasionally be switched between these agents in response to side effects, there is little evidence that this offers the potential for better clinical efficacy.

Compared with levodopa, dopamine agonists are more likely to cause confusion and hallucinations and should be avoided in patients already manifesting these problems. A low threshold for eliminating dopamine agonists is appropriate in elderly patients. Even advanced disease can generally be managed with levodopa therapy alone without compromising control of parkinsonian symptoms, although consultation with a neurologist (preferably a movement disorder specialist) is advised in such advanced cases. Because

TABLE 2
Pharmacologic agents commonly used to treat Parkinson disease in the elderly

Class	Medication	Typical starting dose	Titration*	Usual therapeutic dose	Maximum dose	Common adverse effects†
Dopamine	Carbidopa/levodopa					Nausea, vivid dreams, confusion, hallucinations
	–Regular-release (25/100 mg)	1 tablet tid	tid q5d	1 tablet tid	As tolerated	
	–Sustained-release (50/200 mg)	1 tablet bid	bid q5d	1 tablet bid	As tolerated	
Dopamine agonist	Pramipexole	0.125 mg bid	0.125 mg q3–4d	0.5 mg tid	4.5 mg/day	Nausea, somnolence, confusion, hallucinations, pedal edema, orthostatic hypotension
	Ropinirole	0.25 mg bid	0.25 mg q3–4d	2–3 mg tid	24 mg/day	
COMT inhibitor‡	Entacapone	100 mg bid (taken with levodopa)	Add two 100-mg doses q5d	100 mg with each levodopa dose	200 mg with each levodopa dose	Exacerbation of dopamine side effects, including dyskinesias
Anticholinergics	Trihexyphenidyl	1 mg qd	1 mg q4–5d	2 mg tid	As tolerated	Dry mouth, confusion, blurred vision
	Benztropine	1 mg qd	1 mg q4–5d	2 mg tid	As tolerated	
Antiviral	Amantadine	100 mg qd	100 mg/wk	100 mg bid or tid	400 mg/day	Pedal edema, confusion

* Titration recommendations are tailored to the elderly.

† For drug classes with more than one medication listed, adverse effect listings are for the entire class.

‡ Tolcapone is another commercially available COMT inhibitor, but it is not commonly used because of its associated risk of liver failure (see text). Because both entacapone and tolcapone typically increase peak levels of levodopa, levodopa doses may need to be lowered by 20% to 30%.

COMT = catechol-O-methyltransferase

dopamine agonists and, to a lesser extent, levodopa have been associated with sleep attacks, it is imperative that patients be warned of this risk.[21]

Uncertain role for COMT inhibitors. In theory, there could be long-term benefit from the early use of COMT inhibitors (eg, entacapone), which block one of the major enzymes that break down dopamine, but without supportive evidence, it is difficult to justify the additional cost of introducing a COMT inhibitor at an early stage.

Treatment of tremor

Levodopa, dopamine agonists, and anticholinergic medications can be highly effective for treating parkinsonian tremor.[22] Some patients require 1,000 mg or more of levodopa daily for adequate control. Because anticholinergic medications (and the antiviral drug amantadine) have a high propensity to cause confusion in the elderly, they should be considered second-line agents in most elderly persons. Ethopropazine may produce relatively less confusion than other anticholinergic agents but is available in the United States only from select compounding pharmacies; its usual therapeutic dose is 50 to 100 mg three times daily.

Medication adjustments in the wake of reduced dopaminergic response

Regular medication adjustments are generally needed in response to the progressive degeneration of dopamine-producing cells and to keep pace with PD progression. These adjustments should balance concerns about introducing levodopa (and potentially accelerating motor fluctuations) against the need to adequately treat parkinsonian symptoms. The key is to tailor adjustments to the individual patient. For example, if a patient complains of doing poorly in the morning but not during the rest of the day, only the first morning dose needs to be increased. For unsatisfactory responses due to inadequate dosing, increasing the levodopa dose is likely to provide similar efficacy at significantly less cost than adding a COMT inhibitor. A formulation combining carbidopa/levodopa with the COMT inhibitor entacapone is available, but it is significantly more expensive than using carbidopa/levodopa alone.

'Wearing off' and unpredictable medication responses

Within 3 to 5 years of starting levodopa therapy, many patients begin to experience a decrease in the duration of their response to individual doses of the drug. This "wearing off" has been attributed to reduced storage capacity of ingested as well as endogenous dopamine in axon terminals in the striatum as a result of continued loss of dopamine-producing cells and associated secondary axonal degeneration.

End-of-dose wearing off is fundamentally different from a lack of sufficient response to a given dose level. Although increasing individual doses can extend the effective "on" period (ie, the period of greater mobili-

ty and treatment response), problems of wearing off are generally best treated by reducing the interval between levodopa doses. Because of the longer duration of response to dopamine agonists relative to levodopa, adding or increasing the dose of a dopamine agonist can be a useful approach to problems of wearing off. Also, patients may benefit from switching to sustained-release preparations of carbidopa/levodopa or adding entacapone.

At this stage of PD, entacapone can extend the on time in response to an individual dose of levodopa by up to 30 minutes or more.[23,24] Alternatively, another COMT inhibitor, tolcapone, is available and appears to have greater long-term benefits than entacapone on motor symptoms and in reducing off time.[25] However, tolcapone was reported to be associated with 3 deaths from fulminant hepatic failure among 40,000 patient-treatment years—10 to 100 times the anticipated rate.[26] The drug has not been withdrawn from the US market, however, and no further tolcapone-related deaths have been reported since regular monitoring requirements have been in place.[26] Because of its demonstrated efficacy, tolcapone should be considered for treatment of patients with otherwise medication-resistant disease.

With further disease progression, many patients experience unpredictability of medication responses and sudden off periods. In a minority of patients, particularly those with more advanced disease, competition between neutral amino acids from ingested protein and levodopa for transportation into the central nervous system via a saturable transporter system may influence medication responsiveness. Such patients may need to limit ingestion of protein for at least 1 hour before and after taking levodopa. Poor stomach motility may also contribute to erratic responses by preventing normal levodopa transport to the duodenum. Metoclopramide, often prescribed to treat gastric dysmotility, may aggravate parkinsonism.

Some patients at this stage benefit greatly from a short rest period or nap. Rescue doses of regular carbidopa/levodopa often can effectively treat poor on responses or sudden off periods. A new orally disintegrating levodopa formulation may offer selected patients greater convenience, ease of use, and rapid access to medication, which may increase on time.[27] Another option is apomorphine, an injectable dopamine agonist recently approved in the United States specifically for the intermittent treatment of off episodes in patients with advanced PD. Onset of response to apomorphine is typically within 10 minutes, compared with 20 to 30 minutes or longer for regular carbidopa/levodopa. Besides the need to inject apomorphine, its use is complicated by the need to premedicate, at least initially, with an antinausea agent. Despite these limitations, intermittent subcutaneous apomorphine therapy is generally well tolerated and can reduce off time by up to 50% or more in patients with advanced disease.[28]

Drug-induced dyskinesias

Dyskinesias are associated with on periods, and most patients prefer dyskinesias, regardless of their severity, to severe off periods of immobility. Nevertheless, dyskinesias can be quite debilitating and may require limiting the dose of dopaminergic medications.

Amantadine can be used to treat dyskinesias, but its benefits normally last only for up to 8 months.[29] The neuroleptic clozapine can be effective in treating dopaminergic medication–induced dyskinesias, but its use is limited by the risk of agranulocytosis and the need for weekly drawing of blood samples. Preliminary experience[30] suggests that the atypical neuroleptic quetiapine may also ameliorate dyskinesias. Unlike the smaller doses of quetiapine used to control hallucinations induced by dopaminergic medications, doses of 200 mg or more (generally at bedtime) may be required and can generally be well tolerated even in elderly patients.[30,31] In response to this treatment of dyskinesias, higher doses of dopaminergic medications may be tolerated.

Postural instability

Within 5 to 10 years of diagnosis of PD, most patients encounter balance problems and some may experience regular falls. This feature normally develops slowly, however, and if it is prominent early on, it is a red flag suggesting an alternative diagnosis.

Balance problems usually are not improved by dopaminergic medications. Patients with balance problems should be referred to a physical therapist, who can suggest useful means to avoid falls and recommend such aids as a cane or walker. Such patients can be instructed to recognize and temper potentially risky situations, such as rushing to answer the telephone or carrying dinner plates.

Associated symptoms

Besides problems related to motor function, most patients with PD experience additional bothersome symptoms due to the disease itself or to its treatment. Even when these cause more problems than the motor symptoms, patients and their caregivers may not always freely mention them to the physician.

Dementia. PD-related dementia does not regularly progress as aggressively as that associated with

Alzheimer disease (AD) or dementia with Lewy bodies, so the presence of a rapidly progressive dementia should especially raise consideration of another etiology. At the same time, PD-related dementia eventually develops in a high percentage of patients,[32] albeit at a slower pace. Elimination of such medications as selegiline, amantadine, anticholinergics, and dopamine agonists can often result in significant improvement in cognition, particularly in patients experiencing hallucinations. Generally, these patients can benefit from reducing or eliminating dopamine agonists in favor of levodopa.

Depression. Depression is thought to be due more often to the neurodegenerative process of PD than to reactive depression, in part because the depression in patients with PD tends to be keenly responsive to antidepressant medications.[33] Associated depression is often more debilitating than the underlying parkinsonism and must be treated (see separate article on depression on page S52 of this supplement).

Nausea. Both levodopa and dopamine agonists may produce significant nausea. Patients who experience milder nausea might benefit from taking their medication with meals. Dopamine that is converted from levodopa in the periphery by dopamine decarboxylase is thought to produce nausea by stimulating dopamine receptors in the area postrema in the brainstem. A daily dose of 75 mg of carbidopa (as provided by three doses of carbidopa/levodopa 25/100 mg) is generally necessary to adequately inhibit peripheral production of dopamine. Occasionally, patients may require larger amounts. Supplemental carbidopa (one or two 25-mg tablets) can be taken with the first morning dose or with each dose of carbidopa/levodopa.

Additional problems. Autonomic dysfunction is common in patients with PD and should not in itself be presumed to signify a diagnosis of multiple system atrophy.[34] Such features as impotence, bowel and bladder dysfunction, and orthostatic hypotension are relatively frequent and should each be addressed. A majority of patients with PD sleep poorly, and this can contribute to daytime somnolence. Speech problems can be disabling and may respond well to an intensive voice treatment program.[35]

Surgical intervention

Deep brain stimulation targeting the subthalamic nucleus or globus pallidus interna has become the standard surgical method for treating patients with advanced medically refractory PD symptoms.[36] Deep brain stimulation is particularly effective for treating motor fluctuations, including dyskinesias. Stimulation of the globus pallidus interna directly ameliorates dyskinesias, while stimulation of the subthalamic nucleus benefits patients primarily by enabling them to greatly reduce their dopaminergic medications. Patients generally respond well to deep brain stimulation surgery, and advanced age should not necessarily be a deterrent. However, because this surgery carries a significant risk of worsening dementia, it should be avoided in those with significant dementia.

MULTIPLE SYSTEM ATROPHY

Multiple system atrophy (MSA) is a sporadic disease with an estimated prevalence of 2 to 4 per 100,000 population.[37,38] It is equally prevalent among men and women, occurs most often in the sixth decade of life, and is associated with a mean survival of 6 to 9 years, although some patients have lived with the disease for 15 years or more.[39–42] MSA was previously separated into striatonigral degeneration, olivopontocerebellar atrophy, and Shy-Drager syndrome. However, because these conditions have similar pathologic features, including alpha-synuclein–positive glial cytoplasmic inclusions,[43] they are now thought to represent a single disease. The clinical features of MSA are outlined in Table 1.

Diagnosis

The diagnosis of possible MSA requires one of three criteria (either autonomic failure/urinary dysfunction, parkinsonism, or cerebellar ataxia) plus two characteristic features from the other two clinical criteria domains.[44] A fourth clinical domain (corticospinal dysfunction) is included as a feature but is not a defining criterion. The diagnosis of probable MSA requires the criterion for autonomic failure/urinary dysfunction plus poorly levodopa-responsive parkinsonism or cerebellar ataxia. The diagnosis of definite MSA requires pathologic confirmation.

Although study results differ, most patients with MSA show normal intellectual function with relatively mild memory and executive dysfunction.[45] Unlike patients with PD, patients with MSA and predominantly parkinsonian features typically present with prominent midline and symmetric limb involvement. In MSA, gait instability often develops rapidly, and most patients are wheelchair-dependent within 3 to 5 years. Unlike those with progressive supranuclear palsy, patients with MSA do not normally experience regular falls from the outset. Patients with prominent cerebellar features generally have additional features to suggest MSA but occasionally may present with a pure cerebellar syndrome, including scanning dysarthric speech, limb ataxia, and a wide-based ataxic gait. Autonomic involvement tends to be more severe

than in PD. Erectile dysfunction almost always accompanies MSA in males. Urinary incontinence or retention and orthostatic hypotension are also frequent symptoms. The finding of hypodense signal in the putamen on gradient echo sequences can help to differentiate MSA from PD[46] but is also commonly seen in progressive supranuclear palsy.[47]

Treatment

Some patients with MSA show a limited, mostly temporary response to antiparkinsonian medications. Others, often erroneously diagnosed with PD, may improve considerably when weaned from high doses of antiparkinsonian medications. A trial of at least 1,000 mg/day of levodopa is recommended to assess for potential efficacy, and dopamine agonists may be tried as well, with care taken not to worsen preexisting hypotension. Treated patients often quickly show orofacial and cervical dystonic dyskinesias, which strongly suggest a diagnosis of MSA. Most investigators have suggested that deep brain stimulation has no beneficial role in treating MSA[48] and may even be detrimental.[49] There are no established therapies for the cerebellar ataxic features.

Inspiratory stridor due to vocal cord dysfunction is a common feature in MSA and is associated with poor survival.[50] Continuous positive airway pressure can be well tolerated by most MSA patients with nocturnal stridor and has been suggested to reduce the risk of sudden death during sleep.[51] Aspiration also commonly leads to early death, and initiation of periodic swallowing evaluations is indicated in most patients within 5 years of disease onset.[52] Early involvement of physical, occupational, and speech therapists is critical to the overall well-being of the patient. Because MSA is a devastating illness, the patient and family require emotional support and care planning.

PROGRESSIVE SUPRANUCLEAR PALSY

Progressive supranuclear palsy (PSP) is a rapidly progressive disease that is mainly sporadic, occurs more commonly in men,[53] and has an estimated prevalence of 5 to 6 per 100,000 population.[37,54] It manifests after age 45, peaks early in the seventh decade of life, and is associated with a median survival of approximately 6 years (range, 1 to 17 years).[55,56] The pathology includes prominent neuronal loss and aggregates of abnormal tau protein in the substantia nigra, basal ganglia, and brainstem. Its major clinical features are presented in Table 1.

Diagnosis

A number of criteria have been proposed for the diagnosis of PSP, including the National Institute of Neurological Disorders and the Society for Progressive Supranuclear Palsy (NINDS–SPSP) criteria,[57] which are summarized as follows:

- Possible PSP: gradual progressivity of symptoms with onset at age 40 or later and either vertical supranuclear gaze palsy or both slowing of vertical saccades and prominent postural instability with falls in the first year of onset, plus no evidence of other diseases that could explain these features.
- Probable PSP: vertical supranuclear gaze palsy, prominent postural instability, and falls in the first year of onset, as well as the other features of possible PSP.
- Definite PSP: a history of probable or possible PSP and histopathologic evidence of typical PSP.

Criteria that support the diagnosis of PSP and exclude diseases often confused with PSP are also presented in the NINDS–SPSP report.[57] The criteria for probable PSP are highly specific, making them suitable for therapeutic, analytic epidemiologic, and biologic studies, but not very sensitive. The criteria for possible PSP are substantially sensitive, making them suitable for descriptive epidemiologic studies, but less specific.

Most patients with PSP begin to experience recurrent falls from the outset. Other early symptoms include bradykinesia, dysarthria, dysphagia, and various visual complaints. Early on, most patients show subtle gaze-initiation delays and square-wave jerks. Hallmark vertical and later horizontal gaze palsies are not generally an early feature and may never develop in some cases.[58] While elderly persons often show limited upward gaze, downward gaze palsies are highly suggestive of PSP. Most patients will eventually develop a frontal lobe syndrome characterized by apathy and executive dysfunction.[54] Midbrain atrophy on magnetic resonance imaging (MRI) can be diagnostic. However, imaging is essential to rule out other potentially treatable disorders, including hydrocephalus.

Treatment

The treatment approaches for PSP are similar to those described for MSA. Swallowing problems are especially critical in these patients, and future decisions regarding such issues as eventual percutaneous endoscopic gastrostomy tube placement are best addressed at an early stage, when patients generally still have insight. Botulinum toxin type A may be considered for the treatment of apraxia of eyelid-opening and blepharospasm.

DEMENTIA WITH LEWY BODIES

Dementia with Lewy bodies (DLB) is believed to be a sporadic disease, with an estimated prevalence of 0.3% in those over age 65 and as high as 5% in those

over age 85.[59] Because these patients manifest AD-like dementia and often show parkinsonian features (Table 1), DLB is frequently confused with these conditions. Furthermore, the pathology of DLB has features of PD and AD, being defined by widespread deposition of neocortical and brainstem Lewy bodies and a variable degree of AD-type pathology. However, early on in PD, dementia is usually absent or relatively mild, and if hallucinations occur, they can almost always be attributed to antiparkinsonian medications or to a concurrent illness. Moreover, the motor features in PD tend to be more prominent than in DLB. In AD, extrapyramidal features are generally absent or particularly subtle, especially early on.

Diagnosis

Consensus guidelines for the clinical diagnosis of DLB established the primary criterion as progressive cognitive impairment of sufficient severity to disrupt normal functioning.[60] Other central diagnostic features include the following:

- Fluctuating cognition, with prominent changes in attention and awareness early in the course of illness
- Complex and recurring visual hallucinations
- Parkinsonian features that should not precede the onset of dementia by more than 1 year.

In addition to the primary criterion, two of these three features are required for a diagnosis of probable DLB and one for possible DLB. These criteria were reported to permit a very high diagnostic specificity but a lower sensitivity.[61] It has been suggested, however, that the low sensitivity might be improved by better means of identifying cognitive fluctuations.[61] Episodes of staring into space, periods of disorganized and illogical speech, and excessive daytime drowsiness have also been reported to occur more commonly in DLB than in AD,[62] but these features require further validation.

Treatment

The role of cholinesterase inhibitors in DLB remains controversial.[63] Severe sensitivity reactions have been described with most neuroleptics, including clozapine.[64] However, no similar reaction has been described with quetiapine, and this agent has generally been well tolerated by patients with DLB.[65] The use of quetiapine may be necessary to permit patients to tolerate even low doses of levodopa. Although not adequately established, the effectiveness of levodopa in DLB is probably less than in PD. Dopamine agonists should, as a rule, be avoided, because of their cognitive side effects.

SMALL-VESSEL ISCHEMIC DISEASE

Small-vessel ischemic disease (SVID) is a common, though underrecognized, cause of gait disturbances and dementia in the elderly[66,67] and has been etiologically associated most closely with chronic hypertension.[68,69] When dementia is associated with SVID, the condition is regularly referred to as Binswanger disease.[66] In SVID, small, penetrating arterioles within the white matter and basal gray matter undergo prominent thickening of their media and vascular walls, with lipohyalinotic degeneration.[70,71] These pathologic changes are distinctly different from larger-vessel atherosclerotic disease, which can be associated with multi-infarct dementia, another form of vascular dementia. Its clinical features are outlined in Table 1.

Diagnosis

Diagnostic criteria for Binswanger disease have been proposed[72] but have not been validated. According to these criteria, the following must be present:

- Dementia
- Two of the following:
  (1) A vascular risk factor or evidence of systemic vascular disease
  (2) Evidence of focal cerebrovascular disease (focal neurologic signs, including hyperreflexia and Babinski signs)
  (3) Evidence of "subcortical" dysfunction, such as a parkinsonian, magnetic, or senile gait,[73,74] gegenhalten (involuntary resistance to passive limb movement), or incontinence due to a spastic bladder
- Bilateral leukoaraiosis on computed tomography (CT) or bilateral multiple or diffuse white matter lesions each measuring more than 2 mm^2 on MRI
- Absence of multiple or bilateral cortical lesions on CT or MRI
- Absence of severe dementia (eg, Mini-Mental State Examination score >10).

Patients with SVID present with an insidious or stepwise progression and often have had one or more hemiparetic strokes. The associated dementia is typical of other subcortical dementias and, at least early on, can usually be differentiated from AD by more prominent apathy, perseverative behavior, "executive dysfunction" (including impairment in conceptualization and manipulation of information), and relatively retained insight and memory retrieval.[75] Most patients eventually develop urinary incontinence, which often leads to differential consideration of normal-pressure hydrocephalus. Furthermore, confirmatory white matter changes on T_2-weighted MRI for SVID can also be

seen with transependymal diffusion of cerebrospinal fluid (CSF) in cases of hydrocephalus and, to some extent, may be seen without a clinical correlate.

Treatment

Treatment of SVID is symptomatic, and prevention requires control of potential risk factors, including hypertension.[67]

NORMAL-PRESSURE HYDROCEPHALUS

Normal-pressure hydrocephalus (NPH) occurs predominantly during the sixth and seventh decades of life. Its clinical features are summarized in Table 1. Subarachnoid hemorrhage, meningitis, and cranial trauma are well-established predisposing causes, although it is a misconception that such conditions cause NPH by blocking CSF absorption across the arachnoid villi. Although NPH is a rare condition, it is frequently entertained clinically or mentioned on brain CT and MRI radiology reports in the elderly and should never be overlooked, as it is potentially treatable with surgery. On the other hand, establishing the diagnosis can be challenging, and ventriculoperitoneal shunting should be considered only with the knowledge that rates of immediate and remote surgical complications are high, estimated to be around 38% for permanent neurologic deficits and 6% for death.[76] At the same time, in the appropriate patient, surgery can produce dramatic resolution of gait problems and can stabilize, though not improve, cognitive deficits.[77]

Diagnosis

NPH is classically recognized as a triad of gait disturbance, altered mentation, and sphincter disturbance.[78] The gait disturbance is an early and prominent feature, while cognitive impairment may be subtle or even absent. The diagnosis is unlikely when dementia precedes the gait problem, is severe, or is the predominant clinical feature. Urinary urgency is almost always present early on, but incontinence is typically a later feature. The gait may be ataxic and wide-based, may be characterized by difficulty in initiation ("magnetic gait"), or may appear parkinsonian with short steps and shuffling. Cognitive deficits are characterized by apathy and mental slowness[79] and are usually distinguishable from AD-type dementia but not from other subcortical dementias.

Supportive radiologic imaging findings include ballooning of the frontal horns of the lateral ventricles, normal-sized or occluded sylvian fissures and cortical sulci, and modest to no white matter lesions. MRI can be used to define periventricular and white matter ischemic disease and hippocampal atrophy. Milder ischemic white matter disease should not necessarily preclude surgical consideration and may directly result from NPH. In most cases it is worthwhile to obtain one or more diagnostic large-volume taps (30 to 50 mL of CSF). However, although a positive result appears to be highly predictive, the predictive accuracy of a negative tap may be low.[80] Other diagnostic methods that have been advocated include assessment of the response to 3 to 5 days of more continuous CSF drainage via an external lumbar drain[81–83] and measurement of B waves on continuous intracranial pressure monitoring.[84] Isotope cisternography is generally considered to be unreliable.[76,77,85]

ESSENTIAL TREMOR

Essential tremor (ET) has estimated prevalence rates of 0.4% to 3.9% in the general population and 1.3% to 5.1% in persons older than 60.[86] It is thought to have an autosomal dominant mode of inheritance,[87–90] and susceptibility genes have been localized to chromosomes 2 and 3.[91,92] The pathophysiologic basis for ET is not well understood but probably originates from abnormal cerebellar signaling, possibly involving the inferior olive.[93,94]

Diagnosis

The diagnosis of ET requires one of the following:

- Bilateral postural or kinetic tremor of the hands[95]
- Isolated head tremor without evidence of dystonia.

The exclusion criteria are (1) other abnormal neurologic signs, (2) recent neurologic trauma preceding the onset of tremor, (3) presence of known causes of enhanced physiologic tremor (eg, drugs, anxiety, depression, hyperthyroidism), (4) history or presence of psychogenic tremor, (5) sudden onset or stepwise progression, (6) primary orthostatic tremor (predominantly in the legs upon standing), (7) isolated position-specific or task-specific tremors (eg, occupational tremors, primary writing tremor), and (8) isolated tremor in the voice, tongue, chin, or legs.[96]

ET commonly affects the hands or forearms, head, and larynx. The arms are involved bilaterally, though often asymmetrically. Rest tremor may be present but is not the predominant feature.[88] Amelioration with alcohol and a positive family history are supportive historical information. Occasionally, cognitive and personality disturbances may occur, involving verbal fluency, mental set-shifting, disinhibition, emotional blunting, and depression.[97] Comparable impairments in executive functioning and personality have been described after cerebellar lesions.[98]

Treatment

The anticonvulsant primidone may be the most effective agent for treating ET,[99,100] but it is often poorly tolerated. Beta-blockers are the preferred alternative but may have cardiovascular side effects.[101] Among beta-blockers, although both propranolol and atenolol are often effective, some studies suggest that propranolol may be therapeutically superior to atenolol.[102,103] Benzodiazepines, including alprazolam,[104] and the anticonvulsant topiramate[105,106] can also benefit patients with ET. See Table 3 for recommended dosages of medications for ET.

Deep brain stimulation of the ventral intermediate nucleus of the thalamus can provide good long-term benefits in cases of severe, medically intractable ET, including good efficacy for head tremor with bilateral surgery.[107]

TARDIVE DYSKINESIA

Tardive syndromes are characterized by abnormal involuntary movements (most often choreiform or dystonic) or akathisia (a sensation of restlessness that causes often-uncontrollable movements) caused by exposure to a dopamine-receptor–blocking agent within 6 months of the onset of symptoms and persisting for at least 1 month after cessation of the offending drug.[108] In mild cases, stopping the offending drug can frequently lead to remission, but this condition often persists and can be disabling. Tardive dyskinesia (TD) historically refers specifically to rapid, repetitive, stereotypic movements that mostly involve the oral, buccal, and lingual areas, though this term is now often used more globally to describe various tardive syndromes.

Diagnosis and risk factors

The American Psychiatric Association has required 3 months of exposure to an offending drug for a diagnosis of TD,[109] although TD has been reported occasionally in elderly persons after as little as 1 month of exposure.[110]

Elderly patients, especially those with dementia, are the most susceptible population: the risk for TD from traditional neuroleptic drugs in the elderly is 25% to 30%.[110,111] The risk is substantially lower with second-generation (ie, atypical) neuroleptics, although risperidone has been associated with an annual TD incidence of greater than 2% in elderly patients with dementia.[112] Among neuroleptics, clozapine and quetiapine have the lowest reported incidence of TD and have been convincingly shown to induce TD only in patients who were exposed to additional neuroleptics.[108] Drug-induced parkinsonism, like TD, also occurs much more often in the elderly. In contrast, younger people are primarily at risk for acute neuroleptic-induced dystonia, while age does not appear to influence the development of tardive akathisia (persistent motor restlessness). Higher doses of antipsychotics and concurrent use of anticholinergic medications are associated with a higher risk.

Huntington disease is a rare condition that should not be confused clinically with TD, as it usually starts in early adult life and is rapidly fatal.

Treatment

The most important intervention for TD is preventive: agents that block the dopamine receptor, including metoclopramide, must be prescribed only after establishing medical necessity. When possible, the offending agent should be discontinued immediately with the hope of facilitating a remission. Switching to an atypical neuroleptic may be considered in patients with active psychosis or in whom TD is brought on or worsened as a result of lowering the inciting agent.[113]

Among potential treatments (Table 3), the dopamine depleter reserpine has been used and can be effective, but dose-dependent depression often limits its usefulness.[114] Tetrabenazine, another monoamine depleter, but with additional dopamine-receptor–blocking properties, is expected to be approved soon for use in the United States and may offer a more favorable benefit-to-side effect profile compared with reserpine.[115] A number of other agents, such as vitamin E and benzodiazepines (including clonazepam), may have some efficacy in milder cases, although studies have reported conflicting responses to these agents.[108] Although anticholinergic medications may benefit patients with acute dystonic dyskinesias, they may worsen orofacial dyskinesias.[108] Botulinum toxin injections may be useful for isolated blepharospasm or torticollis. Based on limited case reports, deep brain stimulation appears to be effective for treating medically intractable TD, including its orofacial symptoms.[116,117]

RESTLESS LEGS SYNDROME

Restless legs syndrome (RLS) is thought to have an autosomal dominant pattern of inheritance,[118,119] with an estimated prevalence among adults of 10% to 12%.[120] The prevalence increases to around 19% in those 80 years or older,[121] and symptoms tend to worsen with age. RLS is defined by four obligatory criteria:

- Urge to move the legs
- Worsening of symptoms with rest
- Relief with activity
- Intensification during the evening.

TABLE 3
Pharmacologic treatments for common nonparkinsonian movement disorders in the elderly

Disorder	Class	Medication	Typical starting dose	Titration	Usual therapeutic dose	Maximum dose	Common adverse effects
Essential tremor	Antiepileptics	Primidone	50 mg at bedtime	50 mg/wk	50–100 mg bid	250 mg/day	Sedation, unsteadiness
		Topiramate	25 mg/day	25 mg/wk	50–100 mg bid	400 mg/day	Weight loss, psychomotor slowing
	Beta-blocker	Propranolol	20 mg/day	20 mg/wk	120–160 mg bid	320 mg/day	Hypotension bradycardia, depression, fatigue, bronchospasm*
	Selective beta-blocker	Atenolol	12.5 mg/day	12.5 mg/wk	50–100 mg/day	100 mg/day	
Tardive dyskinesia	Dopamine depleter	Reserpine†	0.125 mg/day	0.125 mg/wk	0.375–2 mg/day	4.5 mg/day	Depression, sedation, hypotension
	Dopamine depleter/ antagonist	Tetrabenazine	25 mg/day	25 mg/wk	100–200 mg/day	200 mg/day	Depression, sedation, hypotension, parkinsonism
	Benzodiazepine	Clonazepam	0.5 mg at bedtime	0.5 mg q3–4d	1–4 mg/day	As tolerated	Sedation, dizziness
	Vitamin	Vitamin E	1,600 IU/day	—	1,600 IU/day	1,600 IU/day	Diarrhea
Restless legs syndrome	Dopamine agonists	Pramipexole	0.125 mg at bedtime	0.125 mg q3–4d	0.25–0.5 mg at bedtime	3 mg/day	Nausea, vivid dreams, hallucinations, confusion, pedal edema‡
		Ropinirole	0.25 mg at bedtime	0.25 mg q3–4d	1–2 mg at bedtime	9 mg/day	
	Dopamine	Carbidopa/ levodopa	25/100 mg at bedtime	25/100 mg q3–4d	25/100 mg at bedtime	As needed	Nausea, vivid dreams, augmentation§
	Narcotic	Methadone	2.5 mg/day	5 mg/wk	5–25 mg/day	40 mg/day	Sedation, constipation

* Adverse effects apply to both beta-blockers (propranolol and atenolol).

† Because dose-dependent depression and other adverse effects are common with high doses, reserpine should be cautiously titrated in the elderly, with close monitoring for potential adverse effects. Doses can be increased above those shown here if depression does not occur.

‡ Adverse effects apply to both dopamine agonists (pramipexole and ropinirole).

§ In view of the risk for augmentation (see text), carbidopa/levodopa should be used only as a last resort.

Management

RLS can cause enormous anxiety and, along with the frequent accompaniment of periodic limb movements of sleep, often leads to sleep deprivation. Offending medications, including selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, lithium, antihistamines, and neuroleptics, should be discontinued. Morning fasting serum ferritin, vitamin B_{12}, and folate levels should be measured, and iron supplementation should be instituted to achieve a ferritin level of less than 50 µg/L (low-normal range).[120]

Patients should be counseled to avoid prolonged idleness and sleep deprivation. Milder cases can occasionally be tempered with a sedative to promote sleep. However, benzodiazepines should be provided to elderly patients only after weighing such associated risks as inducing falls, confusion, and disinhibition. Clonazepam probably offers no therapeutic advantage, and short-acting agents may be preferable.

Among treatment options for RLS (Table 3), dopamine agonists can generally be considered first-line agents, even in the elderly, and symptoms often can be controlled with a single small dose in the evening at the anticipated onset of symptoms. The use of levodopa introduces a high risk of augmentation of RLS, as defined by symptom onset at least 2 hours earlier than was previously the case.[122] Symptoms can be severe and continuous, involving the entire body. Although no controlled trials have been conducted, augmentation appears to be much less of a problem with dopamine agonists,[120] and gabapentin appears to most benefit the minority of patients with painful symptoms.[123] Opiates are also often effective, and addiction is rare in this population.[124,125]

ADDITIONAL DIFFERENTIAL CONSIDERATIONS

Besides those already discussed, a few additional conditions enter the differential diagnosis of movement disorders in the elderly patient.

Corticobasal degeneration is a rare disorder that usually presents after age 60 with motor and cognitive dysfunction. The motor involvement is characterized by highly asymmetric akinesia, rigidity, and apraxia, often with prominent dystonia and alien-limb phenomena. Although occasionally mistaken for PD, these clinical features should generally suggest this condition and, moreover, are generally not responsive to dopaminergic therapy.

Cerebellar ataxia. In an elderly patient with cerebellar ataxia, the history and work-up include such considerations as alcoholism, medication side effects, cerebrovascular disease, hydrocephalus, neoplasm, and a paraneoplastic syndrome.

Primary cerebellar degeneration and spinocerebellar ataxias usually present earlier in adulthood.

Peripheral neuropathies and skeletomuscular disorders commonly contribute to gait disorders in the elderly but are generally readily identifiable on physical examination.

Degenerative spine disease and spinal metastases are more common in the elderly and must always be considered in any patient with a spastic gait or sensory ataxia.

De novo psychogenic movement disorders are comparatively infrequent in the elderly population and can be diagnosed only after exclusion of other potential etiologies.

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Depression in older patients with neurologic illness:
Causes, recognition, management

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ABSTRACT

Depression is common in the elderly, particularly in older persons with neurologic illness. Its etiology in this population is incompletely understood and likely to be multifactorial. Identifying depression in elderly patients with neurologic illness can be a challenge, as many of its features resemble symptoms of the underlying neurologic disease or of the aging process itself. Nevertheless, recognition and effective management of depression in this population is vital, since depression is a major source of excess morbidity and since treatment often results in improved quality of life for patients and their caregivers. Assessing for suidicality is a key diagnostic consideration in this population. Antidepressant medications, psychotherapy, and electroconvulsive therapy all can be effective in treating depression in elderly neurologic patients.

KEY POINTS

Elderly persons with neurologic disease have higher rates of depression than the general elderly population.

Depression is associated with increased physical disability in elderly patients with neurologic illness, and resolution of depression appears to be associated with improved physical function in these patients.

Effective diagnosis of depression in this population is eminently possible with alertness to clues in the patient interview and with careful use of screening questions, particularly to assess for persistent depressed mood and lack of interest and pleasure in life.

Sorting out depressive symptoms from those of the underlying neurologic illness can be difficult and is often confounded by neurologic medications, focal symptomatic lesions, and cognitive impairment.

Age should not be a basis for denying treatment for depression in neurologic patients. The elderly respond to antidepressant therapy at about the same rate as younger age groups, and they also may respond to psychotherapy and electroconvulsive therapy.

Primary care physicians can effectively treat many depressed elders with neurologic disease; referral to a specialist is appropriate for patients with suicidal thoughts and those who have not responded to an adequate course of initial depression management.

All my griefs to this are jolly,
Naught so sad as melancholy.
—Robert Burton (1577–1640)

Depressive illness is one of the most common complications of neurologic disease, particularly in the elderly. A key clinical challenge is knowing whether to attribute an older patient's individual symptoms to the underlying neurologic disease or to depressive illness, given the frequent overlap between the two. Despite this overlap, all physicians who treat older patients with neurologic illness should recognize that persistent depressed mood and lack of interest in life cannot be ascribed to severe physical illness alone. Appropriate clinical assessment can help identify and resolve depression in many of these patients, avoiding the disability, diminished survival, and increased medical costs that accompany depression in this population. This article

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presents an overview of depression in elderly neurologic patients, focusing on its clinical features, epidemiology and etiology, diagnostic considerations, and therapeutic approaches.

CLINICAL FEATURES: LOW MOOD AND ANHEDONIA ARE KEY

The term "depression" describes a spectrum of mood disturbances ranging from mild to severe and from transient to persistent. Depressive symptoms are distributed continuously in any population. They are of clinical significance when they interfere with normal activities and persist for at least 2 weeks, in which case a diagnosis of depressive illness or disorder may be made. The diagnosis depends on the recognition of two cardinal symptoms: (1) persistent and pervasive low mood and (2) loss of interest or pleasure in usual activities (anhedonia).

The *Diagnostic and Statistical Manual of Mental Disorders, 4th edition* (DSM-IV),[1] classifies an illness as a major depressive disorder if, during the same 2-week period, the patient experiences depressed mood or decreased interest or pleasure and at least four of the following symptoms, which represent a change from normal functioning:

- Significant weight loss or gain
- Insomnia or hypersomnia
- Psychomotor retardation or agitation
- Fatigue or loss of energy
- Feelings of worthlessness or inappropriate guilt
- Diminished ability to think or concentrate
- Recurrent thoughts of death or suicide, or suicide attempt.

EPIDEMIOLOGY OF DEPRESSION IN THE ELDERLY

Depression is without question one of the most common and important psychiatric problems in the elderly. Data from the National Institute of Mental Health Epidemiologic Catchment Area Study suggest that a substantial fraction of seniors—perhaps as many as 15% of those residing in the community—have major or minor depressive symptoms.[2] While major depression has generally been believed to occur somewhat less frequently in the elderly than in younger persons, this may be due to underreporting.[3] The prevalence of depression is clearly higher in the medically ill[4] and in those relocating to or living in assisted-living facilities and nursing homes.[5]

Depression accompanying neurologic disease

Elderly patients with neurologic disease clearly seem to have higher rates of depression than the general population of seniors, although there is considerable variability in reported prevalence among studies. Commonly cited rates of major depressive disorder in the neurologically impaired elderly vary from 10% to 40%. Patient selection and diagnostic techniques[6] appear to be the major sources of variability. Interestingly, rates and associations appear to be much the same across a wide range of neurologic conditions.

A recent prospective cohort study[7] that assessed 300 consecutive new neurology outpatients using diagnostic interviews and self-report measures found that almost half met the criteria for one or more DSM-IV anxiety or depressive diagnosis. Major depression was the most common condition, occurring in 27% of patients in the overall series. The major depressive disorders tended to persist, and 46 of 54 patients remained depressed at 8-month follow-up. Significantly, a change in categoric diagnosis on interview from depressed to not depressed was accompanied by a mean drop of 10 points on the Hospital Anxiety and Depression Scale, suggesting real (categorical) change in mental state rather than subtle shifts along a continuum.

Depression and physical symptoms

This same study[7] compared patients with and without emotional disorders, finding that those with emotional disorders reported more physical symptoms, poorer physical function, and more bodily pain. This finding of an association between depression and increased physical disability is in keeping with reports on individual disorders such as stroke,[8,9] Parkinson disease (PD),[10] epilepsy,[11–13] and multiple sclerosis.[14] This relationship is reported consistently and tends to hold whether subjective or objective disability ratings are used. This, of course, does not indicate the direction of causality.

While it is likely that the prevalence of depressive illness is affected by the severity of the neurologic disease,[15] there are two persuasive reasons for believing that depression is an independent risk factor for physical disability in patients with neurologic illness. First, there is strong evidence that, at least after a stroke, depression is an independent risk factor for increased mortality.[16,17] Second, most (but not all) cohort studies and randomized controlled trials have shown that resolution of depression through natural remission or treatment results in an improvement in physical function.[18–20]

Depression and cognitive disorders

The high frequency of depression in patients with cognitive disorders is also notable. At least 20% of patients with Alzheimer disease (AD) may meet cri-

teria for major depression, and an additional 30% may have minor depression.[21] A recent study found the combined prevalence of major and minor depression to be 36% in a cohort of patients with mild cognitive impairment and also revealed a faster pace of cognitive deterioration over 3 years in these depressed patients compared with their nondepressed counterparts.[22]

ETIOLOGY OF DEPRESSION IN NEUROLOGIC ILLNESS

Anxiety, sadness, and somatic discomfort are part of the normal psychological response to life stresses, including medical illness. Clinical depression is a final common pathway resulting from the interaction of biologic, psychological, and social factors. The likelihood of this outcome depends on such factors as genetic and family predisposition for depression, the clinical course of the concurrent medical illness, the nature of the treatment, functional disability, the effectiveness of the patient's coping strategies, and the availability of social and other support.

Other important factors in the expression of depression in older patients with neurologic illness include anatomic and physiologic changes in the brain and sensory systems associated with aging itself. Anatomically, global reductions in focal brain volume have been established,[23,24] as has an increased frequency of several kinds of white matter abnormalities easily seen on MRI.[25] Physiologically, reductions in measures of neuronal function (eg, cerebral glucose metabolism[26]) occur, as do declines in various markers of some relevant neurotransmitters.[27,28] These brain volume and metabolic reductions have been linked convincingly to age-related cognitive impairment, which can affect symptom expression in some forms of depression, and both these changes and the alterations in neurotransmitters may affect the maintenance of mood and/or predispose to or modulate depression as well.[27]

Of particular interest in depression associated with neurologic disease is whether the risk for depression is directly affected by damage to specific brain pathways. Common neurologic diseases, such as PD, multiple sclerosis, and Huntington disease, can present initially with depressive illness. Further, depression and anosognosia can coexist. This would suggest that depression is an integral part of brain disease and is not solely a reaction to chronic illness. Unfortunately, the identification of common pathways for depression and neurologic diseases has so far proved elusive.

Cognitive disorders and depression

The etiology of depression in the cognitive disorders remains incompletely elucidated and is probably multifactorial.[29] Psychological reaction to the diagnosis may play a role in mild cognitive impairment or early dementia, but with established dementia, neuropathologic factors probably become significant. For example, in AD, reduced cell counts[30] and markers of neurotransmitter production[31] in brain regions critical for regulating mood (eg, the locus ceruleus) may reflect neurodegeneration-related damage to these areas. Moreover, the global brain atrophy and volume reduction in specific cortical and subcortical regions reported in late-life depression with intact cognition[32] is found at least as strikingly in Alzheimer-type dementia, so additivity of these findings is probable. In particular, hypercortisolemia-associated hippocampal atrophy, which has been recognized in late-life depression,[33] may add to the well-recognized hippocampal atrophy of AD. Further, white matter lesions, seen with increased frequency on magnetic resonance imaging (MRI) in late-life depression,[34] have also been proposed to be more common in patients with dementia, so additivity may be at work as well. The impact of these lesions on mood is thought to be mediated by circuitry-disruption effects,[35] and the effects of atrophy and white matter lesions are certainly complementary.[36]

Stroke and depression

Much interest has centered on stroke, but it has been difficult to obtain useful estimates of the incidence, correlates, and consequences of poststroke depression.[37] The reason may be the difficulty of identifying patients with affective illnesses as distinct groupings within the population of neurologically impaired patients (see "Diagnosing Depression in the Elderly with Neurologic Disease" below). Studies have also been limited by variable methodologies, small sample sizes, and lack of suitable controls.

Desmond and colleagues[38] attempted to correct some of these deficiencies in a prospective study of depression in 421 elderly stroke patients (mean age, 71.5 ± 8.0 years) and 249 age-matched, stroke-free control subjects. The investigators diagnosed depression in 11.2% of their stroke patients 3 months after stroke compared with 5.2% of the control subjects in the same time frame (odds ratio, 2.52; 95% confidence interval, 1.33 to 4.80). Depression in the stroke patients was significantly correlated with greater severity of stroke, particularly in vascular territories supplying limbic structures, and with dementia and

female sex. The frequency of somatic symptoms, rather than depressed mood, discriminated between patients with and without stroke and between stroke patients with and without dementia. The researchers concluded that clinicians should perhaps rely more on somatic than nonsomatic symptoms to diagnose depression in this population.

Robinson and colleagues[39] developed an impressive animal model of poststroke depression using experimentally produced lesions in the cortex of rats. They hypothesized that lesions in the left frontal lobe are associated with an increased rate of depressive illness, particularly soon after stroke. There are several objections to this view, however, and a recent meta-analysis did not support this localization hypothesis.[40] It seems unlikely that further descriptive studies in humans will yield meaningful insights, as depression after stroke is probably too common and almost certainly too multifactorial for this mode of research to be helpful. Among those who remain interested in this hypothesis, attention is shifting to the role of the limbic system in the development of poststroke depression.[41,42]

A condition termed "vascular depression" has been hypothesized to explain some geriatric depression.[35] This concept emerged from research identifying an increased frequency of white matter pathology on the brain MRIs of some depressed elderly patients,[43] particularly those whose first episodes occurred at an advanced age (ie, > 85 years).[44] Such pathology can range from subtle to definite cerebrovascular disease and can occur in individuals with or without a history of stroke. Such lesions have been reported to be especially prominent in the frontal lobes, and specifically in regions thought to be components of neural circuitry subserving mood and affect. It is through disruption of such circuits that cerebrovascular disease might cause depression.

RECOGNITION AND SCREEENING

In spite of its enormous clinical and public health importance, depressive illness is substantially underdiagnosed and undertreated,[45] particularly when it coexists with physical illness. Depression is often a cause of great distress for patients who have mistakenly assumed that symptoms such as weakness or fatigue are caused by an underlying medical condition.

Attributing symptoms to medical illness is especially common in the elderly, in whom a tendency toward somatic orientation and de-emphasis of cognitive/affective symptoms is recognized.[3] Clinician bias (ie, "ageism") may also promote underrecognition of depression in the elderly with neurologic illness.

It is vital that all clinicians know how to diagnose and manage depressive illness effectively. Doing so is eminently possible with alertness to clues in the interview, especially the patient's manner, and with the use of screening questions for those at risk. Clinicians should particularly screen patients for the two cardinal symptoms of major depression: low mood and lack of pleasure.

Self-report screening instruments, such as the Beck Depression Inventory and the Hospital Anxiety and Depression Scale, cannot replace systematic clinical assessment, but they are useful in drawing attention to depression and other emotional disturbances in clinical settings in which mood is not routinely assessed. Physicians should recognize that persistent depressed mood and lack of interest and pleasure in life cannot be accounted for by severe physical illness alone. The usual response to illness and successful treatment is impressive resilience.

One screening tool developed specifically for use with elderly patients and commonly used both in geriatric research and in clinical practice is the Geriatric Depression Scale (Table 1).[46]

When there is doubt about the diagnosis of depression, clinicians may resort to an empirical trial of treatment. The wider availability of safer medications and psychological therapy makes treatment a more attractive option than in the past.

DIAGNOSING DEPRESSION IN THE ELDERLY WITH NEUROLOGIC DISEASE

Depression in elderly patients with neurologic illness manifests as a mixture of phenomena that may be associated with the neurologic condition and with the aging process itself (including biologic, psychological, and social aspects) as well as with depression. Among neurologic conditions, cerebrovascular disease and the dementias are arguably the most common in the elderly. Depression is especially challenging to assess and manage in elderly patients with these conditions.

Sorting out the source of symptoms

In patients with neurologic disease, a key difficulty is knowing whether to attribute individual symptoms to a depressive illness or to the neurologic disease.[47,48] Several common symptoms of depression are prominent in many neurologic conditions; examples include fatigue (particularly frequent in multiple sclerosis[49,50]), loss of appetite, and diminished concentration. Further, epidemiologic research shows a unimodal distribution of mood symptoms in neurologic

TABLE 1
Geriatric Depression Scale—mood scale, short form

Choose the best answer for how you have felt over the past week:

1. Are you basically satisfied with your life? Yes/**No**
2. Have you dropped many of your activities and interests? **Yes**/No
3. Do you feel that your life is empty? **Yes**/No
4. Do you often get bored? **Yes**/No
5. Are you in good spirits most of the time? Yes/**No**
6. Are you afraid that something bad is going to happen to you? **Yes**/No
7. Do you feel happy most of the time? Yes/**No**
8. Do you often feel helpless? **Yes**/No
9. Do you prefer to stay at home, rather than going out and doing new things? **Yes**/No
10. Do you feel you have more problems with memory than most? **Yes**/No
11. Do you think it is wonderful to be alive now? Yes/**No**
12. Do you feel pretty worthless the way you are now? **Yes**/No
13. Do you feel full of energy? Yes/**No**
14. Do you feel that your situation is hopeless? **Yes**/No
15. Do you think that most people are better off than you are? **Yes**/No

Answers in **bold** indicate depression. Although differing sensitivities and specificities have been obtained across studies, for clinical purposes a score greater than 5 suggests depression and warrants a follow-up interview. Scores greater than 10 almost always indicate depression.

Adapted from reference 46.

disease.[38] Such a continuous distribution throughout the population with neurologic disease, with variation in degree but not in kind, makes identifying distinct subgroups of neurologic patients with and without depression problematic.

Gainotti and colleagues[47] attempted to see if different clusters of symptoms in stroke patients identified different "types" of depression, but they found little evidence to support such a theory.

The problem of classification is especially pronounced in patients with PD. Many depressive symptoms overlap with the core features of PD—motor retardation, attention deficit, sleep disturbance, hypophonia, impotence, weight loss, fatigue, preoccupation with health, and reduced facial expression. This complicates interpretation of diagnostic criteria and standardized rating scales. Anhedonia and sustained sadness, particularly when out of proportion to motor signs, are important diagnostic features of depressive illness in patients with PD.[51]

One approach to this diagnostic challenge is to focus on symptoms other than somatic ones. Instruments such as the Hospital Anxiety and Depression Scale[52] have been designed to do this. But even this is not a complete solution, as the neurobehavioral consequences of cerebral lesions, such as aphasia, indifference, denial, cognitive impairment, and dissociation of subjective from displayed emotion, can all interfere with the diagnosis. There is therefore a risk of tautology if this approach is used.

In addition to major depression (and its most severe form, psychotic depression), elderly patients with neurologic illness frequently suffer from adjustment disorders. This stems from the high rate of negative life events among these patients, who are more likely than their younger counterparts to have comorbidities, face financial difficulties, and suffer the loss of loved ones.

A poorly understood but probably important variable in the expression of geriatric depression in this population is the past history of depression, particularly in patients with late-life onset of neurologic disease. While there is no distinctly geriatric presentation of depression, specific syndromes have been described in this population that might modulate the expression of coexistent neurologic conditions. Among them are "late-onset" geriatric depression (ie, depression in the very old, usually meaning ≥ 85 years), vascular depression, and at least two syndromes (discussed below) associated with cognitive impairment.[53] Late-onset geriatric depression is characterized by a higher incidence of both cognitive and sensory impairment than depression in the younger elderly. Vascular depression highlights a putative contribution of cerebrovascular disease to the expression of depression, even in individuals without a clear history of stroke.[35] The concept of vascular depression as a clinical entity is still investigational and requires further definition, but it is likely to have significant therapeutic and etiologic implications.

Another diagnostic obstacle is the frequent misattribution of the source of symptoms by patients themselves. Patients (and their caregivers) often erroneously attribute depressive symptoms to their neurologic disease and thus unwittingly mislead their physician. For this reason, a high index of suspicion is necessary when confronted with any of the following symptoms: headache, insomnia, reported memory loss, joint or back pain, chest pain, weight loss, nausea/vomiting/constipation, disrupted menses, fatigue/tiredness, and malaise. Changing how questions are oriented at examination, as reflected in

Table 2, can be helpful in overcoming this problem.

Neurologic medications can cloud the picture

Treatments for the neurologic illness can also complicate the clinical picture. For example, mood changes can accompany the symptom fluctuations ("on-off" phenomena) that often occur in patients with PD who have been treated with levodopa over a long period. Some of these patients fulfill criteria for major depressive disorder during the "off" phase but not during the "on" phase.[54,55] Cyclic mood changes (bipolarity) in association with on-off phenomena have also been described.[56]

As another example, beta-interferon therapy has been reported to cause depression (and fatigue) in 40% of patients with multiple sclerosis.[57] However, depression is highly prevalent in patients with untreated multiple sclerosis, and some studies have found no increase in depression following beta-interferon therapy.[58,59] In one prospective study, the rate of depression actually fell with beta-interferon treatment.[60]

Focal symptomatic lesions add further complexity

Specific cerebral lesions can further complicate the clinical picture in patients with neurologic disease. This topic has been comprehensively reviewed by Bogousslavsky and Cummings.[61] Of specific note, aphasia requires that the physician draw inferences about mental state from behavior and nonverbal communication. Intense emotional frustration accompanying expressive aphasia may be secondary to problems in social interaction,[62] and patients who have recovered from receptive aphasia have reported thinking that their examiner was being deliberately incomprehensible.[63] Anosognosia may coexist with depression,[64] suggesting that separate neural systems exist for different aspects of emotion[65] and that depression after stroke cannot be explained solely as a psychological reaction to disability.[66] By contrast, affective dysprosodia is the impairment of the production and comprehension of those language components that communicate inner emotional states in speech.[67] These include stresses, pauses, cadence, accent, melody, and intonation. Its presence is not associated with an actual deficit in the ability to experience emotions but rather in the ability to communicate emotions or recognize them in the speech of others.[67] Affective dysprosodia is particularly associated with right-sided lesions. Depressed patients with dysprosodia appear depressed and say they are depressed but do not "sound" depressed. In contrast, patients with anosognosia appear and sound depressed but may deny that is how they feel.

TABLE 2
Questions to ask when evaluating for depression in a patient with neurologic disease

Depression
Have your symptoms got you down at all?
Do you ever get the feeling that you can't be bothered to do things?
Is there anything you look forward to (or does your illness stop you)?
Has this illness affected your confidence?
Do things ever get so bad you think about death?
Anxiety/panic
Do you ever worry about your symptoms?
When you're worrying like this, is it sometimes hard to stop yourself?
Do you ever have attacks where you have a lot of symptoms all at once? What happened? Was it frightening?
Did you do anything differently because of these attacks?

Perhaps the hardest distinction to make is between depression and apathy. Patients with apathy show little spontaneous action or speech and have delayed, short, or slow responses—or no responses whatsoever.[68] Apathy is frequently associated with hypophonia, perseveration, grasp reflex, compulsive motor manipulations, cognitive and functional impairment, and older age. Hypoactivity of the frontal and anterior temporal regions has been observed in patients with apathy.[69]

Special challenges with cognitive disorders

The nexus of cognitive impairment and depression in neurologic disease merits specific discussion because it affects the elderly disproportionately. Cognitive impairment is a common symptom in late-life depression. Depression can also coexist with and complicate cognitive disorders. Cognitive impairment in the elderly ranges from mild age-related memory disturbance through an increasingly recognized transitional state, termed mild cognitive impairment,[70] to frank dementia.

Dementia in the elderly is most often caused by neurodegenerative disorders, particularly AD, but it can also have frontotemporal origins or be attributable to PD. Non-neurodegenerative conditions, such as cerebrovascular disease and systemic illnesses (eg, hypothyroidism), are also common etiologies. Regardless of cause, some of the "depression-like" symptoms mentioned above that result from neurologic diseases and specifically focal lesions occur with reg-

TABLE 3
Clinical features suggesting Alzheimer disease (AD) or depression

Clinical feature	AD	Depression
Severity of depressive symptoms	Relatively mild or atypical	Relatively severe (ie, level of major depression)
Subjective complaints of cognitive impairment	Less likely	More likely
Onset and progression of depressive symptoms and cognitive deficits	Gradual	Rapid
Performance on tasks assessing effort	Appropriate	Prominent deficit
Breadth of cognitive deficits (eg, language, gnostic, and practice deficits)	Broad	Narrow

ularity in the cognitive disorders.[71] These include apathy, insomnia, weight loss, and crying spells as well as unique problems such as lack of awareness of the level of cognitive deficit. Most geriatric cognitive disorders are progressive, and communication skills routinely diminish with progression. All of these phenomena can mimic depression and confound its diagnosis.

Two discrete syndromes in which cognitive impairment and depression are admixed have been recognized in the elderly—depression with reversible dementia (historically called "pseudodementia") and depression complicating dementia.

Depression with reversible dementia is important because it is common in the elderly and has been increasingly recognized as a risk factor for subsequent irreversible dementia, even in the case of complete recovery from the depressive episode; up to 40% of such patients will be diagnosed with dementia in the following 3 years.[72]

Depression complicating dementia has been studied mainly in relation to AD. It is important because it is a major source of additional morbidity—ie, alleviating depression in patients with dementia can improve functional status even if the course of the underlying cognitive disorder cannot be changed. This makes it critical that clinicians understand how depression may be manifested in patients with dementia so that depressive symptoms are recognized as such and not simply attributed to dementia. Similarly, it is important to learn how to distinguish between dementia-associated cognitive symptoms and those due to major depression (Table 3).[73] The recent proposal of diagnostic criteria for depression in AD[21] may facilitate advances in diagnosis and treatment.

In addition to these syndromes, depression also occurs in individuals with mild cognitive impairment. This is important because it may predict progression to AD, especially if the depression is resistant to antidepressant therapy.[22]

Assessing risk of suicide

When depression is a consideration, assessing the risk of suicide is imperative. A recent prospective study[74] found that 1 in 11 patients (26/300) examined consecutively in general neurology clinics had given serious thought to committing suicide in the prior 2 weeks. Major depression had been diagnosed in almost all of these patients (23/26). While one might assume that suicidal ideation would be more likely in patients with progressive, debilitating neurologic conditions, this was not the case. Of the 26 patients with suicidal ideation, 12 had somatoform symptoms, and most of the remainder had nonprogressive conditions. Of note, the elderly have the highest suicide rate of any segment of society.[75] At least in the United States, the highest rate of all is for elderly men who live alone.[75]

Physicians are often reluctant to inquire about suicidal ideation, in part out of fear of putting ideas in a patient's head. This is unlikely, and, in our experience, patients are often relieved when their doctor prompts them to discuss such thoughts.

The use of a set of progressively more direct questions is recommended, for example:

- Have your symptoms ever got you down?
- Do you ever wonder if you have the strength to go on?
- Does it ever get so bad that you wonder if life is worth living?
- Have you ever thought about ending it all?

Clearly, suicidal ideation exists on a continuum, and not all vague thoughts of an existential nature are a cause for alarm. Table 4 presents criteria for estimating risk, although they are rules of thumb and should not be viewed as prescriptive.

When in doubt, be pragmatic

When the diagnosis of depression in the setting of neurologic disease is uncertain, we suggest that clinicians take a pragmatic approach and make a provisional diagnosis, especially if symptoms of low mood or anhedonia are present and are accompanied by some somatic symptoms (eg, insomnia, anorexia) and lack of engagement with the environment (eg, poor participation in physiotherapy).

MANAGEMENT: GENERAL CONSIDERATIONS

The main aims of the treatment of depression in this population are to improve mood and quality of life, reduce the risk of medical complications, improve compliance with and outcome of physical treatment, and facilitate the appropriate use of health care resources. The development of a treatment plan depends upon a systematic assessment that, whenever possible, should involve partners or other key family members as well as the patient.

Besides major depression, adjustment disorders are also frequent in elderly patients with neurologic illness and occur in relation to significant life events, including health care developments. When mild or brief, these conditions can usually be managed by general health care staff without recourse to specialists. Education, advice, and reassurance are of value. For these reasons, it is important for general health care staff to be familiar with the properties and use of the common antidepressant drugs and the value of brief psychological treatments, such as cognitive behavioral therapy, interpersonal therapy, and problem-solving.

Patients with more enduring or severe symptoms of depression usually require specific forms of treatment, most commonly an antidepressant. Generalists should also be able to assess suicidal thinking and risk. In patients with such ideation or who have not responded to initial depression management, referral to a specialist is the next step.

Expert opinion holds that age should not be a basis for denying treatment.[4] Improvement in the quality of life of the elderly patient and of affected family and caregivers is a worthy goal and may also have wider benefits, such as reduced use of health care services.

TABLE 4
Criteria for estimating suicide risk

Low-risk patient
Suicidal ideation but no fixed plans or attempts
Physically healthy
Supportive environment
No significant premorbid history
Management: Can be kept under clinic review; no specific action required, though referral to a psychiatrist or psychotherapist can be considered
Medium-risk patient
Low-lethality suicide attempt (note: it is the patient's perception of lethality that must be assessed)
Frequent thoughts of suicide
Previous suicide attempts
Persistent depressive symptoms
Serious medical illness
Inadequate social support
Past psychiatric history
Management: Refer to psychiatrist to be seen same week
High-risk patient
Definite plan for suicide (when? where? how?)
Major severe depressive disorder
High-lethality suicide attempt or multiple attempts
Advanced medical disease
Social isolation
Past psychiatric history
Management: Must be referred to psychiatry on an emergency basis

PHARMACOLOGIC THERAPY

Antidepressant medication has been shown to be effective in treating major depression, even if the mood disturbance is deemed to be "exogenous," ie, caused by events or circumstances in the patient's life. There have been relatively few trials of antidepressant therapy in the medically unwell, but the available evidence is in keeping with the treatment of depression generally. The elderly respond at about the same rate as younger age groups,[47] although the time to response may be longer.[48]

Antidepressant options

One of the most commonly asked questions is which antidepressant should be used, as the range of available drugs, and the claims made about them, can be bewildering. There are four main classes of antidepressants:

- Tricyclic antidepressants (TCAs)
- Selective serotonin reuptake inhibitors (SSRIs)
- Monoamine oxidase inhibitors
- Others (eg, serotonin-norepinephrine reuptake inhibitors [SNRIs] and other agents such as mirtazapine and bupropion).

Data from the Cochrane Collaboration[76] and other systematic reviews[77] show that the difference in overall tolerability among the different medications is minimal in healthy adults. In general, patients are slightly less likely to drop out of trials because of unacceptable side effects when taking an SSRI but are slightly less likely to drop out because of treatment inefficacy when taking a TCA.

Prescribing advice for nonspecialists

Rather than continuously experiment with a range of drugs, it is advisable to stick to prescribing one drug from each class to become familiar with its dosing regimens, actions, interactions, and side effects. Nonspecialists should also be aware that there are certain situations in which one class of drug or one drug within a class may be more advisable than another (eg, for elderly patients, individuals with certain comorbidities, and patients taking certain other medications). Specifically, the SSRIs fluoxetine and paroxetine significantly inhibit cytochrome P-450 2D6, which makes them problematic in patients taking certain antiarrhythmics, some beta-blockers (eg, propranolol), and verapamil. Similarly, TCAs are dangerous in the setting of a recent myocardial infarction or a cardiac conduction defect. Because of their anticholinergic properties, TCAs are also less favorable in the elderly (and especially those with dementia) than SSRIs and SNRIs. If TCAs are used in the elderly, secondary amines such as nortriptyline and desipramine are preferable. The SSRIs sertraline and citalopram have been the most widely investigated newer medications in the elderly, and mirtazapine is also often used in this population.

Ensure adequate dose, duration, and compliance

The debate about different agents has obscured a potentially more important issue: medication dosage and compliance. Antidepressants are often prescribed in inadequate doses and more often than not for too short a time.[78] This problem is compounded by the finding that only 30% to 60% of patients comply with prescribed regimens.[78] A recent study of neurology outpatients[79] found that many believed that antidepressants were addictive and could permanently damage the brain.

If patients are to be successfully treated with antidepressants, their physicians need to demonstrate that they understand their problems, have considered individual issues, and are recommending the best treatment available. Before commencing drug therapy, patients should be told about the drug's side effects and be reassured that side effects are often worst during the first 2 weeks of treatment and then diminish. Patients also must be advised that they are unlikely to feel benefits from treatment in the first 4 weeks. They should be given follow-up appointments or be otherwise closely monitored during this period to encourage compliance.

After initial pharmacologic treatment has led to response and, ideally, symptom remission, subsequent treatment can be divided into two phases. First, 4 to 6 months of continuous treatment at full dose are needed to consolidate improvement and prevent early relapse. Second, consideration should be given to preventive maintenance, to reduce the risks of depression recurrence. Maintenance treatment is usually indicated if the patient has had two or more episodes of depression within the past 5 years. Psychological treatment (see below) may also help to prevent recurrence and can be used in combination with drug therapy.

Treatment considerations in stroke

It is generally recommended that treatment for depression in stroke survivors should be started early, to maximize functional outcome, but few randomized clinical trials have evaluated this recommendation. Most studies have reported improved outcomes with regard to mood, but findings have been contradictory in measures of function.[18,19,80–83]

Both SSRIs and TCAs have been found effective for depression in stroke patients, but SSRIs are probably preferable because they have fewer adverse effects, particularly if cognitive or cardiac function is compromised. However, this greater tolerability must be balanced against the finding that the TCA nortriptyline was more effective than the SSRI fluoxetine in the only trial that compared these agents.[80] What is clear is that all stroke patients taking antidepressants should be closely monitored for both treatment effectiveness and adverse effects. Psychological treatment—particularly cognitive behavioral therapy—may also be of value, but it has received only limited evaluation to date.[84,85] One small study suggested that cognitive behavioral therapy is adequate for only a minority of depressed stroke patients and provides some benefit for others, while nearly half of such patients do not benefit at all.[86]

Treatment considerations in multiple sclerosis

The few randomized controlled trials of antidepressant therapy in patients with multiple sclerosis suggest only modest efficacy,[87] as for depression associated with neurologic illness in general.[88]

Treatment considerations in Parkinson disease

Current evidence is insufficient to support definitive recommendations for the treatment of depression in PD.[89] While SSRIs are popular, there have been case reports of exacerbation of motor symptoms with fluoxetine, citalopram, and paroxetine.[90–94] In recent small-scale trials, TCAs have shown better motor outcomes, but medications with marked anticholinergic effects, such as amitriptyline, should be used with

caution because of their effects on cognition and autonomic function.[89] Newer drugs, such as mirtazapine, may offer a compromise. The nonergot dopamine agonist pramipexole, which is indicated for treatment of PD itself, has been found to improve both mood and motivation in PD patients.[95] Case report data suggest that both electroconvulsive therapy and transcranial magnetic stimulation can be used to treat depression in PD, although the latter is associated with short-lived effects and seizures.[89,96]

Treatment considerations in epilepsy

Most experts advocate the use of SSRIs as first-line therapy for depression in patients with epilepsy because of these drugs' limited propensity to lower the seizure threshold. Further consideration needs to be given, however, to possible drug interactions with anticonvulsant medications (paroxetine may have the most favorable profile in this regard). This consideration must be balanced, in turn, against treatment efficacy, since depression is an independent risk factor for unprovoked seizures.[97] Thus, TCAs sometimes produce improved mood and correspondingly improved seizure control, even after allowing for theoretical reduction in seizure threshold.

Treatment considerations in cognitive disorders

The value of pharmacotherapy for depression in patients with cognitive disorders has been explored over the years, with early studies of TCAs showing some equivocal results.[98] Such findings, together with recognition of the TCAs' adverse effects in elderly demented patients, led to a focus on the SSRIs and other newer agents. In an important recent study,[99] the SSRI sertraline was found to be superior to placebo in treating depression in patients with AD.

OTHER TREATMENT MODALITIES

Electroconvulsive therapy

Electroconvulsive therapy (ECT) remains the gold standard for severe depression in adults generally,[100] and its safety and efficacy have been increasingly recognized in the elderly.[101] The use of ECT in depressed patients with neurologic impairment is not new, but its value has not been systematically evaluated in controlled studies of adequate size and design. In PD, for example, small and mostly retrospective studies over many decades have reported benefit in mood and behavior, along with motor improvement of varying degrees and durations.[102] One large recent study of this kind confirmed benefit in 25 patients with PD, a few of whom might have had drug-induced parkinsonism.[103] Similar data exist for poststroke depression,[104] although patient numbers are smaller and the benefit may not be long-lasting. A high rate of response to ECT has been reported in elderly patients with depression who had substantial white matter lesions.[105] ECT has been examined to a limited extent as a treatment for depression in patients with dementia. A retrospective case study of ECT in 31 such patients reported significant improvements in mood and even improvement in cognition.[106]

Treatment-emergent delirium and memory impairment (usually short-lived) have been noted in reports of ECT in patients with various neurologic disorders, as in other populations. While such problems may constrain the use of this therapy, they should not preclude its consideration in medically appropriate patients with refractory depression.

Psychological treatment

Psychological treatment can range from discussion and problem-solving to more specialized cognitive or dynamic behavioral psychotherapies. In many cases, short-term treatment by those who are not mental health specialists can be effective in both primary and secondary care. Such interventions may include education and reassurance about the common reactions to the threats and losses associated with illness, as well as empathic listening to the patient's views, uncertainties, and beliefs about the illness. Education and advice about the medical condition and associated depression may prevent needless worry, reduce feelings of helplessness, and diminish irrational fears. Therapeutic approaches that support or promote active coping strategies are an important aspect of treatment in physically ill patients.

Cognitive behavioral principles may be used by nonspecialists to correct cognitive distortions related to the illness and to support behavioral strategies that contribute to the patient's sense of mastery and well-being. Training in briefer forms of treatment using cognitive behavioral principles for general health care staff may be a worthwhile investment.

Cognitive behavioral therapy, interpersonal therapy, and problem-solving have all been shown to be effective for treating depression,[107–109] although their efficacy has seldom been tested in physically ill populations. Although time-consuming compared with drug treatment, psychological treatment may reduce relapse rates and may be cost-effective in the long run. Some patients may require preliminary pharmacologic treatment to enable them to fully benefit from psychological treatment.

Contrary to perceptions among the public and health care providers, psychotherapy is often effective in treating depression in the elderly. Both interpersonal therapy and cognitive behavioral therapy have demonstrated efficacy comparable to that of antidepressants in this population, and the combination of both was most effective.[108,109]

Psychotherapy in the cognitively impaired should not be dismissed out of hand. Individuals with mild cognitive impairment can certainly benefit from it, and novel forms of supportive psychotherapy are being explored in the demented. Examples include facilitated reminiscing and techniques emphasizing nonverbal communication (eg, therapeutic touch, pet therapy, and music). Aggressive reorientation to reality is generally viewed as inadvisable.

CONCLUSIONS

In elderly patients with neurologic disease, depression often manifests as a mixture of phenomena associated with the neurologic condition or with aging itself in addition to the depressive illness. Effective diagnosis of depression is possible with alertness to clues in the interview and the use of screening questions for those at risk. Generalist physicians can and should assess for suicidal thinking and risk. When the diagnosis of depression in the setting of neurologic disease is uncertain, clinicians do well to take a pragmatic approach and make a provisional diagnosis, especially if low mood or anhedonia is evident and accompanied by somatic symptoms and lack of engagement with the environment.

The objectives of treating depression in this population are to improve mood and quality of life, reduce the risk of medical complications, improve compliance with and outcome of physical treatment, and facilitate appropriate use of health care resources. In many cases, depressed elderly neurologic patients can be effectively treated by generalist clinicians with antidepressant medications and/or psychological therapy. Referral to a specialist is indicated for patients with suicidal ideation or those who have not responded to an initial course of therapy.

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