Updated diagnostic criteria for DLB were published in 2017. Individuals meet the threshold for "probable DLB" if they show findings of a progressive dementia and have at least two of core features of DLB: (1) parkinsonism, (2) cognitive fluctuations, (3) rapid eye movement (REM) sleep behavior disorder (RBD), and (4) recurrent visual hallucinations. A positive biomarker test—including an abnormal striatal DaT SPECT, polysomnography findings consistent with RBD, or sympathetic denervation on myocardial scintigraphy—can also be substituted for one of these four core criteria in order to meet the "probable DLB" diagnostic threshold. The US Food and Drug Administration (FDA) has approved PET radiopharmaceuticals to detect the presence of amyloid plaques (eg, florbetapir) and neurofibrillary tangles (flortaucipir) and may be useful for diagnostic purposes if diagnostic uncertainty remains. The FDA is expected to review applications shortly for diagnostic amyloid-beta blood tests that would allow the detection of cerebral amyloid disorders, including AD, in relevant clinical contexts. Whether these tests may be employed to distinguish different prognostic trajectories in individuals with common early synucleinopathies is a topic worth monitoring—this is especially true given that manifest DLB is characterized by higher cortical amyloid-beta plaque levels than idiopathic PD.

A recent proposal to distinguish the so-called body-first versus brain-first subtypes of PD may blur the line between PD and DLB diagnoses. The proposed subtyping is based on the temporal relationship between the onset of RBD and motor diagnosis of PD. A gut-first subtype would be defined when RBD precedes the motor diagnosis with at least 1 year compared to post-motor symptom emergence of this parasomnia or its absence. This subtyping may have an advantage of early stage prognostication but its utility in more advanced disease is questionable.

Although there are many motor features seen in early PD, the scope of nonmotor features associated with early PD is even larger. These can include (but are not limited to) olfactory impairment, sleep difficulties, depression, anxiety, chronic constipation, limb pain, apathy, erectile dysfunction, cognitive impairment, drooling, rhinorrhea, and other autonomic features. Although some of these features can be a secondary development due to disability accrued from PD, almost all of them are aggravated by primary Lewy body–related neuronal changes seen in various areas of the nervous

system ranging from the enteric nerves of the gastrointestinal tract to the cholinergic nerves arising from the basal forebrain, which innervate the cerebral cortex. Although many of these features become increasingly common with age, the concomitant development of three or more of these features in an older individual without a clear alternate explanation should prompt a work-up for a parkinsonian condition.

Early cognitive changes seen in PD include difficulty with memory, attention, and executive dysfunction, the latter of which refers to planning, multitasking, and decision-making capacity. In some patients, these cognitive features may be stable for many years, whereas in others they may progress to dementia. It is estimated that about 50% of individuals with PD will develop dementia (PDD) within 10 years of their initial diagnosis.

MSA is a parkinsonian disorder characterized by aggressive α-synuclein–related cellular loss in the brain stem, cerebellum, and basal ganglia. The median age of onset is in the sixth decade of life with a mean time to severe disability of approximately 5 years from the time of diagnosis. Progressive cell death occurs not only in dopaminergic cells but in many different neuronal systems including the basal ganglia, substantia nigra, locus coeruleus, pontine nuclei, cerebellar Purkinje cells, and the intermediolateral cell column of the spinal cord. MSA is typically grouped into two clinical categories: MSA-P, where parkinsonism is seen, and MSA-C, where cerebellar features including ataxic gait, dystaxic limb movements, and ataxic speech predominate. Other characteristic features of both MSA-P and MSA-C that differ from PD include severe autonomic symptoms including orthostatic light-headedness, blood pressure fluctuations, and urinary dysfunction. Patients with MSA can also experience nocturnal stridor characterized by laryngeal obstruction secondary to vocal fold hypokinesia, which manifests with a high-pitched inspiratory noise. Unlike obstructive sleep apnea, nocturnal stridor can be acutely life threatening. While emergency tracheostomies have been performed in MSA for life-threatening stridor, this may be inconsistent with overall goals of care for such patients. Following with an otolaryngologist on an annual basis can be an effective method for monitoring this symptom overtime and some patients may benefit from nasal continuous positive airway pressure (CPAP). Unlike other atypical parkinsonian conditions, cognitive impairment is not a typical feature of MSA but may be present in a small subset.

PSP and CBS are both tauopathies associated with parkinsonism. PSP tends to present in the sixth and seventh decades of life with early oculomotor findings including downgaze impairment, axial rigidity, and postural instability. Patients with PSP also develop a frontal-predominant cognitive syndrome characterized by apathy, executive dysfunction, and pseudobulbar effect. CBS is the clinical diagnosis given for patients with suspected CBD, the latter of which refers specifically to neuropathologic findings. Clinically defined CBS is associated with several distinct postmortem histopathologies, including CBD, other forms of tau-related frontotemporal lobar degeneration, such as PSP, and AD. Motor manifestations of CBS also tend to occur in the sixth or seventh decade of life and are characterized by progressive asymmetric rigidity, myoclonus, parkinsonism, and an unusual motor phenomenon termed "alien limb" during which patients experience adventitious semipurposeful movements of one limb. CBS is one of the exceptions to the general rule that asymmetric limb motor involvement favors a diagnosis of PD. Early cognitive changes include praxis difficulties and language impairment. Cortical sensory loss can also be seen. The variable presence of these clinical features and their overlap with features seen in PSP, PD, and frontotemporal dementia (FTD) has led clinicians to use the term CBS to describe clinically probable, though not pathologically confirmed, CBD.

MANAGEMENT

Treatment of patients with PD can be divided into three major categories: medications, physical (and mental health) therapy, and surgery. Although the pharmacologic strategies described below apply primarily to PD, they can also be tried in atypical parkinsonian conditions. MSA, PSP, and CBD, however, are typically associated with a more limited response to medications, underscoring their overall worse prognosis.

Dopaminergic Therapies

Dopamine replacement therapy is the primary medical approach to treating PD, and a variety of dopaminergic agents are available (**Table 61-5**). The most powerful oral drug is levodopa, the immediate precursor of dopamine. Levodopa, an amino acid precursor molecule of dopamine, can enter the brain, whereas dopamine is blocked by the blood-brain barrier. Levodopa is usually administered combined with a peripheral decarboxylase inhibitor

(carbidopa or benserazide) to prevent formation of dopamine in the peripheral tissues, thereby increasing levodopa's bioavailability and also markedly reducing gastrointestinal side effects. The brand name Sinemet is a combination of carbidopa and levodopa; the brand name Madopar is a combination of benserazide and levodopa. Such combination drugs are available in standard (ie, immediate-release) and extended-release formulations. The former allows a more rapid and predictable "on," and the latter allows for a slightly longer plasma half-life, but with a slower and less predictable "on." The combination of the two release formulations can be administered in an attempt to smooth out and extend plasma levels of levodopa. A version of carbidopa/levodopa that dissolves under the tongue (Parcopa) and enters the stomach via swallowing saliva is also available. This orally dissolving formulation has particular usefulness for patients who have swallowing difficulties.

TABLE 61-5 ■ DOPAMINERGIC AGENTS

Dopamine precursor: levodopa
Peripheral decarboxylase inhibitors: carbidopa, benserazide
Dopamine agonists: pramipexole, ropinirole, rotigotine, apomorphine
Catechol-*O*-methyltransferase inhibitors: entacapone, opicapone
Dopamine releaser: amantadine
Peripheral dopamine receptor blocker: domperidone
MAO type B inhibitor: selegiline, selegiline, rasagiline, safinamide
A2A antagonist: istradefylline

MAO, monoamine oxidase.

Although levodopa is the most effective drug to treat the symptoms of PD, over half of patients develop troublesome complications of disabling response fluctuations ("wearing-off") and/or dyskinesias after 5 years of levodopa therapy. Besides being metabolized by aromatic amino acid decarboxylase (commonly known as dopa decarboxylase), levodopa is also metabolized by catechol-O-methyltransferase (COMT) to form 3-O-

methyldopa. Entacapone is a currently available COMT inhibitor. This agent extends the plasma half-life of levodopa with and also increases its peak plasma concentration, and thereby prolongs the duration of action of each dose of levodopa. Its clinical indication is to help reduce motor fluctuations, that is, increase "on" time and reduce "off" time. Because entacapone enhances levodopa's efficacy, it can increase dyskinesias and the dosage of levodopa may need to be lowered. Entacapone is very short acting, and each 200-mg tablet is taken simultaneously with levodopa. Entacapone is also available in a combination pill with carbidopa/levodopa (Stalevo). Tolcapone (100- and 200-mg tablets) is more potent and has a longer duration of action, but it is encumbered by a greater risk of diarrhea and hepatotoxicity, the latter of which has led to its removal from the market in the United States. After levodopa, the next most powerful oral drugs in treating PD symptoms are the dopamine agonists. Several of these are available. The ergot compounds of pergolide, bromocriptine, and cabergoline have the potential to induce fibrosis (cardiac valvulopathy and retroperitoneal, pleuropulmonary, and pericardial fibrosis), so these agents are not recommended; indeed, pergolide has been withdrawn from the US market. Pramipexole and ropinirole appear to be equally effective at therapeutic levels. Dopamine agonists are more likely than levodopa to cause hallucinations, confusion, and psychosis, especially in the older adults. Thus, it is safer to utilize levodopa in patients older than 70 years. On the other hand, clinical trials have shown that dopamine agonists are less likely to produce dyskinesias and the wearing-off phenomenon than levodopa. These differences are most likely due to the relatively lower potency/efficacy and longer half-life of dopamine agonists compared to levodopa. Slow-release preparations of ropinirole and pramipexole are also available. Other problems more likely to occur with dopamine agonists than levodopa are sudden sleep attacks, including falling asleep at the wheel, daytime drowsiness, ankle edema, and impulse control problems such as hypersexuality and compulsive gambling, shopping, and binge eating. The newest dopamine agonist is rotigotine which is applied via a dermal patch to the upper torso or arms. It is useful for those with swallowing difficulties and may help smooth out motor fluctuations and nocturnal akinesia when the last prebedtime dose of levodopa does not last throughout the night. Rotigotine is a high-potency agonist at human dopamine D1, D2, and D3 receptors with a lower potency at D4 and D5 receptors. Therefore, rotigotine

differs from conventional dopamine D2 agonists used in the treatment of PD, such as ropinirole and pramipexole, which lack activity at the D1 and D5 receptors, but resembles that of apomorphine, which has greater efficacy in PD than other dopamine agonists. The preferential D1 receptor agonism may explain rotigotine's higher efficacy in treating freezing of gait in PD compared to pramipexole and ropinirole. Another advantage of rotigotine is the transdermal delivery facilitating more steady drug delivery throughout the day.

Apomorphine may be the most powerful dopamine agonist, but can cause intense nausea and historically has needed to be injected subcutaneously. It is used to provide faster relief to overcome a disabling "off" state. A newly developed formulation of Apomorphine is now available in a sublingual film (Kynmobi) and may be useful for treating patients with precipitous motor fluctuations (see Treatment of "Wearing Off").

Amantadine is adjunctive antiparkinsonian drug with several pharmacologic actions; it has mild antimuscarinic effects, but more importantly, it can activate release of dopamine from nerve terminals, block dopamine uptake into the nerve terminals, and block glutamate N-methyl-D-aspartate (NMDA) receptors. Its dopaminergic actions make it a useful drug to relieve symptoms in approximately two-thirds of patients, but it can induce livedo reticularis, ankle edema, visual hallucinations, and confusion. Its antiglutamatergic action is useful in reducing the severity of levodopa-induced dyskinesias, and in fact, is the only established effective antidyskinetic agent. The dose of amantadine for its anti-PD effect is usually 100 mg twice daily, but its antidyskinetic effect requires higher dosages, usually 300 to 400 mg/day. Unfortunately, the antidyskinetic effect tends to lessen over time. Older individuals often do not tolerate amantadine well because of mental adverse effects of confusion and hallucinations.

Domperidone is a peripherally active dopamine receptor blocker and is useful in preventing gastrointestinal upset from levodopa and the dopamine agonists. It is not available in the United States but is available in other countries including Canada. Monoamine oxidase type B (MAO-B) inhibitors (selegiline, rasagiline) offer mildly effective symptomatic benefit and are without significant hypertensive diet-linked side effects seen with MAO-A inhibitors, and therefore can be used in the presence of levodopa therapy. Although there has been considerable debate about possible protective or disease-modifying benefit of MAO-B inhibitors, numerous well-powered

trials have failed to convincingly demonstrate a neuroprotective benefit. The results of these trials have been interpreted variably, however, given that selegiline and rasagiline appear to have a symptomatic benefit, which has contributed to some methodological concerns regarding specific trial designs. Selegiline, but not rasagiline, is metabolized to L-amphetamine and methamphetamine. Both of these drugs can reduce the severity of motor fluctuations with levodopa. The newly developed drug safinamide is thought to offer greater specificity for MAO-B, which in theory may reduce off target side effects related to diet.

Motor Complications of Dopaminergic Therapies

Many patients on levodopa therapy develop motor complications (**Table 61-6**). These motor complications, also referred to as "motor fluctuations," usually begin as mild wearing-off, which can be defined as when an adequate dose of levodopa does not last at least 6 hours and motor symptoms of bradykinesia, rigidity, or tremor emerge or worsen. Typically, in the first couple of years of treatment, there is a long-duration response so that the timing of doses of levodopa is not important. Over time, the long-duration response becomes lost, and only a short-duration response occurs; patients then develop the wearing-off phenomenon. The "off" episodes tend to be mild at first, but over time become more frequent or severe with more severe parkinsonism. Simultaneously, the duration of the "on" response becomes shorter. Eventually, some patients develop random, sudden "offs" in which the deep state of parkinsonism develops over minutes rather than tens of minutes, and they are less predictable in terms of synchrony with the dosing of levodopa. Many patients who develop response fluctuations also develop abnormal involuntary movements, that is, dyskinesias.

TABLE 61-6 ■ PATTERN OF DEVELOPMENT OF RESPONSE FLUCTUATIONS, DYSKINESIAS, AND OTHER COMPLICATIONS

Dyskinesias (chorea and dystonia)
Peak-dose dyskinesias
Diphasic dyskinesias (beginning and end of dose dyskinesias)
Fluctuations
Wearing-off
Delayed "ons"
Dose failures
Sudden, unpredictable "offs" (on-offs)
Early morning "off" dystonia
"Off" dystonia during day
Nonmotor "offs" (eg, exacerbated fatigue, word-finding difficulty, restlessness, etc.)
Alertness
Drowsy from a dose of levodopa
Reverse sleep-wake cycle
Behavioral and cognitive
Vivid dreams
Mild hallucinations
Severe hallucinations
Delusions
Punding
Apathy
Paranoia
Delirium
Dementia

Treatment of "wearing-off"

The wearing-off phenomenon, when mild, may be ameliorated slightly with the addition of selegiline, rasagiline, or safinamide. Each MAO-B inhibitor potentiates the action of levodopa. A higher dose of levodopa may be necessary but more frequent dosing of levodopa may be the simplest

approach to manage this motor complication. Many patients can require six or more doses of levodopa per day, and then, eventually, can develop dose failures owing to poor gastric emptying. These patients are often considered for duodenal infusion of levodopa or DBS (see Surgical Therapy later).

Continuous-release carbidopa/levodopa (Sinemet CR) can also be effective in patients with mild wearing-off in some patients or use the combination of both immediate- and extended-release formulations. Newer formulations of carbidopa/levodopa have attempted to address the clinical need for more uniform levodopa dosing throughout the day. These include Rytary—a capsule that contains immediate and extended release levodopa with carbidopa. Rytary and Sinemet make use of slightly different doses that may merit close monitoring when transition from one drug to the other. Optimally, Rytary may be a useful Sinemet substitution in patients who depend on levodopa administration every 2 to 4 hours throughout the day, hopefully allowing for less frequent dosing. A short-acting formulation of levodopa delivered in an inhaler (Inbrija) may be useful in the setting of precipitous motor "offs." It may start working within 10 to 30 minutes though —much like inhalers for pulmonary conditions—its efficacy can be altered by the technique of inhaler utilization. Dopamine agonists, which have a longer biological half-life than levodopa, can also be used in combination with immediate-release or continuous-release versions of carbidopa/levodopa. The addition of a dopamine agonist tends to make the "off" state less severe when used in combination with carbidopa/levodopa. COMT inhibitors have been found useful for treating wearing-off. Because of the short half-life of entacapone, it is given with each dose of carbidopa/levodopa and is about as equally effective as rasagiline in reducing the amount of daily "off" time. For those patients who have "offs" at a specific time of day, entacapone can be strategically given just with the dosage of carbidopa/levodopa that precedes this "off" period. Once daily dosing is now possible with a newly developed COMT inhibitor, opicapone. Adenosine A2A receptors are expressed in the striatum and a newly approved A2A-receptor antagonist (istradefylline) may serve to reduce activity of the basal ganglia's indirect pathway, thereby relieving parkinsonian hypokinesia. Istradefylline is a once-daily medication used to reduce off-time when used in conjunction with carbidopa/levodopa in PD patients with motor fluctuations.

Behavioral or sensory "offs" can also occur as do motor "offs," often in the absence of any motor "off," which means a return of parkinsonism. Behavioral and sensory "offs," tend not to be easily recognized, because visibly the treating physician sees no motor changes. Behavioral/sensory "offs" can consist of pain, akathisia, depression, anxiety, dysphoria, or panic, and usually a combination of more than one of these. Sensory "offs," like dystonic "offs," are very disabling. It is often the presence of one of these sensory and behavioral phenomena, more so than motoric parkinsonian or dystonic "offs," that drives the patient to take more and more levodopa, leading a few patients to develop an addictive relationship with dopaminergic medications, so-called dopamine dysregulation syndrome.

Treatment of Dyskinesias

Dyskinesias are involuntary movements and occur in two major forms—chorea and dystonia. Choreiform movements are irregular, nonrhythmic, unsustained dance-like movements that seem to flow from one body part to another and can appear like benign fidgeting. Dystonic movements are more sustained, twisting contractions. Many patients have a combination of choreiform and dystonic dyskinesias.

Peak-dose dyskinesias occur when the plasma concentrations of levodopa or dopamine agonists are at their peak, and the synaptic brain concentration of dopamine is too high. Reducing the individual dosage can resolve this problem of peak-dose dyskinesias. However, the patient may need to take more frequent doses at this lower amount. An alternative approach is to add amantadine, which suppresses the severity of dyskinesias, possibly because of its antiglutamatergic action. Start with a dose of 100 mg BID and increase up to 200 mg BID if necessary. Buspirone in dose up to 20 mg/day may also of benefit in treating dyskinesias in some patients.

Some patients may develop "off" dyskinesias. In the absence of so-called early morning "off" dystonia, which responds well to dopaminergic therapies, such patients are encouraged to consider DBS (see later under Surgical Therapy). Depending on their distribution within the body and the disability associated with them, dystonic dyskinesias can also be treated with local injections of a chemodenervation agent such as botulinum toxin. This treatment can be associated with a significant improvement in quality of life but will also weaken a muscle group and thereby can impact a patient's function, particularly if the dystonic movements are occurring in the hands.

Diphasic dyskinesias are dyskinesias that occur at the beginning and end of dose, not during the time of peak plasma and brain levels of dopaminergic medications. They tend to particularly affect the legs with a mixture of chorea and dystonia.

Dopamine Medication–Related Nonmotor Complications

In addition to motor features, a number of nonmotor problems can also occur as complications from dopaminergic therapy. Mental changes of psychosis, confusion, agitation, hallucinations, paranoid delusions, punding, impulse control disorders, and excessive sleeping are probably related to activation of dopamine receptors in anteroventral striatal regions, or nonstriatal regions, particularly the cortical and limbic structures.

Drug-induced hallucinations tend to be mild, visual in nature rather than auditory, and not frightening. Consideration should be given to reducing the total dose of dopaminergic medication to whatever degree is tolerable for the patient. A complete review of medications is indicated as well to identify any other symptomatic treatments that might be worsening encephalopathy, including benzodiazepines, anticholinergics, and opioids. Adjunctive treatment can begin with the addition of either quetiapine, starting with 25 mg at bedtime or pimavanserin (17 mg 1–2 times daily, although dosing may need to be reduced in patients taking CYP3A4 inhibitors). Pimavanserin is a newer drug that targets serotoninergic neurotransmission through its action as an inverse agonist and antagonist at 5HT-2A receptors. Unlike quetiapine, pimavanserin has prospective clinical trial data supporting its efficacy for treating psychosis in PD. Even so, the relative safety and easy dosing of quetiapine have led to its continued use as symptomatic treatment. Currently, a head-to-head trial is underway aimed at comparing the safety and efficacy of these two drugs in PD with psychosis. The dose should be increased steadily until the hallucinations are brought under control. If quetiapine or pimavanserin are ineffective or if the hallucinations are frightening, clozapine, a stronger antipsychotic that will not worsen motor features of PD, should be considered. As mentioned previously, the reason clozapine is not the first drug of choice in dopaminergic-induced hallucinations is because clozapine causes agranulocytosis in approximately 1% to 2% of patients. Patients must have their blood counts monitored weekly for this potential complication, and then discontinue the drug if leukopenia develops. Both

quetiapine and clozapine often cause drowsiness, so bedtime dosing is recommended.

If the psychosis is severe or if the patient is in an acute delirious state, hospitalization may be necessary, with immediate initiation of antipsychotic medications, and some reduction in anti-PD medication. These medications could even be withdrawn temporarily to overcome the psychosis, but this should be done stepwise over a 3-day period to avoid the neuroleptic malignant-like syndrome that could occur with sudden withdrawal of levodopa.

Dopamine agonist medications are associated with sleep attacks and impulse control disorders. Both of these issues can also be seen with levodopa but are much less common and less severe. Sleep attacks often manifest with a sudden wave of sleepiness that comes on with little warning and can be particularly dangerous for patients who are driving at the time. Impulse control disorders consist of behavioral changes such as compulsive gambling, shopping, and eating, and hypersexual behaviors. Not surprisingly, these changes can often have significant detrimental effects on family relationships. Both of these side effects are, to some degree, dose-dependent and typically necessitate reducing the dose of the dopamine agonists or stopping them altogether. Memantine, an NMDA receptor antagonist, has shown to be of benefit in some patients with dopamine agonist–induced impulse control disorders in PD.

Nondopaminergic Therapies

Nondopaminergic agents (**Table 61-7**) are useful to treat both motor and nonmotor symptoms of PD. Anti-muscarinic drugs have been used since the 1950s to treat parkinsonian tremor but have limited efficacy and frequently lead to cognitive impairment and hallucinations in the elderly population. For this reason, antimuscarinics should be avoided in patients older than 70 years. Furthermore, exposure to antimuscarinic drugs has been linked to a higher risk of developing freezing of gait in PD.

TABLE 61-7 ■ NONDOPAMINERGIC AGENTS

Parkinsonian motor symptoms:
Antimuscarinics (for tremor): trihexyphenidyl, benztropine
Antiglutamatergics (to reduce dyskinesia): amantadine
Muscle relaxants: cyclobenzaprine, diazepam, baclofen
Nonmotor symptom control:
Depression: selective and nonselective serotonin reuptake inhibitors, tricyclics, electroconvulsive therapy
Psychosis (hallucinations, paranoia): clozapine, quetiapine
Insomnia: mirtazapine, trazodone, quetiapine, zolpidem
REM sleep behavior disorder: clonazepam, melatonin
Excessive daytime sleepiness: modafinil
Dementia: donepezil, rivastigmine
Orthostasis: fludrocortisone, midodrine, droxidopa
Restless legs: dopamine agonists, levodopa, gabapentin, opioids

Depression is common in patients with PD, and often precedes the motor symptoms of PD. Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and other antidepressants including bupropion and tricyclic antidepressants are useful antidepressants. If insomnia is a problem for the patient, using an antidepressant that is also a soporific can be doubly advantageous: medications such as the tricyclic nortriptyline (which has fewer anticholinergic effects than amitriptyline) or an SNRI, such as low-dose mirtazapine, are good options. Recent data also suggest cognitive behavioral therapy (CBT) may improve PD depression more than existing medication-based approaches and can be delivered through telephone/virtual appointments.

Benzodiazepines including clonazepam are effective in reducing symptoms of dream enactment behavior attributable to rapid eye movement (REM) sleep behavior disorder (RBD). Nevertheless, they should be used with caution given their potential for cognitive side effects, increased risk of falls, rebound anxiety, and addictive potential.

Psychosis induced by levodopa and the dopamine agonists can usually be controlled by quetiapine and clozapine without worsening the parkinsonism.

Other antipsychotic agents—be they typical or atypical neuroleptic mediations—are more likely to worsen the parkinsonism; therefore, they should be avoided. Clozapine is more effective than quetiapine, but because clozapine treatment requires weekly blood cell counts due to risk of agranulocytosis, low-dose quetiapine should be tried first.

Insomnia in PD requires a detailed history to distinguish specific causes of impaired sleep that may require different management approaches. Common causes of insomnia in PD include restless legs, persistent tremor, nocturnal akinesia, dream enactment behavior, bladder dysfunction, and early morning motor "off" symptoms or dystonia. Both sleep-onset insomnia and sleep-maintenance insomnia occur in PD, though sleep-maintenance insomnia may be more common and troublesome. Sleep-onset insomnia is treated conventionally with low doses of hypnotics and sedating antidepressants such as low-dose mirtazapine or trazodone. In demented patients, low nighttime doses of the atypical antipsychotic quetiapine may be useful if neurobehavioral disturbances occur at night. Sleep maintenance insomnia is due often to motor dysfunction. Bradykinesia with difficulty moving in bed or adjusting bedclothes is a common cause of sleep maintenance insomnia in PD. Levodopa has a relatively short serum half-life and a common experience is loss of levodopa effect in the middle of the night with worsening bradykinesia and nocturnal arousals. Medication schedule manipulations such as instituting or increasing a bedtime dose of levodopa may be useful. Similarly, use at bedtime of extended-release levodopa preparations, adjunctive agents that lengthen the levodopa half-life, or dopamine agonists that possess relatively long half-lives may ameliorate this form of sleep-maintenance insomnia. An additional common source of sleep-maintenance insomnia in more advanced PD is bladder dysfunction, which in men with PD may coexist with prostate enlargement. Specifically, autonomic dysfunction leading to urinary frequency, urgency, and incontinence is common in more advanced PD. Conventional approaches to treating bladder dysfunction may be useful. Nocturnal use of gabapentin can also be of benefit in some patients.

RBD is common in patients with PD, DLB, and MSA and often precedes the appearance of these disorders. RBD manifests with complex, nonstereotyped dream-enactment behavior and is usually associated with vivid or frightening dream content. Normally, dreaming in REM sleep is associated with muscle paralysis to all skeletal muscles outside of the eyes

and diaphragm. This normal REM-associated muscle paralysis is reduced in RBD. RBD in PD, as in other settings, does not seem to cause daytime sleepiness but can result in injuries or disrupt bed partner rest. Infrequent and mild episodes of RBD probably do not require treatment but more severe episodes can be of dangerous to the bed partner or patient. Withdrawal of antidepressants that can precipitate or exacerbate RBD may be worthwhile. Safety measures within the sleeping room may be necessary. These can include use of separate beds, placement of mattresses on the floor, efforts to sleep on the first floor, and removing dangerous objects from the bedroom. The mainstay of medical treatment is use of hour-of-bedtime clonazepam (0.5–2 mg), which appears to be effective and is tolerated well by the majority of patients. Melatonin—though less effective—may be tried first and can be combined with clonazepam. In some patients, cholinesterase inhibitors may also help RBD symptoms. Dopaminergic therapy probably has little or no effect on RBD.

Periodic leg movements of sleep (PLMS) and restless legs syndrome (RLS) are estimated to be twice as common in PD as in matched populations. Despite this association, the relationship between PD and RLS is complex. While both RLS and PLMS may contribute to insomnia in PD, one study has shown no significant worsening in daytime sleepiness seen in PD patients with RLS compared to those without. No evidence exists that RLS predisposes patients to develop PD later in life. Though dopaminergic dysfunction may play a role in both PD and RLS, imaging studies of subjects with RLS without PD have not shown convincing evidence of a nigrostriatal dopaminergic deficit. These findings suggest that RLS may not in fact be a precursor to the cardinal motor symptoms of PD and may not be a "secondary" symptom of PD, but rather a separate disease entity that can be exacerbated by PD. Assessment and management of RLS in PD involve an evaluation for iron deficiency and iron supplementation when appropriate and use of low doses of dopaminergic agents such as long-acting dopamine agonists or L-dopa. In patients with poor or complicated responses to dopaminergic agents, gabapentin, clonazepam, or low-dose opiates may be useful.

Fatigue is an increasingly noted nonmotor symptom in PD of unclear etiology but has shown to be correlated with poor sleep and depression. Clinicians should attempt to differentiate fatigue from excessive daytime sleepiness, the latter of which is often due to poor quality of sleep at night or

adverse effects associated with excess dopaminergic medications, necessitating a different approach to diagnostic work-up and management. Many patients describe fatigue as their first presenting symptom. Management should be aimed at underlying causes, such as depression. If needed, medications such as modafinil or nonprescription therapies such as liberalizing caffeine consumption can provide some benefit.

Mild cognitive symptoms can be seen in some PD patients with early disease and worsen with increasing disease duration. Early features typically include impaired attention, verbal memory, and executive dysfunction summarized as a subcortical-frontal syndrome. Dementia in PD is often associated with the development of significant visuospatial impairments, memory difficulties, and hallucinations—the latter of which may also be seen in response to dopaminergic or anticholinergic drugs. PDD and DLB patients are at a particularly high risk for developing delirium, either in association with new medications or because of underlying acute medical illnesses. Symptoms of delirium often involve profound disorientation and psychosis that can sometimes take weeks to resolve. Cholinergic deficits affecting subcortical and cortical structures are thought to play a significant role in PD cognitive impairment. Cholinesterase inhibitors, including donepezil and rivastigmine, are useful therapies for improving cognitive symptoms at all stages of PD. They are, however, limited in their efficacy due to limited central nervous system (CNS) bioavailability.

Orthostatic hypotension is common in PD and can be due to the disease itself or to dopaminergic medications, the latter of which lower blood pressure. It can also represent an early manifestation of an atypical parkinsonian condition, namely MSA. Fludrocortisone, midodrine, or droxidopa can overcome this symptom to some extent.

Constipation is common in PD. It may be further aggravated by anticholinergic medications. Besides changing dietary habits by increasing intake of more fiber and dried fruits, polypropylene glycol, or lubiprostone can be effective. For those who have bloating because of suppression of peristalsis when they are “off,” keeping them “on” with levodopa can be beneficial.

Diet

There is emerging evidence that dietary pattern may modulate the course of PD, including at the prodromal level. A recent analysis of the Nurses’ Health

Study found that adherence to a Mediterranean diet was inversely associated with the presence of prodromal PD features, including constipation, excessive daytime sleepiness, and depression. Adherence to the Mediterranean diet is also associated with lower risk of PD. These studies are consistent with clinical research models highlighting the relevance of gut-brain axis functions in PD.

Exercise and Physical Activity

An active exercise program encourages patients to have ownership over their own care, allows muscle stretching and full range of joint mobility, increases aerobic capacity, muscle strength, motor skills, and improves a patient's mental attitude toward fighting the disease. Preclinical studies have shown that exercise slows the degeneration of dopamine neurons following local toxin, theoretically because exercise leads to an increase in brain neurotropic factors. There is also increasing evidence to suggest that sedentary behaviors, irrespective of the amount of formal exercise one performs, may have a deleterious impact on not only physical condition but also metabolic functions. These changes increase the risk for frailty among patients with PD subjects leading a decline in health. Encouraging patients to reduce the amount of time they spend seated each day is a good way to empower patients to regulate their own PD prognosis.

A regular routine of physical exercise, be it cardiovascular training or weight-based exercises, should be implemented as soon as the diagnosis is made, but is useful in all stages of disease. Stretching exercises may help to compensate for the tendency of patients to have a reduced range of motion. In moderate-to-advanced stages of PD, formal physical therapy is more valuable by keeping the joints from becoming frozen, and by providing guidance how best to remain independent in mobility, particularly with gait training and prevent injurious falls. One of the nonmotor symptoms of PD is the tendency toward apathy and conservative decision making with decreased motivation. Encouraging activity may help fight these symptoms.

Surgical Therapy

DBS surgery for PD was approved by the US FDA in 2002 and is associated with significant gains in quality of life for PD patients who are good surgical candidates. DBS surgery is typically indicated for PD patients with difficult-to-manage motor complications (fluctuations and/or dyskinesias) or with

medication-refractory parkinsonian tremor. DBS involves placement of an impulse pulse generator (IPG) in the chest that looks much like a pacemaker. A lead from the IPG is tunneled under the skin surface to a specific region of the brain, either the STN or the GPi.

When stimulation is optimized, patients will experience an "on" state without disabling "off" features. Patients are also able to reduce their dose of dopaminergic medications, and in this way, are able to reduce dyskinesias as well. With the exception of tremor, motor features that generally do not improve with dopaminergic medications (eg, postural instability, other axial motor features, some gait freezing) also do not improve with DBS. DBS typically has little effect on the nonmotor features of PD unless they are directly related to on-off fluctuations seen with dopaminergic medications. Currently, DBS for PD is delivered in an "open loop" context, meaning that the type and intensity of stimulation delivered to each electrode is programmed and occurs constitutively once a stimulation paradigm is turned on in the IPG. The next important advance in DBS care will be the testing and validation of "closed loop" systems that can tailor stimulatory inputs to the brain based on DBS-detection of local neurophysiologic biomarkers that fluctuate in real-time depending on the neural correlates of relevant volitional movements.

Patients with significant speech, gait, depression with suicidal ideation or cognitive difficulties are usually not good candidates for DBS, not only because these symptoms do not respond to stimulation, but also because in some patients, these features may become notably worse after DBS, including the risk of suicide. The selection of appropriate candidates for DBS is often best done under the guidance of an experienced movement disorder neurologist. DBS is not suggested for patients with atypical parkinsonian conditions since the majority of these motor features do not respond to dopaminergic medications.

Focused ultrasound (FUS) was FDA-approved in 2018 for the treatment of parkinsonian tremor; it delivers a radiofrequency ablation to the STN and can be directed to other structures as well. FUS does not involve anesthesia and may be an appropriate therapy for those surgical candidates who cannot or do not wish to undergo conventional DBS surgery. One relative advantage is that unlike DBS, FUS does not necessitate future IPG replacements or frequent outpatient programming sessions. A disadvantage though is that FUS is permanent and nonprogrammable; compared to DBS, this limits FUS's

ability to be titrated to an individual's most disabling symptoms as the disease advances.

CARE CONSIDERATIONS

No two patients with PD are alike in their clinical presentation or their rate of disease progression. In addition, not all motor features of PD have the same clinical or prognostic significance. Gait and cognitive difficulties, for example, play a more significant role in patient autonomy, disease staging, and overall disability. Different motor phenotypes in PD have been distinguished, such as tremor-predominant or imbalance-predominant (so-called postural instability and gait difficulties [PIGD]) subtypes. PIGD features, however, tend to be less responsive to common medication strategies including dopaminergic therapies and can worsen at variable rates for reasons that appear to have little to do with dopaminergic neurotransmission.

There is an increasing body of literature implicating nondopaminergic or extranigral brain changes seen with aging as a mediator of disease progression in PD. Cerebral amyloid deposition and a decline in cerebrovascular integrity occur as part of brain aging. In individuals without PD, when these progressive changes exceed a critical threshold, patients who develop clinical symptoms are diagnosed with specific disorders including AD and vascular dementia. When these changes are milder, however, most people are able to use existing neuronal reserve to compensate and prevent the development of clinically significant disability. In PD, where the severe loss of striatal dopaminergic neurons is seen from the earliest stage of diagnosis, neuronal compensation mechanisms are relatively impaired, leading to the development of clinically significant disease features in the presence of even low levels of age-related comorbid brain pathologies (**Figure 61-2**). Longitudinal studies of PD have suggested that the severity of medical comorbidities is a chief determinant of progression to a disability, dementia, and death. For this reason, we recommend that all patients with PD attend carefully to common chronic medical conditions including cardiovascular risk factor reduction through physical exercise, appropriate diet, and medication management of comorbidities like hypertension and diabetes mellitus. The longitudinal role

of a geriatrician or primary care doctor is hence indispensible for individuals with PD.

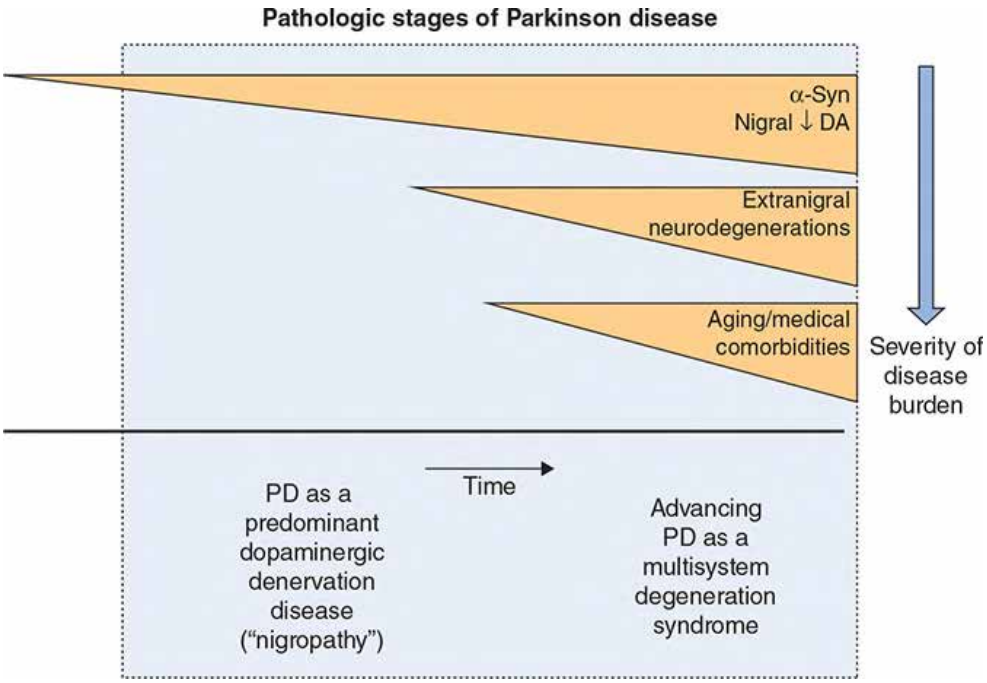

FIGURE 61-2. Schematic diagram depicting the natural history of progressive changes in Parkinson disease (PD) attributable to both dopaminergic and nondopaminergic ("extranigral") pathologies. With advancing disease duration, medical comorbidities and other neuropathologies exert additive/synergistic effects on overall motor and nonmotor disease burden in PD.

Recent data suggest that specialist care through a neurologist specifically is associated with reduced mortality in PD. Neurologists who are familiar with PD can be instrumental in making medication adjustments over time and can serve as an access point for newly approved medications and for DBS once patients have progressed from early-stage to mid-stage PD characterized by motor fluctuations. Multidisciplinary care models for delivering rehabilitative services have been trialed against standard physical therapy in carefully controlled settings and have been shown to improve quality of life. Home-based exercise programs have also been shown to improve off-state motor function in PD in recent randomized trials. Developing reimbursement models to initiate, sustain, and broaden the impact of these clinical trial findings is an important priority for PD patients, advocates, and clinicians. Patients with late-stage PD or with significant disability from atypical parkinsonian conditions often benefit from

consultations with palliative care physicians. This is particularly helpful for later-stage patients who are either confined to a wheelchair or who are considering nursing home placement because of inability to perform activities of daily living. Progressive dysphagia can be seen in some patients with advanced PD or atypical parkinsonian conditions and may necessitate a discussion about feeding tube placement. Discussing goals of care with patients at risk for loss of autonomy can empower patients to have control over a difficult disease.

CONCLUSION

Parkinsonian conditions including PD are common sources of disability in older individuals and are typically responsive to a wide variety of treatments. Longitudinal care with skilled geriatric and neurology providers is perhaps the most important step to ensure an individualized medical approach that prioritizes quality of life.

ACKNOWLEDGMENTS

We wish to thank Dr. Stanley Fahn, the previous author of this chapter.

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Chapter

62

Cerebrovascular Disease

Nirav R. Bhatt, Bernardo Liberato

Although stroke is the fifth leading cause of death in the United States, it remains the single most important cause of disability. Ischemic stroke and transient ischemic attack (TIA) are parts of the same spectrum, and their diagnosis usually implies inadequate blood flow to variable areas in the brain, brain stem, or cerebellum. Many varied pathologic processes lead to either occlusion of an extra- or intracranial artery or vein causing ischemic stroke or TIA, or rupture of an intracranial artery causing hemorrhagic stroke. A precise clinical diagnosis with appropriate localization strategies and determination of likely etiology are key to establishing appropriate treatment in the acute phase as well as planning the most adequate secondary prevention according to best practice and evidence available (**Figures 62-1** and **62-2**). This chapter focuses on identifying the pathology, clinical features, and treatment strategies that allow for the proper care of stroke victims, with a particular emphasis in the older population.

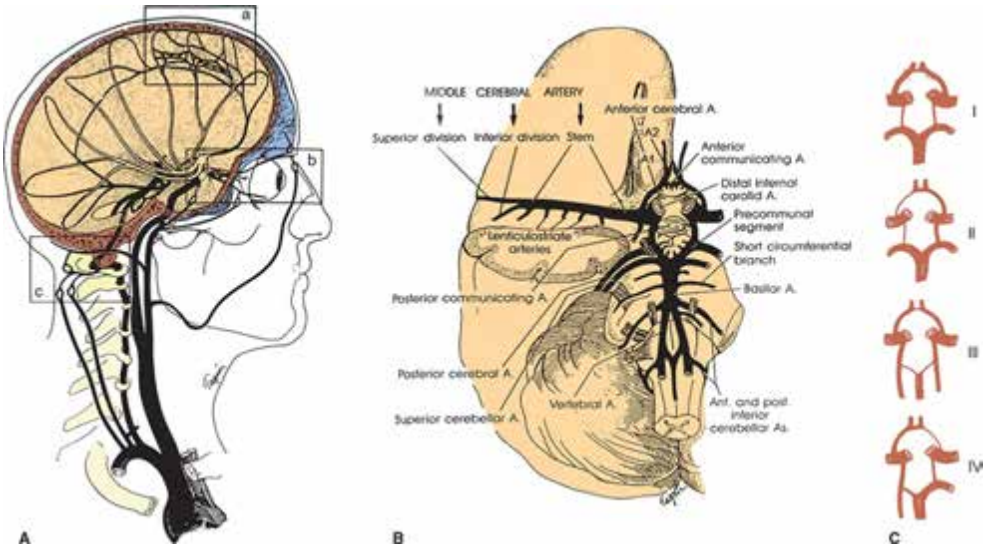

FIGURE 62-1. **A.** Arrangement of the major arteries of the right side carrying blood from the heart to the brain. Also shown are vessels of collateral circulation that may modify the effects of cerebral ischemia (a, b, and c). Not shown is the circle of Willis, which also provides a source for collateral circulation. *a*. The anastomotic channels between the distal branches of the anterior and middle cerebral artery, termed borderzone or watershed anastomotic channels. Note that they also occur between the posterior and middle cerebral arteries and the anterior and posterior cerebral arteries. *b*. The anastomotic channels occurring through the orbit between branches of the external carotid artery and ophthalmic branch of the ICA. *c*. Wholly extracranial anastomotic channels between the muscular branches of the ascending cervical arteries and muscular branches of the occipital artery that anastomose with the distal VA. Note that the occipital artery arises from the external carotid artery, thereby allowing reconstitution of flow in the vertebral from the carotid circulation. **B.** Diagram of the brain stem, cerebellum, inferior right frontal lobe, and temporal lobe transected. Principal branches of the vertebral basilar arterial system are pictured. Small branches of the vertebral and basilar artery that penetrate the medulla and pons are not pictured. The stem of the middle cerebral artery with its small, deep-penetrating lenticulostriate arteries and the circle of Willis with its small, deep-penetrating branches, are shown. **C.** Roman numerals I, II, III, and IV represent some of the possible variations of the circle of Willis caused by atresia of one or more of its arterial components. (A, Reproduced with permission from CM Fisher, MD.)

EPIDEMIOLOGY

Stroke is a leading cause of mortality and morbidity in the United States. In 2018, according to statistics from the Centers for Disease Control and Prevention (CDC) and American Heart Association (AHA), one in every six deaths from cardiovascular disease (CVD) was due to stroke. In the United States, someone has a stroke every 40 seconds and every 4 minutes one death is due to a stroke. That burden is greater in the older population since stroke incidence and mortality increase with age which is reflected in the fact that

approximately 66% of people hospitalized for a stroke will be 65 years or older. Stroke incidence becomes more evident in the aging population and its impact on greater longevity is demonstrated by the fact that 17% of all strokes will occur in patients 85 years and older. According to the AHA, stroke incidence is expected to more than double by 2050 with the greater increase in the population 75 years and older, underscoring the need for greater awareness and knowledge about stroke among those health professionals involved in the care of that group of patients. As in CVD in general, incidence by gender shows a predominance in men in the 60- to 79-year-old age group while women are slightly more affected in the 80 years and older age group.

Learning Objectives

- Understand the pathophysiology and clinical presentations of different types of strokes, and specific symptoms and signs associated with the involvement of each major cerebral artery and location of infarction.
- Learn about the state-of-the-art neuroimaging techniques and other tests available to evaluate and diagnose stroke.
- Acquire latest information about the pharmacology, specific indications, and adverse effects of various drugs and surgical interventions available to treat different stages and types of strokes.
- Learn about the results of pivotal clinical trials forming the basis for latest guidelines to treat different types of strokes.
- Understand the rationale for various preventive strategies commonly used for different types of strokes.

Key Clinical Points

1. **It is important to identify the pathophysiology in each stroke patient, as it drives selection of the best treatment choice.**
2. **Magnetic resonance imaging (MRI) brain scans with diffusion-weighted imaging (DWI) are the best way of identifying cerebral infarcts acutely and accurately. While computed tomography (CT) scan is less sensitive to detect recent infarcts of less than 12 hours, it is the initial method of choice in the hyperacute**

setting since most acute treatment decisions can be made based on its results.

3. Imaging of the cervical and cerebral large arterial system with CT angiography (CTA) or MR angiography (MRA) should be urgently performed to assess the arterial system. CTA offers the best resolution and suffices for acute decision making.
4. Recombinant tissue plasminogen activator (rt-PA) initiated within 4.5 hours of symptom onset has been shown to reduce stroke-related disability. In general, benefits of rt-PA in older adults with stroke outweigh risks.
5. Mechanical thrombectomy for selected patients with large vessel occlusion is highly effective in reducing morbidity and mortality and is supported by Level Ia evidence.
6. Stroke carries a worse prognosis in older individuals overall; however, both intravenous rt-PA and mechanical thrombectomy have been found effective in this population and should be strongly considered when clinically appropriate.
7. Efficacy of carotid endarterectomy and carotid stenting for symptomatic disease with more than 70% stenosis is high and should be performed when clinically indicated. Clinical, demographic, and technical aspects should be considered when choosing the best method.
8. Oral anticoagulation is highly effective in preventing stroke in the setting of atrial fibrillation (AF) especially in the older population. Direct oral anticoagulants (DOACs) are used increasingly and present a better safety profile compared to warfarin.
9. Antiplatelet monotherapy continues to be the cornerstone for secondary prevention of noncardioembolic strokes, with dual antiplatelet therapy reserved for a short course in high-risk TIA/minor stroke. Dual antiplatelet therapy can also be considered in cases of strokes secondary to moderate to severe stenosis seen in intracranial atherosclerotic disease (ICAD).

Overall, prognosis is worse following a stroke in the older adults, and is associated with a higher risk-adjusted mortality, greater disability, longer hospitalization, and reduced chances of being discharged home after an admission to a hospital. However, despite an overall worse prognosis in older adults compared to younger age groups, more aggressive therapeutic and multitargeted secondary prevention strategies have resulted in more favorable stroke outcomes in the older population, including a decline in the crude stroke death rate. Importantly, these promising outcomes are seen across all older age groups including those 85 years and older.

ISCHEMIC STROKE OR TIA SUBTYPE

Pathophysiology and Clinical Presentation

It is important to recognize that ischemic stroke and TIA share the same pathological causation, such that efforts to define the underlying arterial pathophysiology of the ischemic stroke or TIA should be the focus of a treatment strategy. The term "cerebral vascular accident" or "CVA" should be discarded, and the terms "TIA" and "ischemic stroke" should be used with further characterization of the subtype of stroke according to its likely etiology, a definition that goes beyond nomenclature and carries implication when choosing the most appropriate therapeutic and prevention strategies. Despite more recent challenges to the classic etiologic categorization, in clinical practice, ischemic stroke/TIA can still be conveniently divided into five subtypes: (1) large artery atherosclerosis, including intra- and extracranial (25%); (2) small-vessel lacunar (25%); (3) cardioembolic (20%); (4) cryptogenic (25%); and (5) other (5%), such as arterial dissection, venous sinus occlusion, and arteritis. The prevalence of various ischemic strokes or TIA subtypes vary across different ethnic population groups. Specifically, African-Americans are at a relatively higher risk of having a lacunar stroke and atherothrombotic stroke, particularly that portion of atherothrombotic stroke caused by intracranial arterial atherosclerosis. Likewise, Asians have a higher frequency of intracranial arterial atherosclerotic disease. Conversely, extracranial atherosclerotic disease shows a predilection for Caucasians.

When transient or sustained focal neurologic symptoms or signs develop in a patient, history, general physical examination, and neurologic examination are important to diagnose stroke, localize the affected territory of the brain or spinal cord and the corresponding vascular distribution, and even suggest the pathophysiologic subtype. Strokes and TIAs require not only immediate imaging of the brain parenchyma but also noninvasive assessment of the extra- and intracranial arterial vasculature focusing on the arteries supplying the suspected symptomatic arterial territory. CT scan of the head is the neuroimaging modality of choice for the hyperacute evaluation of a suspected stroke, mostly to rule out other pathologies that could mimic an ischemic stroke, particularly hemorrhagic stroke. CT has nearly perfect sensitivity for acute intracerebral hemorrhage (ICH) (approaching 100%) and good sensitivity for acute subarachnoid hemorrhage (SAH) (~ 90%). Sensitivity for ischemic infarction in the acute setting is, however, much lower. Ischemic infarction may not be demonstrable by noncontrast CT for 12 to 14 hours after symptom onset. In addition, infarction involving only the cortical surface supratentorially, or infarction in the posterior fossa, can often be obscured by bone artifact. Therefore, the main reason for obtaining a head CT scan in the acute phase is to exclude intracranial hemorrhage and detect early signs of ischemia as well as define the extent of early ischemic changes. In the acute phase, vascular imaging, usually with CTA of head and neck, is mandatory to look for vessel pathology that could be responsible for the ischemic changes suggested by the neurological examination. Only with the precise knowledge of parent vessel pathology, or its absence, can therapy be properly considered. Also, given the well-defined role for mechanical thrombectomy (MT) in select patients with a large vessel occlusion (LVO) demonstrated on CTA, such imaging modality is essential part of the acute stroke evaluation. Even though MRI is the gold standard for identification of an ischemic stroke, its role in the hyperacute evaluation is limited given the longer examination time. Brain MRI, however, is indicated for most ischemic stroke patients early on after hospital admission, and other vascular imaging modalities that can be considered include a combination of MRA, carotid duplex ultrasound, and transcranial Doppler (TCD) (see **Figure 62-2**). A combination of these imaging modalities is often necessary before a definite etiology can be determined and an appropriate preventive strategy can be devised. The following sections outline each of the four ischemic stroke and TIA subtypes, and intracerebral and SAH, in terms of their pathophysiologic

process and clinical presentation. A discussion of a focused diagnostic approach to confirm that clinically presumed diagnosis follows. Based on the particular TIA or stroke subtype and its causative pathologic process, acute, subacute, and preventive management strategies can then be addressed.

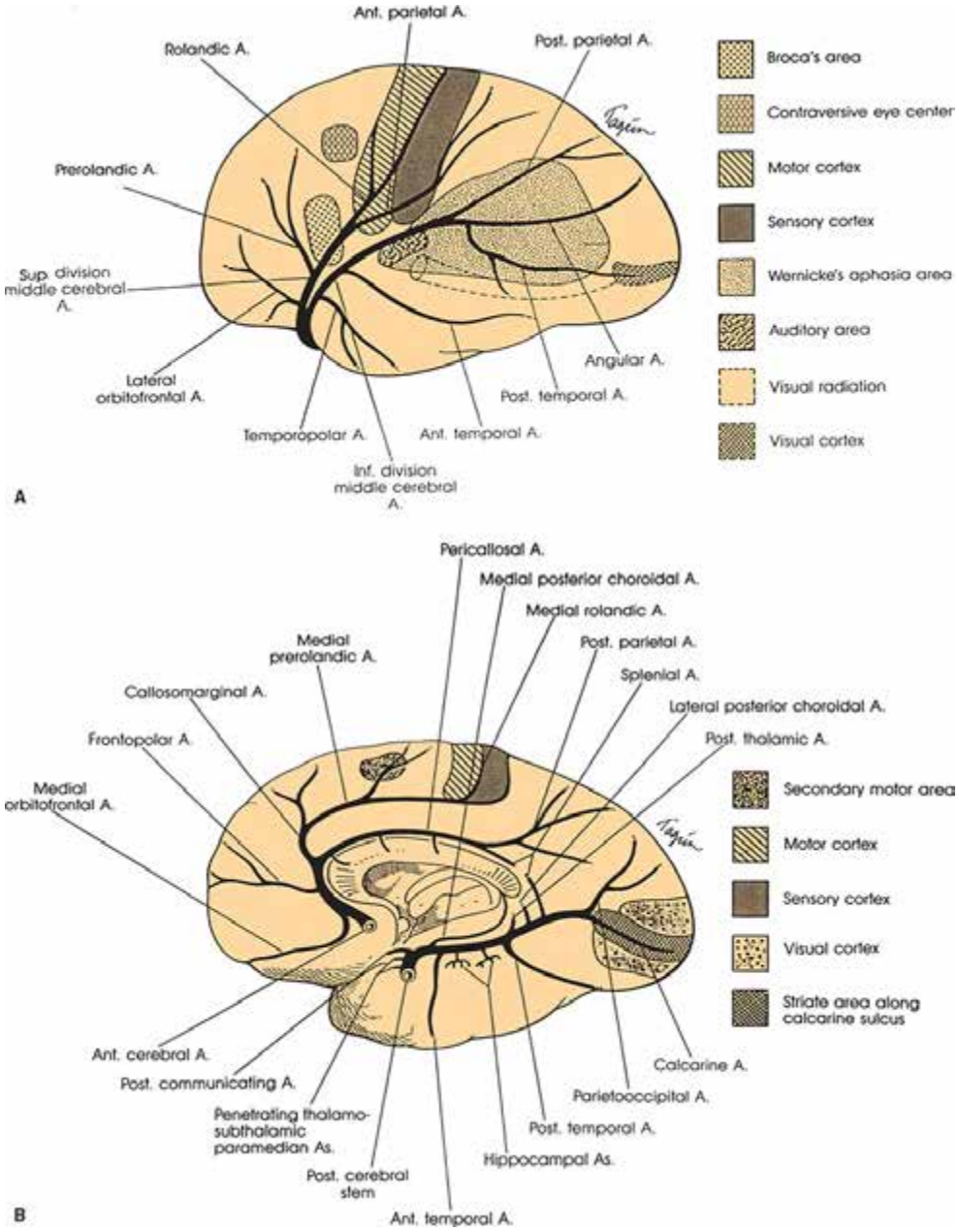

FIGURE 62-2. **A.** Diagram of a cerebral hemisphere, lateral aspect, showing the branches and distribution of the middle cerebral artery and the principal regions of cerebral localization. Note the bifurcation of the middle cerebral artery into a superior and inferior division. **B.** Diagram of a cerebral hemisphere, medial aspect, showing the branches and distribution of the anterior

cerebral artery and the principal regions of cerebral localization. (Reproduced with permission from CM Fisher, MD.)

Definition

The classical definition of a TIA is that of sudden focal neurological symptoms lasting less than 24 hours. This definition is purely a clinical one and does not take into consideration neuroimaging findings on MRI after an acute ischemic episode. The more complete definition establishes that if an acute focal neurological dysfunction shows an imaging correlate (DWI positivity on MRI) it is considered a stroke regardless of the persistence or not of the initial focal symptoms. In that case, it is called a minor stroke. For the majority of patients with persistent focal deficits beyond 24 hours (clinical stroke), neuroimaging will show a correlated lesion on MRI. The semantics do not carry great relevance for the diagnostic work-up for these patients since both a TIA and a stroke demand urgent and complete investigation. Its major importance lies in the fact that TIA or minor strokes carry an overall risk of about 10% for recurrent stroke in the following 90 days, the greatest risk being in the first 48 hours after its occurrence. This risk varies with the type of underlying vessel pathology, neuroimaging, and clinical features of the event. Based on clinical features, scales have been created to help stratify the short-term risk of recurrence of a TIA. The most commonly used scale is the ABCD2 scale where clinical features, when present, receive points and the sum of them will translate into higher risk of recurrence. The clinical features and the points assigned to each are as follows:

1. **A**ge > 60 years – 1 point
2. **B**lood pressure on presentation > 140/90 – 1 point
3. **C**linical features of the TIA—isolated speech (1 point), unilateral weakness (2 points)
4. **D**uration—< 10 min – 0 points; 10–59 min – 1 point; ≥ 60 min – 2 points
5. History of **D**iabetes—1 point

The sum of the points yields the final score and a score ≥ 4 represents an elevated risk for recurrence. This score was used in many acute prevention trials as criteria for enrolling patients (see below). The early time frame for