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

MARK S. BARON, MD

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

From the Virginia Commonwealth University School of Medicine and the Southeast Parkinson's Disease Research, Education and Clinical Center (PADRECC), Hunter Holmes McGuire VA Medical Center, Richmond, VA.

Address: Mark S. Baron, MD, Director, Southeast Parkinson's Disease Research, Education and Clinical Center, Hunter Holmes McGuire VA Medical Center, 1201 Broad Rock Road, Richmond, VA 23249; baron@med.va.gov.

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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.

REFERENCES

1. Mayeux R, Denaro J, Hemenegildo N, et al. A population-based investigation of Parkinson's disease with and without dementia. Arch Neurol 1992; 49:494–497.
2. Strickland D, Bertoni JM. Parkinson's prevalence estimated by a state registry. Mov Disord 2004; 19:318–323.
3. Muller J, Wenning GK, Jellinger K, McKee A, Poewe W, Litvan I. Progression of Hoehn and Yahr stages in parkinsonian disorders: a clinicopathologic study. Neurology 2000; 55:888–891.
4. de Rijk MC, Rocca WA, Anderson DW, Melcon MO, Breteler MM, Maraganore DM. A population perspective on diagnostic criteria for Parkinson's disease. Neurology 1997; 48:1277–1281.
5. Muller J, Wenning GK, Jellinger K, McKee A, Poewe W, Litvan I. Progression of Hoehn and Yahr stages in Parkinsonian disorders: a clinicopathologic study. Neurology 2000; 55:888–891.
6. Morens DM, Grandinetti A, Reed D, White LR, Ross GW. Cigarette smoking and protection from Parkinson's disease: false association or etiologic clue? Neurology 1995; 45:1041–1051.
7. Gorell JM, Rybicki BA, Johnson CC, Peterson EL. Smoking and Parkinson's disease: a dose-response relationship. Neurology 1999; 52:115–119.
8. Tanner CM, Goldman SM, Aston DA, et al. Smoking and Parkinson's disease in twins. Neurology 2002; 58:581–588.
9. Ascherio A, Zhang SM, Hernan MA, et al. Prospective study of caffeine consumption and risk of Parkinson's disease in men and women. Ann Neurol 2001; 50:56–63.
10. Chen H, Zhang SM, Hernan MA, et al. Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease. Arch Neurol 2003; 60:1059–1064.
11. Pearce RKB, Banerji T, Jenner P, Marsden CD. De novo administration of ropinirole and bromocriptine induces less dyskinesia than L-dopa in the MPTP-treated marmoset. Mov Disord 1998; 13:234–241.
12. Rascol O, Brooks DJ, Korczyn AD, De Deyn PP, Clarke CE, Lang AE. A five-year study of the incidence of dyskinesia in patients with early Parkinson's disease who were treated with ropinirole or levodopa. 056 Study Group. N Engl J Med 2000; 342:1484–1491.
13. Golbe LI. Young-onset Parkinson's disease: a clinical review. Neurology 1991; 41(2 pt 1):168–173.
14. Block G, Liss C, Reines S, Irr J, Nibbelink D. Comparison of immediate-release and controlled-release carbidopa/levodopa in Parkinson's disease: a multicenter 5-year study. Eur Neurol 1997; 37:23–27.
15. Lieberman AN, Neophytides A, Leibowitz M, et al. Comparative efficacy of pergolide and bromocriptine in patients with advanced Parkinson's disease. Adv Neurol 1983; 37:95–108.
16. Pezzoli G, Martignoni E, Pacchetti C, et al. Pergolide compared with bromocriptine in Parkinson's disease: a multicenter, crossover, controlled study. Mov Disord 1994; 9:431–436.
17. Guttman M. Double-blind comparison of pramipexole and bromocriptine treatment with placebo in advanced Parkinson's disease. International Pramipexole-Bromocriptine Study Group. Neurology 1997; 49:1060–1065.
18. Korczyn AD, Brunt ER, Larsen JP, Nagy Z, Poewe WH, Ruggieri S. A 3-year randomized trial of ropinirole and bromocriptine in early Parkinson's disease. The 053 Study Group. Neurology 1999; 53:364–370.
19. Mizuno Y, Yanagisawa N, Kuno S, et al, Japanese Pramipexole Study Group. Randomized, double-blind study of pramipexole with placebo and bromocriptine in advanced Parkinson's disease. Mov Disord 2003; 18:1149–1156.
20. Van Camp G, Flamez A, Cosyns B, et al. Treatment of Parkinson's disease with pergolide and relation to restrictive valvular heart disease. Lancet 2004; 363:1179–1183.
21. Paus S, Brecht HM, Köster J, Seeger G, Klockgether T, Wüllner U. Sleep attacks, daytime sleepiness, and dopamine agonists in Parkinson's disease. Mov Disord 2003; 18:659–667.
22. Marjama-Lyons J, Koller W. Tremor-predominant Parkinson's disease. Approaches to treatment. Drugs Aging 2000; 16:273–278.
23. Rinne UK, Larsen JP, Siden A, Worm-Petersen J. Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. Nomecomt Study Group. Neurology 1998; 51:1309–1314.
24. Larsen JP, Worm-Petersen J, Siden A, Gordin A, Reinikainen K, Leinonen M, NOMESAFE Study Group. The tolerability and efficacy of entacapone over 3 years in patients with Parkinson's disease. Eur J Neurol 2003; 10:137–146.
25. Factor SA, Molho ES, Feustel PJ, Brown DL, Evans SM. Long-term comparative experience with tolcapone and entacapone in advanced Parkinson's disease. Clin Neuropharmacol 2001; 24:295–299.
26. Keating GM, Lyseng-Williamson KA. Tolcapone-related liver dysfunction: implications for use in Parkinson's disease therapy. CNS Drugs 2005; 19:165–184.
27. Nausieda PA, Pfeiffer RF, Tagliati M, Kastenholz KV, DeRoche C, Slevin JT. A multicenter, open-label, sequential study comparing preferences for carbidopa-levodopa orally disintegrating tablets and conventional tablets in subjects with Parkinson's disease. Clin Ther 2005; 27:58–63.
28. Factor SA. Literature review: intermittent subcutaneous apomorphine therapy in Parkinson's disease. Neurology 2004; 62(suppl 4):S12–S17.
29. Thomas A, Iacono D, Luciano AL, Armellino K, DiIorio A, Onofrj M. Duration of amantadine benefit on dyskinesia of severe Parkinson's disease. J Neurol Neurosurg Psychiatry 2004; 75:141–143.
30. Baron MS, Dalton WB. Quetiapine as a treatment for dopaminergic-induced dyskinesias in Parkinson's disease. Mov Disord 2003;

18:1208–1209.
31. Jaskiw GE, Thyrum PT, Fuller MA, Arvanitis LA, Yeh C. Pharmacokinetics of quetiapine in elderly patients with selected psychotic disorders. Clin Pharmacokinet 2004; 43:1025–1035.
32. Aarsland D, Andersen K, Larsen JP, Lolk A. Prevalence and characteristics of dementia in Parkinson disease: an 8-year prospective study. Arch Neurol 2003; 60:387–392.
33. McDonald WM, Richard IH, DeLong MR. Prevalence, etiology, and treatment of depression in Parkinson's disease. Biol Psychiatry 2003; 54:363–375.
34. Magalhaes M, Wenning GK, Daniel SE, Quinn NP. Autonomic dysfunction in pathologically confirmed multiple system atrophy and idiopathic Parkinson's disease—a retrospective comparison. Acta Neurol Scand 1995; 91:98–102.
35. Ramig LO, Sapir S, Countryman S, et al. Intensive voice treatment (LSVT®) for patients with Parkinson's disease: a 2 year follow up. J Neurol Neurosurg Psychiatry 2001; 71:493–498.
36. The Deep-Brain Stimulation for Parkinson's Disease Study Group. Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med 2001; 345:956–963.
37. Schrag A, Ben-Shlomo Y, Quinn NP. Prevalence of progressive supranuclear palsy and multiple system atrophy: a cross-sectional study. Lancet 1999; 354:1771–1775.
38. Tison F, Yekhlef F, Chrysostome V, Sourgen C. Prevalence of multiple system atrophy. Lancet 2000; 355:495–496.
39. Wenning GK, Ben-Shlomo Y, Magalhaes M, Daniel SE, Quinn NP. Clinical features and natural history of multiple system atrophy: an analysis of 100 cases. Brain 1994; 117:835–845.
40. Ben-Shlomo Y, Wenning G, Tison F, Quinn NP. Survival of patients with pathologically proven multiple system atrophy: a meta-analysis. Neurology 1997; 48:384–393.
41. Testa D, Monza D, Ferrarini M, Soliveri P, Girotti F, Filippini G. Comparison of natural histories of progressive supranuclear palsy and multiple system atrophy. Neurol Sci 2001; 22:247–251.
42. Watanabe H, Saito Y, Terao S, et al. Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients. Brain 2002; 125:1070–1083.
43. Papp MI, Kahn JE, Lantos PL. Glial cytoplasmic inclusions in the CNS of patients with multiple system atrophy (striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome). J Neurol Sci 1989; 94:79–100.
44. Gilman S, Low PA, Quinn N, et al. Consensus statement on the diagnosis of multiple system atrophy. J Neurol Sci 1999; 163:94–98.
45. Stocchi F, Brusa L. Cognition and emotion in different stages and subtypes of Parkinson's disease. J Neurol 2000; 247(suppl 2):II114–II121.
46. Kraft E, Trenkwalder C, Auer DP. T_2*-weighted MRI differentiates multiple system atrophy from Parkinson's disease. Neurology 2002; 59:1265–1267.
47. Seppi K, Schocke MFH, Esterhammer R, et al. Diffusion-weighted imaging discriminates progressive supranuclear palsy from PD, but not from the parkinson variant of multiple system atrophy. Neurology 2003; 60:922–927.
48. Chou KL, Forman MS, Trojanowski JQ, Hurtig HI, Baltuch GH. Subthalamic nucleus deep brain stimulation in a patient with levodopa-responsive multiple system atrophy. Case report. J Neurosurg 2004; 100:553–556.
49. Tarsy D, Apetauerova D, Ryan P, Norregaard T. Adverse effects of subthalamic nucleus DBS in a patient with multiple system atrophy. Neurology 2003; 61:247–249.
50. Yamaguchi M, Arai K, Asahina M, Hattori T. Laryngeal stridor in multiple system atrophy. Eur Neurol 2003; 49:154–159.
51. Iranzo A, Santamaria J, Tolosa E, et al. Long-term effect of CPAP in the treatment of nocturnal stridor in multiple system atrophy. Neurology 2004; 63:930–932.
52. Higo R, Tayama N, Watanabe T, Nitou T, Ugawa Y. Videofluoroscopic and manometric evaluation of swallowing function in patients with multiple system atrophy. Ann Otol Rhinol Laryngol 2003; 112:630–636.
53. Santacruz P, Uttl B, Litvan I, Grafman J. Progressive supranuclear palsy: a survey of the disease course. Neurology 1998; 50:1637–1647.
54. Nath U, Ben-Shlomo Y, Thomson RG, et al. The prevalence of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) in the UK. Brain 2001; 124:1438–1449.
55. De Bruin VM, Lees AJ. Subcortical neurofibrillary degeneration presenting as Steele-Richardson-Olszewski and other related syndromes: a review of 90 pathologically verified cases. Mov Disord 1994; 9:381–389.
56. Litvan I, Mangone CA, McKee A, et al. Natural history of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) and clinical predictors of survival: a clinicopathological study. J Neurol Neurosurg Psychiatry 1996; 60:615–620.
57. Litvan I, Agid Y, Calne D, et al. Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop. Neurology 1996; 47:1–9.
58. Vidailhet M, Rivaud S, Gouider-Khouja N, et al. Eye movements in parkinsonian syndromes. Ann Neurol 1994; 35:420–426.
59. Mega MS, Masterman DL, Benson DF, et al. Dementia with Lewy bodies: reliability and validity of clinical and pathologic criteria. Neurology 1996; 47:1403–1409.
60. Rahkonen T, Eloniemi-Sulkava U, Rissanen S, Vatanen A, Viramo P, Sulkava R. Dementia with Lewy bodies according to the consensus criteria in a general population aged 75 years or older. J Neurol Neurosurg Psychiatry 2003; 74:720–724.
61. McKeith IG, Ballard CG, Perry RH, et al. Prospective validation of consensus criteria for the diagnosis of dementia with Lewy bodies. Neurology 2000; 54:1050–1058.
62. Ferman TJ, Smith GE, Boeve BF, et al. DLB fluctuations: specific features that reliably differentiate DLB from AD and normal aging. Neurology 2004; 62:181–187.
63. Wild R, Pettit T, Burns A. Cholinesterase inhibitors for dementia with Lewy bodies. Cochrane Database Syst Rev 2003:CD003672.
64. Burke WJ, Pfeiffer RF, McComb RD. Neuroleptic sensitivity to clozapine in dementia with Lewy bodies. J Neuropsychiatry Clin Neurosci 1998; 10:227–229.
65. Fernandez HH, Trieschmann ME, Burke MA, Friedman JH. Quetiapine for psychosis in Parkinson's disease versus dementia with Lewy bodies. J Clin Psychiatry 2002; 63:513–515.
66. Caplan LR. Binswanger's disease–revisited. Neurology 1995; 45:626–633.
67. Roman GC, Erkinjuntti T, Wallin A, Pantoni L, Chui HC. Subcortical ischaemic vascular dementia. Lancet Neurol 2002; 1:426–436.
68. Awad IA, Spetzler RF, Hodak JA, Awad CA, Carey R. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly. I. Correlation with age and cerebrovascular risk factors. Stroke 1986; 17:1084–1089.
69. van Swieten JC, Geyskes GG, Derix MMA, et al. Hypertension in the elderly is associated with white matter lesions and cognitive decline. Ann Neurol 1991; 30:825–830.
70. Blass JP, Hoyer S, Nitsch R. A translation of Otto Binswanger's article, 'The delineation of the generalized progressive paralyses.' 1894. Arch Neurol 1991; 48:961–972.
71. DeReuck J, Crevits L, De Coster W, Sieben G, vander Eecken H. Pathogenesis of Binswanger chronic progressive subcortical encephalopathy. Neurology 1980; 30:920–928.
72. Bennett DA, Wilson RS, Gilley DW, Fox JH. Clinical diagnosis of Binswanger's disease. J Neurol Neurosurg Pyschiatry 1990; 53:961–965.
73. Caplan LR, Schoene WC. Clinical features of subcortical arteriosclerotic encephalopathy (Binswanger disease). Neurology 1978; 28:1206–1215.
74. Thompson PD, Marsden CD. Gait disorder of subcortical arteriosclerotic encephalopathy: Binswanger's disease. Mov Disord 1987; 2:1–8.
75. Traykov L, Baudic S, Raoux N, et al. Patterns of memory impairment and perseverative behavior discriminate early Alzheimer's disease from subcortical vascular dementia. J Neurol Sci 2005; 229–230:75–79.
76. Hebb AO, Cusimano MD. Idiopathic normal pressure hydrocephalus: a systematic review of diagnosis and outcome. Neurosurgery 2001; 49:1166–1184.

77. Savolainen S, Hurskainen H, Paljärvi L, Alafuzoff I, Vapalahti M. Five-year outcome of normal pressure hydrocephalus with or without a shunt: predictive value of the clinical signs, neuropsychological evaluation and infusion test. Acta Neurochir (Wien) 2002; 144:515–523.
78. Adams RD, Fisher CM, Hakim S, Ojemann RG, Sweet WH. Symptomatic occult hydrocephalus with "normal" cerebrospinal-fluid pressure: a treatable syndrome. N Engl J Med 1965; 273:117–126.
79. Thomsen AM, Børgesen SE, Bruhn P, Gjerris F. Prognosis of dementia in normal-pressure hydrocephalus after a shunt operation. Ann Neurol 1986; 20:304–310.
80. Malm J, Kristensen B, Karlsson T, Fagerlund M, Elfverson J, Ekstedt J. The predictive value of cerebrospinal fluid dynamic tests in patients with the idiopathic adult hydrocephalus syndrome. Arch Neurol 1995; 52:783–789.
81. Di Lauro L, Mearini M, Bollati A. The predictive value of 5 days CSF diversion for shunting in normal pressure hydrocephalus. J Neurol Neurosurg Psychiatry 1986; 49:842–843.
82. Haan J, Thomeer RTWM. Predictive value of temporary external lumbar drainage in normal pressure hydrocephalus. Neurosurgery 1988; 22:388–391.
83. Chen IH, Huang CI, Liu HC, Chen KK. Effectiveness of shunting in patients with normal pressure hydrocephalus predicted by temporary, controlled-resistance, continuous lumbar drainage: a pilot study. J Neurol Neurosurg Psychiatry 1994; 57:1430–1432.
84. Symon L, Dorsch NWC. Use of long-term intracranial pressure measurement to assess hydrocephalic patients prior to shunt surgery. J Neurosurg 1975; 42:258–273.
85. Krauss JK, Halve B. Normal pressure hydrocephalus: survey on contemporary diagnostic algorithms and therapeutic decision-making in clinical practice. Acta Neurochir (Wien) 2004; 146:379–388.
86. Louis ED, Ottman R, Hauser WA. How common is the most common adult movement disorder? Estimates of the prevalence of essential tremor throughout the world. Mov Disord 1998; 13:5–10.
87. Rautakorpi I, Takala J, Marttila RJ, Sievers K, Rinne UK. Essential tremor in a Finnish population. Acta Neurol Scand 1982; 66:58–67.
88. Rajput A, Robinson CA, Rajput AH. Essential tremor course and disability: a clinicopathologic study of 20 cases. Neurology 2004; 62:932–936.
89. Tanner CM, Goldman SM, Lyons KE, et al. Essential tremor in twins: an assessment of genetic vs environmental determinants of etiology. Neurology 2001; 57:1389–1391.
90. Lorenz D, Frederiksen H, Moises H, Kopper F, Deuschl G, Christensen K. High concordance for essential tremor in monozygotic twins of old age. Neurology 2004; 62:208–211.
91. Higgins JJ, Pho LT, Nee LE. A gene (ETM) for essential tremor maps to chromosome 2p22–p25. Mov Disord 1997; 12:859–864.
92. Gulcher JR, Jonsson P, Kong A, et al. Mapping of a familial essential tremor gene, FET1, to chromosome 3q13. Nat Genet 1997; 17:84–87.
93. Deuschl G, Wenzelburger R, Löffler K, Raethjen J, Stolze H. Essential tremor and cerebellar dysfunction: clinical and kinematic analysis of intention tremor. Brain 2000; 123:1568–1580.
94. Pinto AD, Lang AE, Chen R. The cerebellothalamocortical pathway in essential tremor. Neurology 2003; 60:1985–1987.
95. Brennan KC, Jurewicz EC, Ford B, Pullman SL, Louis ED. Is essential tremor predominantly a kinetic or a postural tremor? A clinical and electrophysiological study. Mov Disord 2002; 17:313–316.
96. Elble RJ. Diagnostic criteria for essential tremor and differential diagnosis. Neurology 2000; 54(11 suppl 4):S2–S6.
97. Lombardi WJ, Woolston DJ, Roberts JW, Gross RE. Cognitive deficits in patients with essential tremor. Neurology 2001; 57:785–790.
98. Schmahmann JD, Sherman JC. The cerebellar cognitive affective syndrome. Brain 1998; 121:561–579.
99. Gorman WP, Cooper R, Pocock P, Campbell MJ. A comparison of primidone, propranolol, and placebo in essential tremor, using quantitative analysis. J Neurol Neurosurg Psychiatry 1986; 49:64–68.
100. Koller WC, Royse VL. Efficacy of primidone in essential tremor. Neurology 1986; 36:121–124.
101. Sullivan KL, Hauser RA, Zesiewicz TA. Essential tremor. Epidemiology, diagnosis, and treatment. Neurologist 2004; 10:250–258.
102. Jefferson D, Jenner P, Marsden CD. Beta-adrenoreceptor antagonists in essential tremor. J Neurol Neurosurg Psychiatry 1979; 42:904–909.
103. Leigh PN, Marsden CD, Twomey A, Jefferson D. Beta-adrenoceptor antagonists and essential tremor. Lancet 1981; 1:1106.
104. Huber SJ, Paulson GW. Efficacy of alprazolam for essential tremor. Neurology 1988; 38:241–243.
105. Connor GS. A double-blind placebo-controlled trial of topiramate treatment for essential tremor. Neurology 2002; 59:132–134.
106. Gatto EM, Roca MCU, Raina G, Micheli F. Low doses of topiramate are effective in essential tremor: a report of three cases. Clin Neuropharmacol 2003; 26:294–296.
107. Lyons KE, Pahwa R. Deep brain stimulation and essential tremor. J Clin Neurophysiol 2004; 21:2–5.
108. Fernandez HH, Friedman JH. Classification and treatment of tardive syndromes. Neurologist 2003; 9:16–27.
109. Baldessarini RJ, Cole JO, Davis JM, et al. Tardive dyskinesia: summary of a Task Force Report of the American Psychiatric Association. Am J Psychiatry 1980; 137:1163–1172.
110. Jeste DV, Lacro JP, Palmer B, Rockwell E, Harris MJ, Caligiuri MP. Incidence of tardive dyskinesia in early stages of low-dose treatment with typical neuroleptics in older patients. Am J Psychiatry 1999; 156:309–311.
111. Woerner MG, Alvir JMJ, Saltz BL, Lieberman JA, Kane JM. Prospective study of tardive dyskinesia in the elderly: rates and risk factors. Am J Psychiatry 1998; 155:1521–1528.
112. Jeste DV, Okamoto A, Napolitano J, Kane JM, Martinez RA. Low incidence of persistent tardive dyskinesia in elderly patients with dementia treated with risperidone. Am J Psychiatry 2000; 157:1150–1155.
113. Emsley R, Turner HJ, Schronen J, Botha K, Smit R, Oosthuizen PP. A single-blind, randomized trial comparing quetiapine and haloperidol in the treatment of tardive dyskinesia. J Clin Psychiatry 2004; 65:696–701.
114. Bacher NM, Lewis HA. Reserpine and tardive dyskinesia. Am J Psychiatry 1984; 141:719.
115. Ondo WG, Hanna PA, Jankovic J. Tetrabenazine treatment for tardive dyskinesia: assessment by randomized videotape protocol. Am J Psychiatry 1999; 156:1279–1281.
116. Trottenberg T, Paul G, Meissner W, Maier-Hauff K, Taschner C, Kupsch A. Pallidal and thalamic neurostimulation in severe tardive dystonia. J Neurol Neurosurg Psychiatry 2001; 70:557–559.
117. Schrader C, Peschel T, Petermeyer M, Dengler R, Hellwig D. Unilateral deep brain stimulation of the internal globus pallidus alleviates tardive dyskinesia. Mov Disord 2004; 19:583–585.
118. Lavigne GJ, Montplaisir JY. Restless legs syndrome and sleep bruxism: prevalence and association among Canadians. Sleep 1994; 17:739–743.
119. Walters AS, Hickey K, Maltzman J, et al. A questionnaire study of 138 patients with restless legs syndrome: the 'Night-Walkers' survey. Neurology 1996; 46:92–95.
120. Allen RP, Picchietti D, Hening WA, et al, for the International Restless Legs Syndrome Study Group. Restless legs syndrome: diagnostic criteria, special considerations, and epidemiology: a report from the restless legs syndrome diagnosis and epidemiology workshop at the National Institutes of Health. Sleep Med 2003; 4:101–119.
121. Phillips B, Young T, Finn L, Asher K, Hening WA, Purvis C. Epidemiology of restless legs symptoms in adults. Arch Intern Med 2000; 160:2137–2141.
122. Allen RP, Earley CJ. Augmentation of the restless legs syndrome with carbidopa/levodopa. Sleep 1996; 19:205–213.
123. Garcia-Borreguero D, Larrosa O, de la Llave Y, Verger K, Masramon X, Hernandez G. Treatment of restless legs syndrome with gabapentin: a double-blind, cross-over study. Neurology 2002; 59:1573–1579.
124. Walters AS, Winkelmann J, Trenkwalder C, et al. Long-term follow-up on restless legs syndrome patients treated with opioids. Mov Disord 2001; 16:1105–1109.
125. Ondo WG. Methadone for refractory restless legs syndrome. Mov Disord 2005; 20:345–348.