Chapter 28: Pharmacologic Management of Parkinsonism & Other Movement Disorders

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CASE STUDY

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A 76-year-old retired banker complains of a shuffling gait with occasional falls over the last year. He has developed a stooped posture, drags his left leg when walking, and is unsteady on turning. He remains independent in all activities of daily living, but he has become more forgetful and occasionally sees his long-deceased father in his bedroom. Examination reveals hypomimia, hypophonia, a slight rest tremor of the right hand and chin, mild rigidity, and impaired rapid alternating movements in all limbs. Neurologic and general examinations are otherwise normal. What is the likely diagnosis and prognosis?

The patient is started on a dopamine agonist, and the dose is gradually built up to the therapeutic range. Was this a good choice of medications?

Six months later, the patient and his wife return for follow-up. It now becomes apparent that he is falling asleep at inappropriate times, such as at the dinner table, and when awake, he spends much of the time in arranging and rearranging the table cutlery or in picking at his clothes. To what is his condition due, and how should it be managed? Would you recommend surgical treatment?

Several types of abnormal movement are recognized. **Tremor** consists of a rhythmic oscillatory movement around a joint and is best characterized by its relation to activity. Tremor at rest is characteristic of parkinsonism, when it is often associated with rigidity and an impairment of voluntary activity. Tremor may occur during maintenance of sustained posture (postural tremor) or during movement (intention tremor). A conspicuous postural tremor is the cardinal feature of benign essential or familial tremor. Intention tremor occurs in patients with a lesion of the brainstem or cerebellum, especially when the superior cerebellar peduncle is involved; it may also occur as a manifestation of toxicity from alcohol or certain other drugs.

Chorea consists of irregular, unpredictable, involuntary muscle jerks that occur in different parts of the body and impair voluntary activity. In some instances, the proximal muscles of the limbs are most severely affected, and because the abnormal movements are then particularly violent, the term *ballismus* has been used to describe them. Chorea may be hereditary or acquired and may occur as a complication of a number of general medical disorders and of therapy with certain drugs.

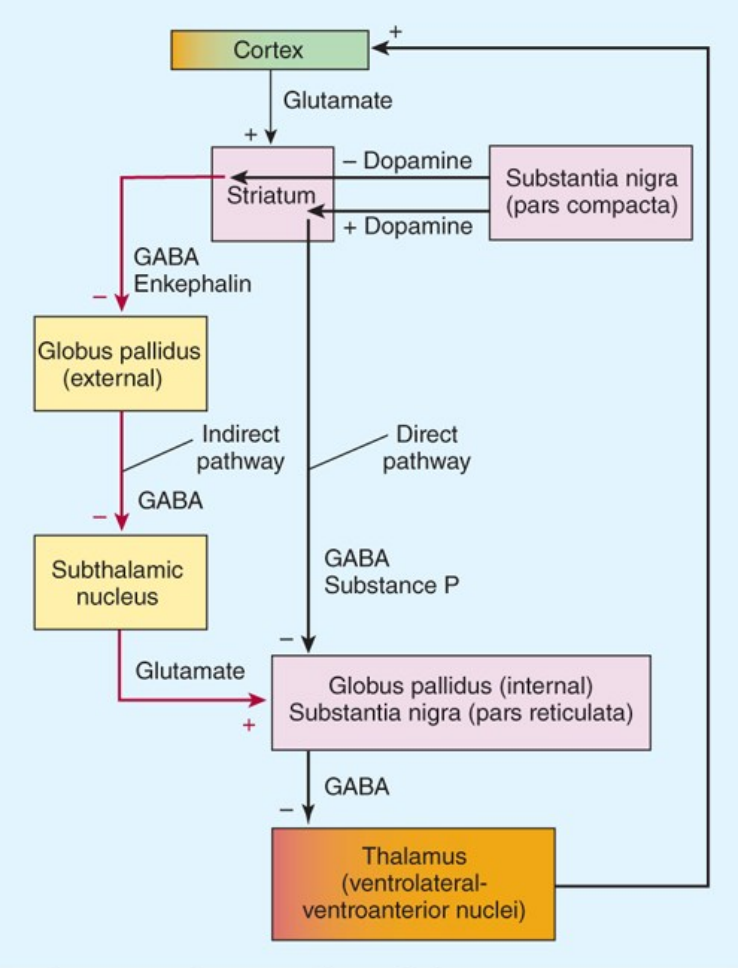
Abnormal movements may be slow and writhing in character **(athetosis)** and, in some instances, are so sustained that they are more properly regarded as abnormal postures **(dystonia).** Athetosis or dystonia may occur with perinatal brain damage, with focal or generalized cerebral lesions, as an acute complication of certain drugs, as an accompaniment of diverse neurologic disorders, or as an isolated inherited phenomenon of uncertain cause known as isolated generalized torsion dystonia or dystonia musculorum deformans. Various genetic loci have been reported depending on the age of onset, mode of inheritance, and response to dopaminergic therapy. The physiologic basis is uncertain, and treatment is unsatisfactory. Patients with dystonia commonly have psychiatric complications, such as depression, that affect the quality of life. These may be secondary to the dystonia or a nonmotor manifestation of the underlying disorder.

Tics are sudden coordinated abnormal movements that tend to occur repetitively, particularly about the face and head, especially in children, and can be suppressed voluntarily for short periods of time. Common tics include repetitive sniffing or shoulder shrugging. Tics may be single or multiple and transient or chronic. Gilles de la Tourette syndrome is characterized by chronic multiple tics; its pharmacologic management is discussed at the end of this chapter.

Many of the movement disorders have been attributed to disturbances of the basal ganglia. The basic circuitry of the basal ganglia involves three interacting neuronal loops that include the cortex and thalamus as well as the basal ganglia themselves (Figure 28–1). However, the precise function of these anatomic structures is not yet fully understood, and it is not possible to relate individual symptoms to involvement at specific sites.

FIGURE 28–1

Functional circuitry between the cortex, basal ganglia, and thalamus. The major neurotransmitters are indicated. In Parkinson disease, there is degeneration of the pars compacta of the substantia nigra, leading to overactivity in the indirect pathway (red) and increased glutamatergic activity by the subthalamic nucleus.



PARKINSONISM & PARKINSON DISEASE

Parkinsonism is characterized by a combination of rigidity, bradykinesia, tremor, and postural instability that can occur for a variety of reasons but is usually idiopathic (Parkinson disease or paralysis agitans). Bradykinesia should be present before a diagnosis of Parkinson disease is made. Focal dystonic features may be present. Cognitive decline occurs in many patients as the disease advances. Other nonmotor symptoms include affective disorders (anxiety or depression); confusion, cognitive impairment, or personality changes; apathy; fatigue; abnormalities of autonomic function (eg, sphincter or sexual dysfunction, dysphagia and choking, sweating abnormalities, sialorrhea, or disturbances of blood pressure regulation); sleep disorders; and sensory complaints or pain. The disease is incurable, is generally progressive, and leads to increasing disability with time, but pharmacologic treatment may relieve motor symptoms and improve the quality of life for many years. Patients with Parkinson disease may develop hyposmia, constipation, depression, anxiety, or rapid-eye-movement (REM) sleep behavior disorder in a preclinical phase before onset of the motor

disturbance.

Parkinsonism may also have a hereditary basis, may follow exposure to various toxins (eg, manganese dusts, carbon disulfide, carbon monoxide), may develop after multiple subcortical white-matter infarcts or recurrent head injury (as in boxers), and may occur in association with other neurologic disorders.

Pathogenesis

The pathogenesis of Parkinson disease seems to relate to a combination of impaired degradation of proteins, intracellular protein accumulation and aggregation, oxidative stress, mitochondrial damage, inflammatory cascades, and apoptosis. Studies in twins suggest that genetic factors are important, especially when the disease occurs in patients under age 50. Recognized genetic abnormalities account for 10–15% of cases. Mutations of the α-synuclein gene at 4q21 or duplication and triplication of the normal synuclein gene are associated with Parkinson disease, which is now widely recognized as a *synucleinopathy*. Mutations of the leucine-rich repeat kinase 2 (*LRRK2*) gene at 12cen, and the *UCHL1* gene may also cause autosomal dominant parkinsonism. Mutations in the *parkin* gene (6q25.2–q27) cause early-onset, autosomal recessive, familial parkinsonism, or sporadic juvenile-onset parkinsonism. Several other genes or chromosomal regions have been associated with familial forms of the disease. Environmental or endogenous toxins may also be important in the etiology of the disease. Epidemiologic studies reveal that cigarette smoking, coffee, anti-inflammatory drug use, and high serum uric acid levels are protective, whereas the incidence of the disease is increased in those working in teaching, health care, or farming, and in those with lead or manganese exposure or with vitamin D deficiency.

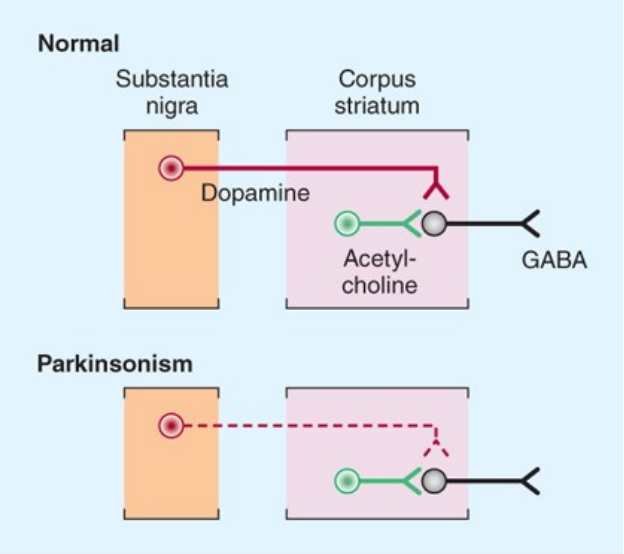
The finding of Lewy bodies (intracellular inclusion bodies containing α-synuclein) in fetal dopaminergic cells transplanted into the brain of parkinsonian patients some years previously has provided some support for suggestions that Parkinson disease may represent a prion disease.

Staining for α-synuclein has revealed that pathology is more widespread than previously recognized, developing initially in the olfactory nucleus and lower brainstem (stage 1 of Braak scale), then the higher brainstem (stage 2), the substantia nigra (stage 3), the mesocortex and thalamus (stage 4), and finally the entire neocortex (stage 5). The motor features of Parkinson disease develop at stage 3 on the Braak scale.

The normally high concentration of dopamine in the basal ganglia of the brain is reduced in parkinsonism, and pharmacologic attempts to restore dopaminergic activity with levodopa and dopamine agonists alleviate many of the motor features of the disorder. An alternative but complementary approach has been to restore the normal balance of cholinergic and dopaminergic influences on the basal ganglia with antimuscarinic drugs. The pathophysiologic basis for these therapies is that in idiopathic parkinsonism, there is a loss of dopaminergic neurons in the substantia nigra that normally inhibit the output of GABAergic cells in the corpus striatum (Figure 28–2). Drugs that induce parkinsonian syndromes either are dopamine receptor antagonists (eg, antipsychotic agents; see Chapter 29) or lead to the destruction of the dopaminergic nigrostriatal neurons (eg, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine [MPTP]; see below). Various other neurotransmitters, such as norepinephrine, are also depleted in the brain in parkinsonism, but these deficiencies are of uncertain clinical relevance.

FIGURE 28–2

Schematic representation of the sequence of neurons involved in parkinsonism. A simplified version of the involved circuitry is shown. **Top:** Dopaminergic neurons (red) originating in the substantia nigra normally inhibit the GABAergic output from the striatum, whereas cholinergic neurons (green) exert an excitatory effect. **Bottom:** In parkinsonism, there is a selective loss of dopaminergic neurons (dashed, red).



Source: Bertram G. Katzung, Todd W. Vanderah: Basic & Clinical Pharmacology, Fifteenth Edition

LEVODOPA

Dopamine does not cross the blood-brain barrier and if given into the peripheral circulation has no therapeutic effect in parkinsonism. However, (–)-3-(3,4-dihydroxyphenyl)-L-alanine (levodopa), the immediate metabolic precursor of dopamine, does enter the brain (via an L-amino acid transporter, LAT), where it is decarboxylated to dopamine (see Figure 6–5). Several noncatecholamine dopamine receptor agonists have also been developed and may lead to clinical benefit, as discussed in the text that follows.

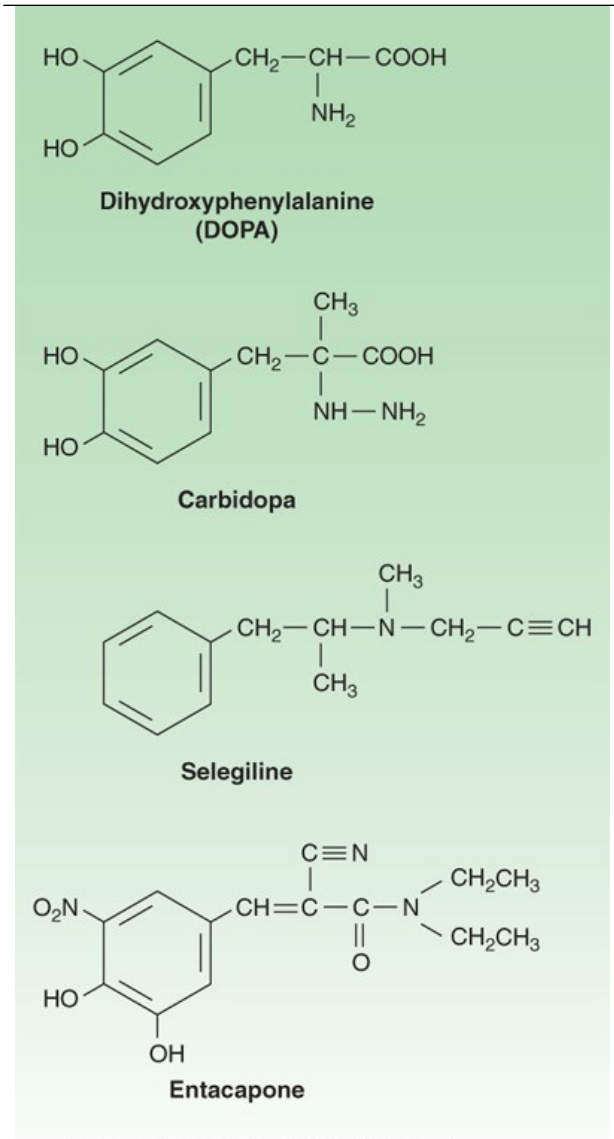
Dopamine receptors are discussed in detail in Chapters 21 and 29. They exist in five subtypes. D_1 and D_5 receptors are classified as the D_1 receptor family based on genetic and biochemical factors; D_2, D_3, and D_4 are grouped as belonging to the D_2 receptor family. Dopamine receptors of the D_1 type are located in the pars compacta of the substantia nigra and presynaptically on striatal axons coming from cortical neurons and from dopaminergic cells in the substantia nigra. The D_2 receptors are located postsynaptically on striatal neurons and presynaptically on axons in the substantia nigra belonging to neurons in the basal ganglia. The benefits of dopaminergic antiparkinsonism drugs appear to depend mostly on stimulation of the D_2 receptors. However, D_1-receptor stimulation may also be required for maximal benefit, and one of the newer drugs is D_3 selective. Dopamine agonist or partial agonist ergot derivatives such as lergotrile and bromocriptine that are powerful stimulators of the D_2 receptors have antiparkinsonism properties, whereas certain dopamine blockers that are selective D_2 antagonists can induce parkinsonism.

Chemistry

Dopa is the amino acid precursor of dopamine and norepinephrine (discussed in Chapter 6). Its structure is shown in Figure 28–3. Levodopa is the levorotatory stereoisomer of dopa.

FIGURE 28–3

Some drugs used in the treatment of parkinsonism.

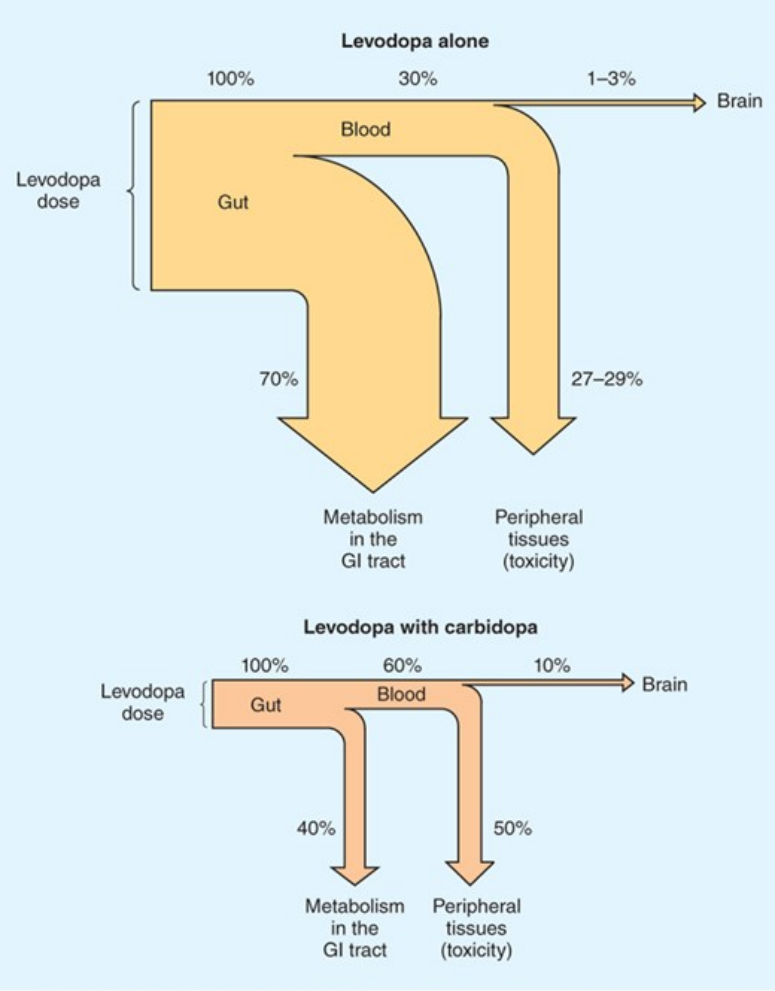


Pharmacokinetics

Levodopa is rapidly absorbed from the small intestine, but its absorption depends on the rate of gastric emptying and the pH of the gastric contents. Ingestion of food delays the appearance of levodopa in the plasma. Moreover, certain amino acids from ingested food can compete with the drug for absorption from the gut and for transport from the blood to the brain. Plasma concentrations usually peak between 1 and 2 hours after an oral dose, and the plasma half-life is usually between 1 and 3 hours, although it varies considerably among individuals. About two thirds of the dose appears in the urine as metabolites within 8 hours of an oral dose, the main metabolic products being 3-methoxy-4-hydroxyphenyl acetic acid (homovanillic acid, HVA) and dihydroxyphenylacetic acid (DOPAC). Unfortunately, only about 1–3% of administered levodopa actually enters the brain unaltered; the remainder is metabolized extracerebrally, predominantly by decarboxylation to dopamine, which does not penetrate the blood-brain barrier. Accordingly, levodopa must be given in large amounts when used alone. However, when given in combination with a dopa decarboxylase inhibitor that does not penetrate the blood-brain barrier, the peripheral metabolism of levodopa is reduced, plasma levels of levodopa are higher, plasma half-life is longer, and more dopa is available for entry into the brain (Figure 28–4). Indeed, concomitant administration of a peripheral dopa decarboxylase inhibitor such as carbidopa may reduce the daily requirements of levodopa by approximately 75%.

FIGURE 28–4

Fate of orally administered levodopa and the effect of carbidopa, estimated from animal data. The width of each pathway indicates the absolute amount of the drug at each site, whereas the percentages shown denote the relative proportion of the administered dose. The benefits of co-administration of carbidopa include reduction of the amount of levodopa required for benefit and of the absolute amount diverted to peripheral tissues and an increase in the fraction of the dose that reaches the brain. GI, gastrointestinal. (Data from Nutt JG, Fellman JH: Pharmacokinetics of levodopa, Clin Neuropharmacol 1984;7(1):35-49.)



Clinical Use

The best results of levodopa treatment are obtained in the first few years of treatment. This is sometimes because the daily dose of levodopa must be reduced over time to avoid adverse effects at doses that were well tolerated initially. Some patients become less responsive to levodopa, perhaps because of loss of dopaminergic nigrostriatal nerve terminals or some pathologic process directly involving striatal dopamine receptors. For such reasons, the benefits of levodopa treatment often begin to diminish after about 3 or 4 years of therapy, regardless of the initial therapeutic response. Although levodopa therapy does not stop the progression of parkinsonism, its early initiation lowers the mortality rate. However, long-term therapy may lead to a number of problems in management such as the on-off phenomenon discussed below. The most appropriate time to introduce levodopa therapy must therefore be determined individually.

When levodopa is used, it is generally given in combination with **carbidopa** (Figure 28–3), a peripheral dopa decarboxylase inhibitor, which reduces peripheral conversion to dopamine. Combination treatment is started with a small dose, eg, carbidopa 25 mg, levodopa 100 mg three times daily, and gradually increased. It should be taken 30–60 minutes before meals. Most patients ultimately require carbidopa 25 mg, levodopa 250 mg three or four

times daily. It is generally preferable to keep treatment with this agent at a low level (eg, carbidopa-levodopa 25/100 three times daily) when possible, and if necessary, to add a dopamine agonist, to reduce the risk of development of response fluctuations. A controlled-release formulation of carbidopa-levodopa is available and may be helpful in patients with established response fluctuations or as a means of reducing dosing frequency. Even more helpful for response fluctuations is an extended-release formulation **(Rytary)** that consists of capsules containing beads that release carbidopa and levodopa (present in a 1:4 ratio) at different rates over a prolonged time as they dissolve in the stomach. It is substituted for the regular (immediate-release) formulation using dosing guidelines provided by its manufacturer (Table 28–1).

TABLE 28-1

Substitution of Rytary for immediate-release carbidopa/levodopa.

Current Levodopa Total Daily Dose (mg)	Rytary Dose (Carbidopa/Levodopa) (mg)[1]
Zero	23.75/95, 1 cap TID
400–549	23.75/95, 3 caps TID
550–749	23.75/95, 4 caps QID
750–949	36.25/145, 3 caps TID
950–1249	48.75/195, 3 caps TID
1250 or more	48.75/195, 4 caps TID or 61.25/245, 3 caps TID

[1]Dose levels recommended by the manufacturers.

A formulation of carbidopa-levodopa (10/100, 25/100, 25/250) that disintegrates in the mouth and is swallowed with the saliva **(Parcopa)** is available commercially and is best taken about 1 hour before meals. The combination **(Stalevo)** of levodopa, carbidopa, and a catechol-*O*-methyltransferase (COMT) inhibitor (entacapone) is discussed in a later section. Finally, therapy by *infusion* of carbidopa-levodopa into the duodenum or upper jejunum appears to be safe and is superior to a number of oral combination therapies in patients with advanced levodopa-responsive parkinsonism with response fluctuations. A permanent access tube is inserted via a percutaneous endoscopic gastrostomy in patients who have responded well to carbidopa-levodopa gel administered through a nasoduodenal tube. A morning bolus (100–300 mg of levodopa) is delivered via a portable infusion pump, followed by a continuous maintenance dose (40–120 mg/h), with supplemental bolus doses as required.

Levodopa can ameliorate many of the clinical motor features of parkinsonism, but it is particularly effective in relieving bradykinesia and any disabilities resulting from it. When it is first introduced, about one third of patients respond very well and one third less well. Most of the remainder either are unable to tolerate the medication or simply do not respond at all, especially if they do not have classic Parkinson disease.

Adverse Effects

A. Gastrointestinal Effects

When levodopa is given without a peripheral decarboxylase inhibitor, anorexia and nausea and vomiting occur in about 80% of patients. These adverse effects can be minimized by taking the drug in divided doses, with or immediately after meals, and by increasing the total daily dose very slowly. Antacids taken 30–60 minutes before levodopa may also be beneficial. The vomiting has been attributed to stimulation of the chemoreceptor trigger zone located in the brainstem but outside the blood-brain barrier. Fortunately, tolerance to this emetic effect develops in many patients. If not, an additional dose of carbidopa (Lodosyn; 25 mg) taken with the regular carbidopa-levodopa dose is often helpful, even though the usual maximum requirement of carbidopa is 75 mg daily. Domperidone (not available in the USA) may also relieve persistent nausea. Antiemetics such as phenothiazines should be avoided because they reduce the antiparkinsonism effects of levodopa and may exacerbate the disease.

When levodopa is given in combination with carbidopa, adverse gastrointestinal effects are much less frequent and troublesome, occurring in less than 20% of cases, so that patients can tolerate proportionately higher doses.

B. Cardiovascular Effects

A variety of cardiac arrhythmias have been described in patients receiving levodopa, including tachycardia, ventricular extrasystoles, and rarely, atrial fibrillation. This effect has been attributed to increased catecholamine formation peripherally. The incidence of such arrhythmias is low, even in the presence of established cardiac disease, and may be reduced still further if the levodopa is taken in combination with a peripheral decarboxylase inhibitor.

Postural hypotension is common, but often asymptomatic, and tends to diminish with continuing treatment. Hypertension may also occur, especially in the presence of nonselective monoamine oxidase inhibitors or sympathomimetics or when massive doses of levodopa are being taken.

C. Behavioral Effects

A wide variety of adverse mental effects have been reported, including depression, anxiety, agitation, insomnia, somnolence, sleep attacks, confusion, delusions, hallucinations, nightmares, euphoria, and other changes in mood or personality. Such adverse effects are more common in patients taking levodopa in combination with a decarboxylase inhibitor rather than levodopa alone, presumably because higher levels are reached in the brain. They may be precipitated by intercurrent illness or surgery. It may be necessary to reduce or withdraw the medication. Several atypical antipsychotic agents that have low affinity for dopamine D_2 receptors (clozapine, olanzapine, quetiapine, and risperidone; see Chapter 29) are now available and may be particularly helpful in counteracting such behavioral complications. **Pimavanserin** (34 mg daily), a selective serotonin 5-HT_{2A} inverse agonist, is also helpful for treating the hallucinations and delusions of Parkinson disease psychosis. It should not be used for dementia-related psychosis and should be avoided in patients with QT prolongation.

The **dopamine dysregulation syndrome** is characterized by compulsive overuse of dopaminergic medication as well as by other impulsive behaviors; such impulse control disorders are more common with dopamine agonists than levodopa and are discussed later. Management involves the close regulation of dopaminergic intake.

Punding designates the performance of stereotyped, complex, but purposeless motor activity, such as sorting or lining up various objects or repetitive grooming behavior. It responds to reduction in dose of dopaminergic agents or to atypical antipsychotic agents.

D. Dyskinesias and Response Fluctuations

Dyskinesias occur in up to 80% of patients receiving levodopa therapy for more than 10 years. The character of dopa dyskinesias varies between patients but tends to remain constant in individual patients. Choreoathetosis of the face and distal extremities is the most common presentation. The development of dyskinesias is dose related, but there is considerable individual variation in the dose required to produce them. Their pathogenesis is unclear, but they may relate to an unequal distribution of striatal dopamine. Dopaminergic denervation plus chronic pulsatile stimulation of dopamine receptors with levodopa has been associated with development of dyskinesias. A lower incidence of dyskinesias occurs when levodopa is administered continuously (eg, intraduodenally or intrajejunally) and with drug delivery systems that enable a more continuous delivery of dopaminergic medication. Reduction of levodopa dose will alleviate dyskinesias, but motor symptoms of parkinsonism then worsen. Mild dyskinesias require no treatment. Amantadine may help to reduce more troublesome dyskinesias, as may clozapine; a number of other compounds are being studied as possible antidyskinetic agents.

Certain fluctuations in clinical response to levodopa occur with increasing frequency as treatment continues. In some patients, these fluctuations relate to the timing of levodopa intake (**wearing-off** reactions or **end-of-dose akinesia**). In other instances, fluctuations in clinical state are unrelated to the timing of doses **(on-off phenomenon).** In the on-off phenomenon, off-periods of marked akinesia alternate over the course of a few hours with on-periods of improved mobility but often marked dyskinesia. For patients with severe off-periods who are unresponsive to other measures, subcutaneously injected apomorphine may provide temporary benefit but may increase dyskinesias. The on-off phenomenon is most likely to occur in patients who responded well to treatment initially. The exact mechanism is unknown.

E. Miscellaneous Adverse Effects

Mydriasis may occur and may precipitate an attack of acute glaucoma in some patients. Other reported but rare adverse effects include various blood dyscrasias; a positive Coombs' test with evidence of hemolysis; hot flushes; aggravation or precipitation of gout; abnormalities of smell or taste; brownish discoloration of saliva, urine, or vaginal secretions; priapism; and mild—usually transient—elevations of blood urea nitrogen and of serum transaminases, alkaline phosphatase, and bilirubin.

Drug Holidays

A drug holiday (discontinuance of the drug for 3–21 days) may temporarily improve responsiveness to levodopa and alleviate some of its adverse effects but is usually of little help in the management of the on-off phenomenon. Furthermore, a drug holiday carries the risks of aspiration pneumonia, venous thrombosis, pulmonary embolism, and depression resulting from the immobility accompanying severe parkinsonism. For these reasons and because of the temporary nature of any benefit, drug holidays are not recommended.

Drug Interactions

Pharmacologic doses of pyridoxine (vitamin B_6) enhance the extracerebral metabolism of levodopa and may therefore prevent its therapeutic effect unless a peripheral decarboxylase inhibitor is also taken. Levodopa should not be given to patients taking monoamine oxidase A inhibitors or within 2 weeks of their discontinuance because such a combination can lead to hypertensive crises.

Contraindications

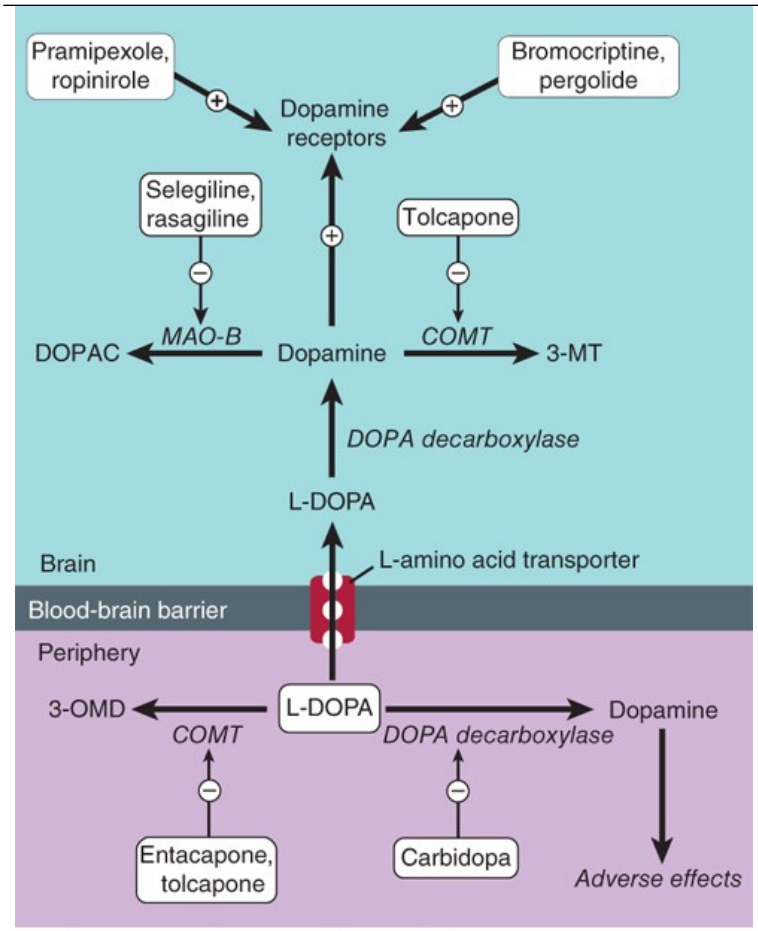
Levodopa should not be given to psychotic patients because it may exacerbate the mental disturbance. It is also contraindicated in patients with angle-closure glaucoma, but those with chronic open-angle glaucoma may be given levodopa if intraocular pressure is well controlled and can be monitored. When combined with carbidopa, the risk of cardiac dysrhythmia is slight, even in patients with cardiac disease. Patients with active peptic ulcer must be managed carefully, since gastrointestinal bleeding has occasionally occurred with levodopa. Because levodopa is a precursor of skin melanin and conceivably may activate malignant melanoma, it should be used with particular care in patients with a history of melanoma or with suspicious undiagnosed skin lesions; such patients should be monitored regularly by a dermatologist.

DOPAMINE RECEPTOR AGONISTS

Drugs acting directly on postsynaptic dopamine receptors may have a beneficial effect in addition to that of levodopa (Figure 28–5). Unlike levodopa, they do not require enzymatic conversion to an active metabolite, act directly on the postsynaptic dopamine receptors, have no potentially toxic metabolites, and do not compete with other substances for active transport into the blood and across the blood-brain barrier. Moreover, drugs selectively affecting certain (but not all) dopamine receptors may have more limited adverse effects than levodopa. A number of dopamine agonists have antiparkinsonism activity. The older dopamine agonists (bromocriptine and pergolide) are ergot (ergoline) derivatives (see Chapter 16) and are rarely—if ever—used to treat parkinsonism. Their side effects are of more concern than those of the newer agents (pramipexole and ropinirole).

FIGURE 28–5

Pharmacologic strategies for dopaminergic therapy of Parkinson disease. Drugs and their effects are indicated (see text). COMT, catechol-*O*-methyltransferase; DOPAC, dihydroxyphenylacetic acid; L-DOPA, levodopa; MAO, monoamine oxidase; 3-MT, 3-methoxytyramine; 3-OMD, 3-*O*-methyldopa.



There is no evidence that one agonist is superior to another; individual patients, however, may respond to one but not another of these agents. Moreover, their duration of action varies and is lengthened by extended-release preparations. Apomorphine is a potent dopamine agonist but is discussed separately in a later section in this chapter because it is used primarily as a rescue drug for patients with disabling response fluctuations to levodopa.

Dopamine agonists have an important role as first-line therapy for Parkinson disease, and their use is associated with a lower incidence of the response fluctuations and dyskinesias that occur with long-term levodopa therapy. Dopaminergic therapy is therefore often initiated with a dopamine agonist, although, compared with levodopa, the agonists generally provide less symptomatic benefit and are more likely to cause mental side effects, somnolence, and edema. In other instances, a low dose of carbidopa plus levodopa (eg, Sinemet, 25/100 three times daily) is introduced, and a dopamine agonist is then added. In either case, the dose of the dopamine agonist is built up gradually depending on response and tolerance. Dopamine agonists may also be given to patients with parkinsonism who are taking levodopa and who have end-of-dose akinesia or on-off phenomenon or are becoming resistant to treatment with levodopa. In such circumstances, it is generally necessary to lower the dose of levodopa to prevent intolerable adverse effects. The response to a dopamine agonist is generally disappointing in patients who have never responded to levodopa.

Bromocriptine

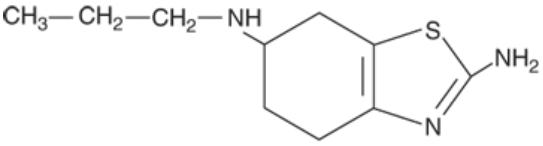
Bromocriptine is a D_2 agonist; its structure is shown in Table 16–7. This drug has been widely used to treat Parkinson disease in the past but is now rarely used for this purpose, having been superseded by the newer dopamine agonists. The usual daily dose of bromocriptine for parkinsonism varies between 7.5 and 30 mg. To minimize adverse effects, the dose is built up slowly over 2 or 3 months depending on response or the development of adverse reactions.

Pergolide

Pergolide, another ergot derivative, directly stimulates both D_1 and D_2 receptors. It too has been widely used for parkinsonism but is no longer available in the United States because its use has been associated with the development of valvular heart disease. It is nevertheless still used in some countries.

Pramipexole

Pramipexole is not an ergot derivative, but it has preferential affinity for the D_3 receptor. It is effective as monotherapy for mild parkinsonism and is also helpful in patients with advanced disease, permitting the dose of levodopa to be reduced and smoothing out response fluctuations. Pramipexole may ameliorate affective symptoms. A possible neuroprotective effect has been suggested by its ability to scavenge hydrogen peroxide and enhance neurotrophic activity in mesencephalic dopaminergic cell cultures.

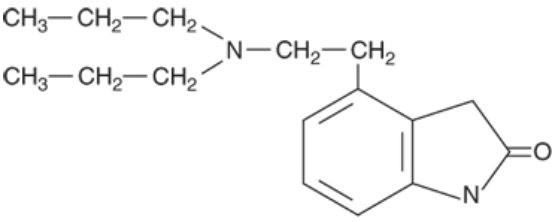


Pramipexole

Pramipexole is rapidly absorbed after oral administration, reaching peak plasma concentrations in approximately 2 hours, and is excreted largely unchanged in the urine. It is started at a dosage of 0.125 mg three times daily, doubled after 1 week, and again after another week. Further increments in the daily dose are by 0.75 mg at weekly intervals, depending on response and tolerance. Most patients require between 0.5 and 1.5 mg three times daily. Renal insufficiency may necessitate dosage adjustment. An extended-release preparation is now available and is taken once daily at a dose equivalent to the total daily dose of standard pramipexole. The extended-release preparation is generally more convenient for patients and avoids swings in blood levels of the drug over the day.

Ropinirole

Another nonergoline derivative, ropinirole (now available in a generic preparation) is a relatively pure D_2 receptor agonist that is effective as monotherapy in patients with mild disease and as a means of smoothing the response to levodopa in patients with more advanced disease and response fluctuations. It is introduced at 0.25 mg three times daily, and the total daily dose is then increased by 0.75 mg at weekly intervals until the fourth week and by 1.5 mg thereafter. In most instances, a dosage between 2 and 8 mg three times daily is necessary. Ropinirole is metabolized by CYP1A2; other drugs metabolized by this isoform may significantly reduce its clearance. A prolonged-release preparation taken once daily is available.



Ropinirole

Rotigotine

The dopamine agonist rotigotine, delivered daily through a skin patch, is approved for treatment of early Parkinson disease. It supposedly provides more continuous dopaminergic stimulation than oral medication in early parkinsonism; its efficacy in more advanced disease is less clear. Benefits and side effects are similar to those of other dopamine agonists but reactions may also occur at the application site and are sometimes serious.

Adverse Effects of Dopamine Agonists

A. Gastrointestinal Effects

Anorexia and nausea and vomiting may occur when a dopamine agonist is introduced and can be minimized by taking the medication with meals. Constipation, dyspepsia, and symptoms of reflux esophagitis may also occur. Bleeding from peptic ulceration has been reported.

B. Cardiovascular Effects

Postural hypotension may occur, particularly at the initiation of therapy. Painless digital vasospasm is a dose-related complication of long-term treatment with the ergot derivatives (bromocriptine or pergolide). When cardiac arrhythmias occur, they are an indication for discontinuing treatment. Peripheral edema is sometimes problematic. Cardiac valvulopathy may occur with pergolide.

C. Dyskinesias

Abnormal movements similar to those introduced by levodopa may occur and are reversed by reducing the total dose of dopaminergic drugs being taken.

D. Mental Disturbances

Confusion, hallucinations, delusions, and other psychiatric reactions may develop as a feature of Parkinson disease or as complications of dopaminergic treatment and are more common and severe with dopamine receptor agonists than with levodopa. They tend to occur earlier in older patients and become more common as the disease advances. There appears to be no difference between the various dopamine agonists in their ability to induce these disorders. They may respond to atypical antipsychotic agents such as clozapine, olanzapine, quetiapine, and risperidone or to pimavanserin.

Disorders of impulse control may occur either as an exaggeration of a previous tendency or as a new phenomenon and may lead to compulsive gambling, shopping, betting, sexual activity, and other behaviors (see Chapter 32). Their prevalence varies in different reports but may be as high as 45% in parkinsonian patients treated with dopamine agonists. They relate to activation of D_2 or D_3 dopamine receptors in the mesocorticolimbic system, may occur with one dopamine agonist and not another, and may occur at any time after the initiation of treatment. They have been associated with increasing dose and duration of treatment; in some patients, a dose reduction may ameliorate them. They resolve on withdrawal of the offending medication. Impulse control disorders are generally under-reported by patients and their families and often unrecognized by health care professionals. Risk factors include an impulsive personality, a history of drug use or other addictive behaviors, and a family history of gambling disorders.

A withdrawal syndrome develops in occasional patients tapered off a dopamine agonist. It consists of a combination of distressing physical and psychological symptoms that are refractory to levodopa and other dopaminergic medications, may persist for months or longer, and for which no other cause can be found. Anxiety, agitation, panic attacks, depression, suicidal ideation, irritability, fatigue, postural hypotension, nausea, vomiting, diaphoresis, and drug cravings may occur. Risk factors include impulse control behavior disorders and higher dopamine agonist dosage. There is no effective treatment. The dopamine agonist should be reintroduced and tapered more gradually if possible.

E. Miscellaneous

Headache, nasal congestion, increased arousal, pulmonary infiltrates, pleural and retroperitoneal fibrosis, and erythromelalgia are other reported adverse effects of the ergot-derived dopamine agonists. Erythromelalgia consists of red, tender, painful, swollen feet and, occasionally, hands, at times associated with arthralgia; symptoms and signs clear within a few days of withdrawal of the causal drug. In rare instances, an uncontrollable tendency to fall asleep at inappropriate times has occurred, particularly in patients receiving pramipexole or ropinirole; this requires discontinuation of the medication.

Contraindications

Dopamine agonists are contraindicated in patients with a history of psychotic illness or recent myocardial infarction, or with active peptic ulceration. The ergot-derived agonists are best avoided in patients with peripheral vascular disease.

MONOAMINE OXIDASE INHIBITORS

Two types of monoamine oxidase have been distinguished in the nervous system. Monoamine oxidase A metabolizes norepinephrine, serotonin, and dopamine; monoamine oxidase B metabolizes dopamine selectively. **Selegiline** (deprenyl) (Figure 28–3), a selective irreversible inhibitor of monoamine oxidase B at normal doses (at higher doses it inhibits monoamine oxidase A as well), retards the breakdown of dopamine (Figure 28–5); in consequence, it enhances and prolongs the antiparkinsonism effect of levodopa (thereby allowing the dose of levodopa to be reduced) and may reduce mild on-off or wearing-off phenomena. It is therefore used as adjunctive therapy for patients with a declining or fluctuating response to levodopa. The standard dose of selegiline is 5 mg with breakfast and 5 mg with lunch. Selegiline may cause insomnia when taken later during the day.

Selegiline has only a minor therapeutic effect on parkinsonism when given alone. Studies in animals suggest that it may reduce disease progression, but trials to test the effect of selegiline on the progression of parkinsonism in humans have yielded ambiguous results. The findings in a large multicenter study were taken to suggest a beneficial effect in slowing disease progression but may simply have reflected a symptomatic response.

Rasagiline, another monoamine oxidase B inhibitor, is more potent than selegiline in preventing MPTP-induced parkinsonism and is being used for early treatment in patients with mild symptoms. The standard dosage is 1 mg/d. Rasagiline is also used as adjunctive therapy at a dosage of 0.5 or 1 mg/d to prolong the effects of carbidopa-levodopa in patients with advanced disease and response fluctuations. A large double-blind, placebo-controlled, delayed-start study (the ADAGIO trial) to evaluate whether it had neuroprotective benefit (ie, slowed the disease course) yielded unclear results: a daily dose of 1 mg met all the end points of the study and did seem to slow disease progression, but a 2-mg dose failed to do so. These findings are difficult to explain and the decision to use rasagiline for neuroprotective purposes therefore remains an individual one.

A third monoamine oxidase B inhibitor, **safinamide,** has been used to reduce response fluctuations in patients taking carbidopa-levodopa, diminishing off-periods in patients with wearing-off effect or on-off phenomena. It is not effective as monotherapy for Parkinson disease. The starting dose is 50 mg orally once daily, increased after 2 weeks to 100 mg once daily.

Monoamine oxidase B inhibitors should not be taken by patients receiving meperidine, tramadol, methadone, propoxyphene, cyclobenzaprine, or St. John's wort. The antitussive dextromethorphan should also be avoided by patients taking one of the monoamine oxidase B inhibitors; indeed, it is wise to advise patients to avoid all over-the-counter cold preparations. Rasagiline, selegiline, or safinamide should not be taken with other monoamine oxidase inhibitors and should be used with care in patients receiving tricyclic antidepressants or serotonin reuptake inhibitors because of the theoretical risk of acute toxic interactions of the serotonin syndrome type (see Chapter 16), but this is rarely encountered in practice. The adverse effects of levodopa, especially dyskinesias, mental changes, nausea, and sleep disorders, may be increased by these drugs. Hypertension may be precipitated or aggravated.

The combined administration of levodopa and an inhibitor of both forms of monoamine oxidase (ie, a nonselective inhibitor) must be avoided, because it may lead to hypertensive crises, probably due to the peripheral accumulation of norepinephrine.

CATECHOL-*O*-METHYLTRANSFERASE INHIBITORS

Inhibition of dopa decarboxylase is associated with compensatory activation of other pathways of levodopa metabolism, especially catechol-*O*-methyltransferase (COMT), and this increases plasma levels of 3-*O*-methyldopa (3-OMD). Elevated levels of 3-OMD have been associated with a poor therapeutic response to levodopa, perhaps in part because 3-OMD competes with levodopa for an active carrier mechanism that governs its transport across the intestinal mucosa and the blood-brain barrier. Selective COMT inhibitors such as **tolcapone** and **entacapone** also prolong the action of levodopa by diminishing its peripheral metabolism (Figure 28–5). Levodopa clearance is decreased, and relative bioavailability of levodopa is thus increased. Neither the time to reach peak concentration nor the maximal concentration of levodopa is increased. These agents may be helpful in patients receiving levodopa who have developed response fluctuations—leading to a smoother response, more prolonged on-time, and the option of reducing total daily levodopa dose. Tolcapone and entacapone are both widely available, but entacapone is generally preferred because it has not been associated with hepatotoxicity.

The pharmacologic effects of tolcapone and entacapone are similar, and both are rapidly absorbed, bound to plasma proteins, and metabolized before excretion. However, tolcapone has both central and peripheral effects, whereas the effect of entacapone is peripheral. The half-life of both drugs is approximately 2 hours, but tolcapone is slightly more potent and has a longer duration of action. Tolcapone is taken in a standard dosage of 100 mg three times daily; some patients require a daily dose of twice that amount. By contrast, entacapone (200 mg) needs to be taken with each dose of levodopa, up to six times daily.

Adverse effects of the COMT inhibitors relate in part to increased levodopa exposure and include dyskinesias, nausea, and confusion. It is often

necessary to lower the daily dose of levodopa by about 30% in the first 48 hours to avoid or reverse such complications. Other adverse effects include diarrhea, abdominal pain, orthostatic hypotension, sleep disturbances, and an orange discoloration of the urine. Tolcapone may cause an increase in liver enzyme levels and has been associated rarely with death from acute hepatic failure; accordingly, it should not be used in patients with abnormal liver function test results. Its use in the USA requires signed patient consent (as provided in the product labeling) plus monitoring of liver function tests every 2–4 weeks during the first 6 months and periodically but less frequently thereafter. The medication should be withdrawn and not reintroduced if hepatic damage becomes evident. No such toxicity has been reported with entacapone.

The commercial preparation named **Stalevo** consists of a combination of levodopa with both carbidopa and entacapone. It is available in three strengths: Stalevo 50 (50 mg levodopa plus 12.5 mg carbidopa and 200 mg entacapone), Stalevo 100 (100 mg, 25 mg, and 200 mg, respectively), and Stalevo 150 (150 mg, 37.5 mg, and 200 mg, respectively). Use of this preparation simplifies the drug regimen and requires the consumption of fewer tablets than otherwise. The combination agent may provide greater symptomatic benefit than carbidopa-levodopa alone. However, despite the convenience of a single combination preparation, use of Stalevo rather than carbidopa-levodopa has been associated with earlier occurrence and increased frequency of dyskinesia. There is no evidence that the use of Stalevo is associated with an increased risk for cardiovascular events (myocardial infarction, stroke, cardiovascular death).

Opicapone is a new long-acting, peripherally selective, catechol-O-methyl transferase inhibitor that is taken once daily at bedtime, in a 50-mg dose. It is marketed in Europe as Ongentys but is not yet available in the USA. As with the other COMT inhibitors, it decreases the duration of daily off-periods and increases on-time in patients with a fluctuating response to levodopa.

APOMORPHINE

Subcutaneous injection of apomorphine hydrochloride **(Apokyn),** a potent nonergoline dopamine agonist that interacts with postsynaptic D_2 receptors in the caudate nucleus and putamen, is effective for the temporary relief ("rescue") of off-periods of akinesia in patients on optimized dopaminergic therapy. It is rapidly taken up in the blood and then the brain, leading to clinical benefit that begins within about 10 minutes of injection and persists for up to 2 hours. The optimal dose is identified by administering increasing test doses until adequate benefit is achieved or a maximum of 0.6 mL (6 mg) is reached, with the supine and standing blood pressures monitored before injection and then every 20 minutes for an hour after it. Most patients require a dose of 0.3–0.6 mL (3–6 mg), and this should be given usually no more than about three times daily, but occasionally up to five times daily.

Nausea is often troublesome, especially at the initiation of apomorphine treatment; accordingly, oral pretreatment with the antiemetic trimethobenzamide (300 mg three times daily) for 3 days is recommended before apomorphine is introduced and is then continued for at least 1 month, if not indefinitely. Other adverse effects include dyskinesias, drowsiness, insomnia, chest pain, sweating, hypotension, syncope, constipation, diarrhea, mental or behavioral disturbances, panniculitis, and bruising at the injection site. Apomorphine should be prescribed only by physicians familiar with its potential complications and interactions. It should not be used in patients taking serotonin 5-HT_3 antagonists because severe hypotension may result.

AMANTADINE

Amantadine, an antiviral agent, was by chance found to have relatively weak antiparkinsonism properties. Its mode of action in parkinsonism is unclear, but it may potentiate dopaminergic function by influencing the synthesis, release, or reuptake of dopamine. It has been reported to antagonize the effects of adenosine at adenosine A_{2A} receptors, which may inhibit D_2 receptor function. Release of catecholamines from peripheral stores has also been documented. Amantadine is an antagonist of the NMDA-type glutamate receptor, suggesting an antidyskinetic effect. It is available in an immediate-release formulation (**Symmetrel;** standard dose, 100 mg orally two or three times daily) and extended-release formulations (**Gocovri,** once daily at bedtime; **Osmolex,** 129–322 mg once daily in the morning).

Pharmacokinetics

Peak plasma concentrations of amantadine are reached 1–4 hours after an oral dose of the immediate-release preparation. The plasma half-life is between 2 and 4 hours, with most of the drug being excreted unchanged in the urine.

Clinical Use

Amantadine is less efficacious than levodopa, and its benefits may be short-lived, often disappearing after only a few weeks of treatment. Nevertheless, during that time it may favorably influence the bradykinesia, rigidity, and tremor of parkinsonism. Amantadine may also help in reducing iatrogenic dyskinesias in patients with advanced disease.

Adverse Effects

Amantadine has a number of undesirable central nervous system effects, all of which can be reversed by stopping the drug. These include restlessness, depression, suicidal ideation, irritability, impulse-control disorders, somnolence, insomnia, agitation, excitement, hallucinations, confusion, and psychosis. Overdosage may produce an acute toxic psychosis. With doses several times higher than recommended, convulsions have occurred.

Livedo reticularis sometimes occurs in patients taking amantadine and usually clears within 1 month after the drug is withdrawn. Other dermatologic reactions have also been described. Peripheral edema, another well-recognized complication, is not accompanied by signs of cardiac, hepatic, or renal disease and responds to diuretics. Other adverse reactions to amantadine include headache, heart failure, postural hypotension, urinary retention, and gastrointestinal disturbances (eg, anorexia, nausea, constipation, and dry mouth).

Amantadine should be used with caution in patients with a history of seizures, heart failure, or moderate or severe renal disease. Discontinuation of the medication should be gradual, as abrupt withdrawal may lead to an acute confusional state, hyperpyrexia, and abrupt worsening of parkinsonism.

ISTRADEFYLLINE

Istradefylline is an analog of caffeine and a selective antagonist of the adenosine A_{2A} receptor. It can be taken orally (20 or 40 mg daily) to reduce off-periods and improve motor function in patients taking carbidopa-levodopa. It was approved by the FDA in 2019 and experience with it is still limited. Side effects include dyskinesias, dizziness, constipation, nausea, hallucinations, and sleeplessness. Hallucinations, psychoses, or impulsive or compulsive behaviors may necessitate dose reductions or discontinuation of the drug.

ACETYLCHOLINE-BLOCKING DRUGS

A number of centrally acting antimuscarinic preparations are available that differ in their potency and in their efficacy in different patients. Some of these drugs were discussed in Chapter 8. These agents may improve the tremor and rigidity of parkinsonism but have little effect on bradykinesia. They are more effective than placebo. Some of the more commonly used drugs are listed in Table 28–2.

TABLE 28–2

Some drugs with antimuscarinic properties used in parkinsonism.

Drug	Usual Daily Dose (mg)
Benztropine mesylate	1–6
Biperiden	2–12
Orphenadrine	150–400
Procyclidine	7.5–30
Trihexyphenidyl	6–20

Clinical Use

Treatment is started with a low dose of one of the drugs in this category, the dosage gradually being increased until benefit occurs or until adverse effects limit further increments. If patients do not respond to one drug, a trial with another member of the drug class is warranted and may be successful.

Adverse Effects

Antimuscarinic drugs have a number of undesirable central nervous system and peripheral effects (see Chapter 8) and are poorly tolerated by the elderly or cognitively impaired. Dyskinesias occur in rare cases. Acute suppurative parotitis sometimes occurs as a complication of dryness of the mouth.

If medication is to be withdrawn, this should be accomplished gradually rather than abruptly to prevent acute exacerbation of parkinsonism. For contraindications to the use of antimuscarinic drugs, see Chapter 8.

SURGICAL PROCEDURES

Ablative surgical procedures for parkinsonism have generally been replaced by functional, reversible lesions induced by high-frequency deep brain stimulation, which has a lower morbidity.

Stimulation of the subthalamic nucleus or globus pallidus by an implanted electrode and stimulator has yielded good results for the management of the clinical fluctuations or the dyskinesias occurring in moderate parkinsonism. The anatomic substrate for such therapy is indicated in Figure 28–1. Such procedures are contraindicated in patients with secondary or atypical parkinsonism, dementia, or failure to respond to dopaminergic medication. The level of antiparkinsonian medication can often be reduced in patients undergoing deep brain stimulation, and this may help to ameliorate dose-related adverse effects of medication. Patients with medically refractory tremor-predominant parkinsonism who are reluctant to undergo surgery may respond to focused ultrasound thalamotomy.

In a controlled trial of the transplantation of dopaminergic tissue (fetal substantia nigra tissue), symptomatic benefit occurred in younger (less than 60 years old) but not older parkinsonian patients. In another trial, benefits were inconsequential. Furthermore, uncontrollable dyskinesias occurred in some patients in both studies, perhaps from a relative excess of dopamine from continued fiber outgrowth from the transplant. Additional basic studies are required before further trials of cellular therapies—in particular, stem cell therapies—are undertaken, and such approaches therefore remain investigational.

NEUROPROTECTIVE THERAPY

Among the compounds that have been investigated as potential neuroprotective agents to slow disease progression are antioxidants, antiapoptotic agents, glutamate antagonists, intraparenchymally administered glial-derived neurotrophic factor, and anti-inflammatory drugs. None of these agents has been shown to be effective in this context, however, and their use for therapeutic purposes is not indicated at this time. Coenzyme Q10, creatine, pramipexole, and pioglitazone have not been found to be effective despite early hopes to the contrary. The possibility that rasagiline has a protective effect was discussed earlier.

Isradipine (10 mg daily), a dihydropyridine calcium-channel blocker with relatively high affinity for $C_{av}1.3$ channels, is currently under study in a phase 3 randomized controlled trial as a disease-modifying therapy for Parkinson disease.

An increased serum urate level is associated with reduced risk of developing Parkinson disease and a slower rate of disease progression. The urate precursor, inosine, raises the serum urate level and is currently undergoing phase 3 trials in parkinsonism patients for any disease-modifying effect.

Two other agents that look promising as disease-modifying agents are in advanced stages of testing: deferiprone is a potent iron chelator and exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist (see Chapter 41) that affects various cellular processes likely to be involved in the etiology of Parkinson disease.

Active and passive immunization against α-synuclein or an α-synuclein-mimicking peptide is also being explored. The procedures are generally well-tolerated, without treatment-associated adverse events other than mild injection-site reactions, and lead to generation of antibodies against α-synuclein. In a small safety study, a monoclonal antibody to α-synuclein reduced the serum level of α-synuclein by up to 97% in parkinsonian patients,

with no severe adverse effects. A phase 2 clinical study is ongoing.

GENE THERAPY

Several phase 1 (safety) or phase 2 trials of gene therapy for Parkinson disease have been completed in the USA. All trials involved infusion into the striatum of adeno-associated virus type 2 as the vector for the gene. The genes were for glutamic acid decarboxylase (GAD, to facilitate synthesis of GABA, an inhibitory neurotransmitter), infused into the subthalamic nucleus to cause inhibition; for aromatic acid decarboxylase (AADC), infused into the putamen to increase metabolism of levodopa to dopamine; and for neurturin (a growth factor that may enhance the survival of dopaminergic neurons), infused into the putamen. All agents were deemed safe, and the data suggested efficacy. A phase 2 study of the GAD gene has been completed and the results are encouraging, but one for neurturin infused into the substantia nigra as well as the putamen was disappointing. A phase 1b trial of AADC is ongoing. The results of a European study involving bilateral intrastriatal delivery of ProSavin, a lentiviral vector-based gene therapy with three genes (decarboxylase, tyrosine hydroxylase, and GTP-cyclohydrolase 1) aimed at restoring local and continuous dopamine production in patients with advanced Parkinson disease, have also been encouraging.

THERAPY FOR NONMOTOR MANIFESTATIONS

Persons with cognitive decline may respond to rivastigmine (1.5–6 mg twice daily), memantine (5–10 mg daily), or donepezil (5–10 mg daily) (see Chapter 60); with affective disorders to antidepressants or anxiolytic agents (see Chapter 30); with psychosis to atypical antipsychotic agents or pimavanserin; with excessive daytime sleepiness to modafinil (100–400 mg in the morning) (see Chapter 9); and with bladder and bowel disorders to appropriate symptomatic therapy (see Chapter 8).

GENERAL COMMENTS ON DRUG MANAGEMENT OF PATIENTS WITH PARKINSONISM

Parkinson disease generally follows a progressive course. Moreover, the benefits of levodopa therapy often diminish as the disease advances, and serious adverse effects may complicate long-term levodopa treatment. Nevertheless, dopaminergic therapy at a relatively early stage may be most effective in alleviating motor symptoms of parkinsonism and may also favorably affect the mortality rate due to the disease. Therefore, several strategies have evolved for optimizing dopaminergic therapy, as summarized in Figure 28–5. Symptomatic treatment of mild parkinsonism is probably best avoided until there is some degree of disability or functional limitation or until symptoms begin to impact the patient's lifestyle or cause significant social impairment.

When symptomatic treatment becomes necessary, a trial of rasagiline, selegiline, amantadine, or an antimuscarinic drug (in young patients) may be worthwhile. With disease progression, dopaminergic therapy becomes necessary. This can conveniently be initiated with a dopamine agonist, either alone or in combination with low-dose carbidopa-levodopa therapy, unless risk factors for impulse control disorders are present. Alternatively, especially in older patients, a dopamine agonist can be omitted and the patient started immediately on carbidopa-levodopa, which is the most effective symptomatic treatment of the motor disturbances of parkinsonism. Physical therapy is helpful in improving mobility. In patients with severe parkinsonism and long-term complications of levodopa therapy such as the on-off phenomenon, a trial of treatment with the newer extended-release formulation of carbidopa-levodopa (Rytary), a COMT inhibitor, or rasagiline may be helpful. Regulation of dietary protein intake may also improve response fluctuations. Deep brain stimulation is often helpful in patients with response fluctuations or dyskinesias who fail to respond adequately to these measures. Treating patients who are young or have mild parkinsonism with rasagiline may delay disease progression and merits consideration, although evidence of benefit is incomplete.

DRUG-INDUCED PARKINSONISM

Reserpine and the related drug tetrabenazine deplete biogenic monoamines from their storage sites, whereas haloperidol, metoclopramide, and the phenothiazines block dopamine receptors. These drugs may therefore produce a parkinsonian syndrome, usually within 3 months after introduction. The disorder tends to be symmetric, with inconspicuous tremor, but this is not always the case. The syndrome is related to high dosage and clears over several weeks or months after withdrawal. If treatment is necessary, antimuscarinic agents are preferred. Levodopa is of no help if neuroleptic drugs are continued and may in fact aggravate the mental disorder for which antipsychotic drugs were prescribed originally.

In 1983, a drug-induced form of parkinsonism was discovered in individuals who attempted to synthesize and use a narcotic drug related to meperidine but actually synthesized and self-administered MPTP, as discussed in the Box: MPTP & Parkinsonism.

ATYPICAL PARKINSONISM SYNDROMES

Several disorders characterized by parkinsonism differ from classic Parkinson disease because of inconspicuous tremor, symmetry of the neurologic findings, and the presence of additional findings (eg, dysautonomia, cerebellar deficits, eye movement abnormalities, or early cognitive and behavioral changes). These disorders include **multisystem atrophy, progressive supranuclear palsy, corticobasal degeneration** (in which parkinsonism may be markedly asymmetric), and **diffuse Lewy body disease.** The prognosis is worse than for Parkinson disease, and the response to antiparkinsonian treatment may be limited. Treatment is symptomatic.

OTHER MOVEMENT DISORDERS

Tremor

Tremor consists of rhythmic oscillatory movements. Physiologic postural tremor, which is a normal phenomenon, is enhanced in amplitude by anxiety, fatigue, thyrotoxicosis, and intravenous epinephrine or isoproterenol. **Propranolol** reduces its amplitude and, if administered intra-arterially, prevents the response to isoproterenol in the perfused limb, presumably through some peripheral action. Certain drugs—especially the bronchodilators, valproate, tricyclic antidepressants, and lithium—may produce a dose-dependent exaggeration of the normal physiologic tremor that is reversed by discontinuing the drug. Although the tremor produced by sympathomimetics such as terbutaline (a bronchodilator) is blocked by propranolol, which antagonizes both β_1 and β_2 receptors, it is not blocked by metoprolol, a β_1-selective antagonist; this suggests that such tremor is mediated mainly by the β_2 receptors.

Essential tremor is a postural tremor, sometimes familial with autosomal dominant inheritance, which is clinically similar to physiologic tremor. Dysfunction of β_1 receptors has been implicated in some instances, since the tremor may respond dramatically to standard doses of metoprolol as well as to propranolol. The tremor may involve the hands, head, voice, and—much less commonly—the legs. Patients may become functionally limited or socially withdrawn, quality of life is affected, and some patients report being seriously disabled by the tremor.

The most useful therapeutic approach is with propranolol, but whether the response depends on a central or peripheral action is unclear. The pharmacokinetics, pharmacologic effects, and adverse reactions of propranolol are discussed in Chapter 10. Total daily doses of propranolol on the order of 120 mg or more (range, 60–320 mg) are usually required, divided into two doses; reported adverse effects have been few. Propranolol should be used with caution in patients with heart failure, heart block, asthma, depression, or hypoglycemia. Other adverse effects include fatigue, malaise, lightheadedness, and impotence. Patients can be instructed to take their own pulse and call the physician if significant bradycardia develops. Long-acting propranolol is also effective and is preferred by many patients because of its convenience. Some patients prefer to take a single dose of propranolol when they anticipate their tremor is likely to be exacerbated, for example, by social situations. Metoprolol is sometimes useful in treating tremor when patients have concomitant pulmonary disease that contraindicates use of propranolol.

Drugs potentiating $GABA_A$ receptors in the central nervous system (such as phenobarbital, primidone, topiramate, and benzodiazepines) also improve tremor, but phenobarbital is not used clinically because of its sedating effect. **Primidone** (an antiepileptic drug; see Chapter 24), in gradually increasing doses up to 250 mg three times daily, is also effective in providing symptomatic control in some cases. Patients with tremor are very sensitive to primidone and often cannot tolerate the doses used to treat seizures; they should be started on 50 mg once daily and the daily dose increased by 50 mg every 2 weeks depending on response. In many instances a dose of 125 mg two or three times daily is sufficient.

MPTP & Parkinsonism

Reports in the early 1980s of a rapidly progressive form of parkinsonism in young persons opened a new area of research in the etiology and treatment of parkinsonism. The initial report described apparently healthy young people who attempted to support their opioid habit with a meperidine analog synthesized by an amateur chemist. They unwittingly self-administered 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and subsequently developed a very severe form of parkinsonism.

MPTP is a protoxin that is converted by monoamine oxidase B to *N*-methyl-4-phenylpyridinium (MPP^+). MPP^+ is selectively taken up by cells in the substantia nigra through an active mechanism normally responsible for dopamine reuptake. MPP^+ inhibits mitochondrial complex I, thereby inhibiting oxidative phosphorylation. The interaction of MPP^+ with complex I probably leads to cell death and thus to striatal dopamine depletion and parkinsonism.

Recognition of the effects of MPTP suggested that spontaneously occurring Parkinson disease may result from exposure to an environmental toxin that is similarly selective in its target. However, no such toxin has yet been identified. It also suggested a successful means of producing an experimental model of Parkinson disease in animals, especially nonhuman primates. This model is useful in the development of new antiparkinsonism drugs. Pretreatment of exposed animals with a monoamine oxidase B inhibitor such as selegiline prevents the conversion of MPTP to MPP^+ and thus protects against the occurrence of parkinsonism. This observation has provided one reason to believe that selegiline or rasagiline may retard the progression of Parkinson disease in humans.

Topiramate, another antiepileptic drug, may also be helpful in a dose of 400 mg daily, built up gradually. **Alprazolam** (in doses up to 3 mg daily) or **gabapentin** (100–2400 mg/d; typically 1200 mg/d) is helpful in some patients. Gabapentin binds to the α2δ subunit of calcium channels. It produces less consistent relief of tremor but is associated with fewer side effects than primidone. Other patients are helped by intramuscular injections of botulinum toxin, but dose-dependent weakness may complicate symptomatic benefit. Thalamic stimulation by an implanted electrode and stimulator is worthwhile in advanced cases refractory to pharmacotherapy. Thalamotomy by magnetic resonance imaging-guided focused ultrasound or stereotactic radiosurgery is also effective in reducing upper-extremity tremor. Diazepam, chlordiazepoxide, mephenesin, and antiparkinsonism agents have been advocated in the past but are generally of little benefit. Small quantities of alcohol may suppress essential tremor for a short time but should not be recommended as a treatment strategy because of possible behavioral and other complications of alcohol.

Intention tremor is present during movement but not at rest; sometimes it occurs as a toxic manifestation of alcohol or drugs such as phenytoin. Withdrawal or reduction in dosage provides dramatic relief. There is no satisfactory pharmacologic treatment for intention tremor due to other neurologic disorders.

Rest tremor is usually due to parkinsonism.

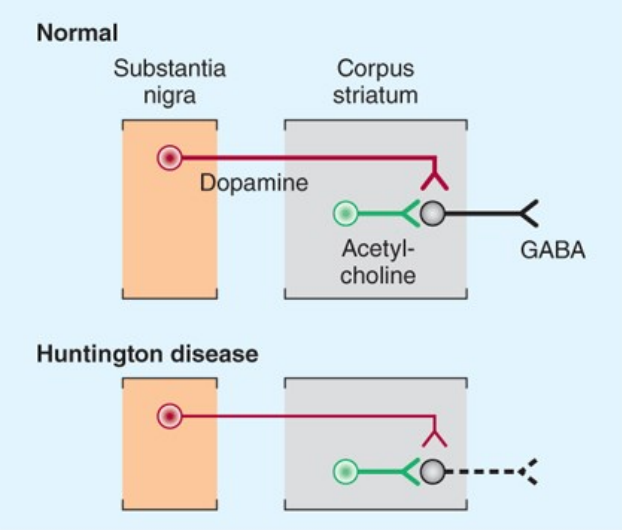
Huntington Disease

Huntington disease is an autosomal dominant inherited disorder caused by an abnormality (expansion of a CAG trinucleotide repeat that codes for a polyglutamine tract) of the *huntingtin* gene on chromosome 4. An autosomal recessive form may also occur. Huntington disease-like (HDL) disorders are not associated with an abnormal CAG trinucleotide repeat number of the *huntingtin* gene. Autosomal dominant (*HDL1*, 20pter-p12; *HDL2*, 16q24.3) and recessive forms (*HDL3*, 4p15.3) occur.

Huntington disease is characterized by progressive chorea and dementia that usually begin in adulthood. The development of chorea seems to be related to an imbalance of dopamine, acetylcholine, GABA, and perhaps other neurotransmitters in the basal ganglia (Figure 28–6). Pharmacologic studies indicate that chorea results from functional overactivity in dopaminergic nigrostriatal pathways, perhaps because of increased responsiveness of postsynaptic dopamine receptors or deficiency of a neurotransmitter that normally antagonizes dopamine. Drugs that impair dopaminergic neurotransmission, either by depleting central monoamines (eg, reserpine, tetrabenazine) or by blocking dopamine receptors (eg, phenothiazines, butyrophenones), often alleviate chorea, whereas dopamine-like drugs such as levodopa tend to exacerbate it.

FIGURE 28–6

Schematic representation of the sequence of neurons involved in Huntington chorea. The complex anatomical circuitry has been simplified. **Top:** Dopaminergic neurons (red) originating in the substantia nigra normally inhibit the output of the spiny GABAergic neurons from the striatum, whereas cholinergic neurons (green) exert an excitatory effect. **Bottom:** In Huntington chorea, some cholinergic neurons may be lost, but even more GABAergic neurons (black) degenerate.



Both GABA and the enzyme (glutamic acid decarboxylase) concerned with its synthesis are markedly reduced in the basal ganglia of patients with Huntington disease, and GABA receptors are usually implicated in inhibitory pathways. There is also a significant decline in concentration of choline acetyltransferase, the enzyme responsible for synthesizing acetylcholine, in the basal ganglia of these patients. These findings may be of pathophysiologic significance and have led to attempts to alleviate chorea by enhancing central GABA or acetylcholine activity, but with disappointing results. As a consequence, the most commonly used drugs for controlling dyskinesia in patients with Huntington disease are still those that interfere with dopamine activity. With all the latter drugs, however, reduction of abnormal movements may be associated with iatrogenic parkinsonism.

Tetrabenazine (12.5–50 mg orally three times daily) depletes cerebral dopamine and reduces the severity of chorea. It has less troublesome adverse effects than reserpine, which has also been used for this purpose. Tetrabenazine is metabolized by cytochrome P450 (CYP2D6), and genotyping has therefore been recommended to determine metabolizer status (CYP2D6 expression) in patients needing doses exceeding 50 mg/d. For poor metabolizers, the maximum recommended dose is 50 mg daily (25 mg/dose); otherwise, a maximum dose of 100 mg daily can be used. Treatment with postsynaptic dopamine receptor blockers such as phenothiazines and butyrophenones may also be helpful. **Haloperidol** is started in a small dose, eg, 1 mg twice daily, and increased every 4 days depending on the response. If haloperidol is not helpful, treatment with increasing doses of **fluphenazine** in a similar dose, eg, 1 mg twice daily, sometimes helps. Several recent reports suggest that **olanzapine** may also be useful; the dose varies with the patient, but 10 mg daily is often sufficient, although doses as high as 30 mg daily are sometimes required. The pharmacokinetics and clinical properties of these drugs are considered in greater detail elsewhere in this book. Selective serotonin reuptake inhibitors may reduce depression, aggression, and agitation. However, strong CYP2D6 inhibitors should be used with caution, as it may be necessary to decrease the dose of tetrabenazine taken concurrently.

Deutetrabenazine is a selective inhibitor of the vesicular monoamine 2 transporter (VMAT2) that modulates dopamine stores. It seems as effective as tetrabenazine for treating the chorea of Huntington disease and improving overall motor function, and may have fewer side effects. The dose is built up weekly from 6 mg daily to a maximum of 24 mg twice daily with food (18 mg twice daily in poor CYP2DG metabolizers). It may cause agitation, restlessness, and parkinsonism. Other adverse effects are sedation, dry mouth, diarrhea, insomnia, and fatigue. QT prolongation may occur. Deutetrabenazine is contraindicated in patients on monoamine oxidase inhibitors, reserpine, or tetrabenazine, and in those who are severely depressed or suicidal.

Other important aspects of management include genetic counseling, speech therapy, physical and occupational therapy, dysphagia precautions, and provision of social services.

Other Forms of Chorea

Benign hereditary chorea is inherited (usually autosomal dominant; possibly also autosomal recessive) or arises spontaneously. Chorea develops in early childhood and does not progress during adult life; dementia does not occur. In patients with *TITF-1* gene mutations, thyroid and pulmonary abnormalities may also be present (brain-thyroid-lung syndrome). Familial chorea may also occur as part of the chorea-acanthocytosis syndrome, together with orolingual tics, vocalizations, cognitive changes, seizures, peripheral neuropathy, and muscle atrophy; serum β-lipoproteins are normal. Mutations of the gene encoding chorein at 9q21 may be causal. Treatment of these hereditary disorders is symptomatic. Tetrabenazine (0.5 mg/kg/d for children and 37.5 mg/d for adults) may improve chorea in some instances. The efficacy in this context of the newer selective VMAT2 blockers deutetrabenazine and valbenazine is unclear.

Treatment is directed at the underlying cause when chorea occurs as a complication of general medical disorders such as thyrotoxicosis, polycythemia vera rubra, systemic lupus erythematosus, hypocalcemia, and hepatic cirrhosis. Drug-induced chorea is managed by withdrawal of the offending substance, which may be levodopa, an antimuscarinic drug, amphetamine, lithium, phenytoin, or an oral contraceptive. Neuroleptic drugs may also produce an acute or tardive dyskinesia (discussed below). Sydenham's chorea is temporary and usually so mild that pharmacologic management of the dyskinesia is unnecessary, but dopamine-blocking drugs are effective in suppressing it.

Ballismus

The biochemical basis of ballismus is unknown, but the pharmacologic approach to management is the same as for chorea. Treatment with tetrabenazine, haloperidol, perphenazine, or other dopamine-blocking drugs may be helpful.

Athetosis & Dystonia

The physiologic basis of these disorders is unknown, and there is no satisfactory medical treatment for them. A subset of patients respond well to levodopa medication (dopa-responsive dystonia), which is therefore worthy of trial. Occasional patients with dystonia may respond to diazepam, amantadine, antimuscarinic drugs (in high dosage), carbamazepine, baclofen, haloperidol, or phenothiazines. A trial of these pharmacologic approaches is worthwhile, though often not successful. Patients with focal dystonias such as blepharospasm or torticollis often benefit from injection of botulinum toxin into the overactive muscles. Deep brain stimulation may be helpful in medically intractable cases. The role of repetitive transcranial magnetic stimulation and transcranial direct current stimulation to induce plastic changes in the brain is being explored.

Tics

The pathophysiologic basis of tics is unknown. Chronic multiple tics **(Gilles de la Tourette syndrome)** may require symptomatic treatment if the disorder is severe or is having a significant impact on the patient's life. Education of patients, family, and teachers is important. Comprehensive behavioral intervention may help adults with Tourette syndrome. Pharmacologic therapy may be necessary when tics interfere with social life or otherwise impair activities of daily living.

Treatment is with drugs that block dopamine receptors or deplete dopamine stores, such as fluphenazine, pimozide, and tetrabenazine. These drugs reduce the frequency and intensity of tics by about 60%. **Pimozide,** a dopamine receptor antagonist, may be helpful in patients as a first-line treatment or in those who are either unresponsive to or intolerant of the other agents mentioned. Treatment is started at 1 mg/d, and the dosage is increased by 1 mg every 5 days; most patients require 7–16 mg/d. It has similar side effects to haloperidol but may cause irregularities of cardiac rhythm. **Haloperidol** has been used for many years to treat tic disorders. Patients are better able to tolerate this drug if treatment is started with a small dosage (eg, 0.25 or 0.5 mg daily) and then increased gradually (eg, by 0.25 mg every 4 or 5 days) over the following weeks depending on response and tolerance. Most patients ultimately require a total daily dose of 3–8 mg. Adverse effects include extrapyramidal movement disorders, sedation, dryness of the mouth, blurred vision, and gastrointestinal disturbances. **Deutetrabenazine** and **aripiprazole** (see Chapter 29) have also been found effective in treating tics, and **valbenazine** is under study. **Ecopipam,** a novel dopamine D_1 receptor blocker, produced significant reduction in tic severity in children with Tourette syndrome in a phase 2b randomized controlled clinical trial. The drug was well tolerated and further studies are planned.

Although not approved by the US Food and Drug Administration (FDA) for the treatment of tics or Tourette syndrome, certain α_2-adrenergic agonists may be preferred as an initial treatment because they are less likely to cause extrapyramidal side effects than neuroleptic agents. **Clonidine** reduces

motor or vocal tics in about 50% of children so treated. It may act by reducing activity in noradrenergic neurons in the locus coeruleus. It is introduced at a dose of 2–3 mcg/kg/d, increasing after 2 weeks to 4 mcg/kg/d and then, if required, to 5 mcg/kg/d. It may cause an initial transient fall in blood pressure. The most common adverse effect is sedation; other adverse effects include reduced or excessive salivation and diarrhea. **Guanfacine,** another α_2-adrenergic agonist, has also been used. Both of these drugs may be particularly helpful for behavioral symptoms, such as impulse control disorders.

Atypical antipsychotics, such as risperidone and aripiprazole, may be especially worthwhile in patients with significant behavioral problems. Clonazepam, baclofen, topiramate, and carbamazepine have also been used to treat tics in preference to dopamine receptor blockers with their potential side effects. The pharmacologic properties of these drugs are discussed elsewhere in this book.

Injection of botulinum toxin A at the site of problematic tics is sometimes helpful when these are focal simple tics. Treatment of any associated attention deficit disorder (eg, with clonidine patch, guanfacine, pemoline, methylphenidate, or dextroamphetamine) or obsessive-compulsive disorder (with selective serotonin reuptake inhibitors or clomipramine) may be required.

Deep brain stimulation is sometimes worthwhile in otherwise intractable cases.

Drug-Induced Dyskinesias

Levodopa or dopamine agonists produce diverse dyskinesias as a dose-related phenomenon in patients with Parkinson disease; dose reduction reverses them. Chorea may also develop in patients receiving phenytoin, carbamazepine, amphetamines, lithium, and oral contraceptives, and it resolves with discontinuance of the offending medication. Dystonia has resulted from administration of dopaminergic agents, lithium, serotonin reuptake inhibitors, carbamazepine, and metoclopramide; and postural tremor from theophylline, caffeine, lithium, valproic acid, thyroid hormone, tricyclic antidepressants, and isoproterenol.

The pharmacologic basis of the acute dyskinesia or dystonia sometimes precipitated by the first few doses of a phenothiazine is not clear. In most instances, parenteral administration of an antimuscarinic drug such as benztropine (2 mg intravenously), diphenhydramine (50 mg intravenously), or biperiden (2–5 mg intravenously or intramuscularly) is helpful, whereas in other instances diazepam (10 mg intravenously) alleviates the abnormal movements.

Tardive dyskinesia, a disorder characterized by a variety of abnormal movements, is a common complication of long-term neuroleptic or metoclopramide drug treatment (see Chapter 29). Its precise pharmacologic basis is unclear. A reduction in dose of the offending medication, a dopamine receptor blocker, commonly worsens the dyskinesia, whereas an increase in dose may suppress it. The drugs most likely to provide immediate symptomatic benefit are those interfering with dopaminergic function, either by depletion (eg, reserpine, tetrabenazine) or receptor blockade (eg, phenothiazines, butyrophenones). Paradoxically, the receptor-blocking drugs are the ones that also cause the dyskinesia.

Deutetrabenazine and **valbenazine** are selective inhibitors of VMAT2, which modulates dopamine release, and both ameliorate tardive dyskinesia. Deutetrabenazine was discussed earlier. Valbenazine is started in a dose of 40 mg once daily for one week and then increased to 80 mg once daily. Somnolence and QT prolongation may occur. Adverse effects include anticholinergic effects, impaired balance and falls, headache, akathisia, arthralgia, and nausea and vomiting. Valbenazine should not be used with monoamine oxidase inhibitors; its dose should be reduced in patients receiving a strong inhibitor of CYP2D6 (eg, paroxetine, fluoxetine) or CYP3A4 (eg, carbamazepine, phenytoin).

Tardive dystonia is usually segmental or focal; generalized dystonia is less common and occurs in younger patients. Treatment is the same as for tardive dyskinesia, but anticholinergic drugs may also be helpful; focal dystonias may also respond to local injection of botulinum A toxin. **Tardive akathisia** is treated similarly to drug-induced parkinsonism. **Rabbit syndrome,** another neuroleptic-induced disorder, is manifested by rhythmic vertical movements about the mouth; it may respond to anticholinergic drugs.

Because the tardive syndromes that develop in adults are often irreversible and have no satisfactory treatment, care must be taken to reduce the likelihood of their occurrence. Antipsychotic medication should be prescribed only when necessary and should be withheld periodically to assess the need for continued treatment and to unmask incipient dyskinesia. Thioridazine, a phenothiazine with a piperidine side chain, is an effective antipsychotic agent that seems less likely than most to cause extrapyramidal reactions, perhaps because it has little effect on dopamine receptors in the striatal system. Finally, antimuscarinic drugs should not be prescribed routinely in patients receiving neuroleptics, because the combination may increase the likelihood of dyskinesia.

Neuroleptic malignant syndrome is a rare complication of treatment with neuroleptics and certain antiemetic agents (such as metoclopramide and promethazine); a somewhat similar syndrome may occur with withdrawal of dopaminergic therapy in parkinsonian patients. It is characterized by rigidity, fever, changes in mental status, and autonomic dysfunction (see Table 16–4). Symptoms typically develop over 1–3 days (rather than minutes to hours as in malignant hyperthermia) and may occur at any time during treatment. Treatment includes withdrawal of antipsychotic drugs, lithium, and anticholinergics; reduction of body temperature; and rehydration. Dantrolene, dopamine agonists, levodopa, or amantadine may be helpful, but there is a high mortality rate (up to 20%) with neuroleptic malignant syndrome.

Restless Legs Syndrome

Restless legs syndrome is characterized by an unpleasant creeping discomfort that seems to arise deep within the legs and occasionally the arms. Symptoms occur particularly when patients are relaxed, especially when they are lying down or sitting, and they lead to an urge to move about. Such symptoms may delay the onset of sleep. A sleep disorder associated with periodic movements during sleep may also occur. The cause is unknown, but the disorder is especially common among pregnant women and also among uremic or diabetic patients with neuropathy. In most patients, no obvious predisposing cause is found, but several genetic loci have been associated with it.

Symptoms may resolve with correction of coexisting iron-deficiency anemia or with avoidance of caffeine, sleep deprivation, and various medications that can provoke or exacerbate them, such as serotonergic antidepressants, neuroleptics, metoclopramide, and antihistamines. They often respond to pharmacologic agents. Dopaminergic therapy is the preferred treatment and should be initiated with long-acting dopamine agonists (eg, oral **pramipexole** 0.125–0.75 mg or **ropinirole** 0.25–4.0 mg once daily) or with the rotigotine skin patch to avoid the augmentation that may be associated especially with carbidopa-levodopa (25/100 or 50/200 taken about 1 hour before bedtime). Augmentation refers to the earlier onset or enhancement of symptoms; earlier onset of symptoms at rest; and a briefer response to medication. When augmentation occurs with levodopa, a dopamine agonist should be substituted. If it occurs in patients receiving an agonist, the daily dose should be divided, another agonist tried, or other medications substituted. Dopamine agonist therapy may be associated with development of impulse control disorders.

Gabapentin is effective in reducing the severity of restless legs syndrome and is taken once or twice daily (in the evening and before sleep). The starting dose is 300 mg daily, building up depending on response and tolerance (to approximately 1800 mg daily). Oral gabapentin enacarbil (600 or 1200 mg once daily) or **pregabalin** (150–300 mg daily, in divided doses) may also help. **Clonazepam,** 1 mg daily, is also sometimes worthwhile, especially for those with intermittent symptoms. When **opiates** are required, those with long half-lives or low addictive potential should be used. Oxycodone is often effective; the dose is individualized.

Wilson Disease

A recessively inherited disorder of copper metabolism due to mutations in the copper-transporting gene, *ATP7B*, Wilson disease is characterized biochemically by reduced serum copper and ceruloplasmin concentrations, pathologically by markedly increased concentration of copper in the brain and viscera, and clinically by signs of hepatic and neurologic dysfunction. Neurologic signs include tremor, choreiform movements, rigidity, hypokinesia, and dysarthria and dysphagia. Siblings of affected patients should be screened for asymptomatic Wilson disease.

Treatment should start promptly, even in presymptomatic cases, continue indefinitely, and be monitored by laboratory tests and neurologic examination. It involves the removal of excess copper, followed by maintenance of copper balance. Dietary copper should also be kept below 2 mg daily. **Penicillamine** (dimethylcysteine) has been used for many years as the primary agent to remove copper. It is a chelating agent that forms a ring complex with copper (see Chapter 57). It is readily absorbed from the gastrointestinal tract and rapidly excreted in the urine. A common starting dose in adults is 500 mg three or four times daily. After remission occurs, it may be possible to lower the maintenance dose, generally to not less than 1 g daily, which must thereafter be continued indefinitely. Adverse effects include nausea and vomiting, nephrotic syndrome, a lupus-like syndrome, pemphigus, myasthenia, arthropathy, optic neuropathy, and various blood dyscrasias. In about 10% of instances, neurologic worsening occurs with penicillamine. Treatment should be monitored by frequent urinalysis and complete blood counts and serum creatinine determination. Patients receiving penicillamine should also take pyridoxine, 25 mg daily, unless it is part of the penicillamine formulation, to prevent pyridoxine deficiency.

Trientine hydrochloride, another chelating agent, is preferred by many over penicillamine because of the lesser likelihood of drug reactions or neurologic worsening. It may be used in a daily dose of 1–1.5 g. Trientine appears to have few adverse effects other than mild anemia due to iron deficiency in a few patients. **Tetrathiomolybdate** may be better than trientine for preserving neurologic function in patients with neurologic involvement and is taken both with and between meals. It is not yet commercially available or approved by the FDA.

Zinc acetate administered orally increases the fecal excretion of copper and can be used in combination with these other agents. The dose is 50 mg three times a day. Zinc sulfate (200 mg/d orally) has also been used to decrease copper absorption. Zinc blocks copper absorption from the gastrointestinal tract by induction of intestinal cell metallothionein. Its main advantage is its low toxicity compared with that of other anticopper agents, although it may cause gastric irritation when introduced.

Liver transplantation is sometimes necessary to restore hepatic function and ameliorate portal hypertension when medical treatment is inadequate. The role of hepatocyte transplantation and gene therapy is currently under investigation.

SUMMARY Drugs Used for Selected Movement Disorders

Subclass, Drug	Mechanism of Action	Effects	Clinical Applications	Pharmacokinetics, Toxicities, Interactions
LEVODOPA AND COMBINATIONS				
• Levodopa	Transported into the central nervous system (CNS) and converted to dopamine (which does not enter the CNS); also converted to dopamine in the periphery	Ameliorates all motor symptoms of Parkinson disease and causes significant peripheral dopaminergic effects (see text)	Parkinson disease: Most efficacious therapy but not always used as the first drug due to development of disabling response fluctuations over time	Oral • ~6–8 h effect • *Toxicity:* Gastrointestinal upset, arrhythmias, dyskinesias, on-off and wearing-off phenomena, behavioral disturbances • *Interactions:* Use with carbidopa greatly diminishes required dosage and is now standard • use with COMT or MAO-B inhibitors prolongs duration of effect
• *Levodopa + carbidopa (Sinemet, others): Carbidopa inhibits peripheral metabolism of levodopa to dopamine and reduces required dosage and toxicity; carbidopa does not enter CNS* • *Levodopa + carbidopa + entacapone (Stalevo): Entacapone is a catechol-O-methyltransferase (COMT) inhibitor (see below)*				
DOPAMINE AGONISTS				
• Pramipexole	Direct agonist at D_3 receptors, nonergot	Reduces symptoms of parkinsonism • smooths out fluctuations in levodopa response	Parkinson disease: Can be used as initial therapy • also effective in on-off phenomenon	Oral • ~8 h effect • *Toxicity:* Nausea and vomiting, postural hypotension, dyskinesias, confusion, impulse control disorders, sleepiness
• *Ropinirole: Similar to pramipexole; nonergot; relatively pure D_2 agonist* • *Bromocriptine: Ergot derivative; potent agonist at D_2 receptors; more toxic than pramipexole or ropinirole; now rarely used for antiparkinsonian effect* • *Apomorphine: Nonergot; subcutaneous route useful for rescue treatment in levodopa-induced dyskinesia; high incidence of nausea and vomiting*				
MONOAMINE OXIDASE (MAO) INHIBITORS				
• Rasagiline	Inhibits MAO-B selectively; higher doses also inhibit MAO-A	Increases dopamine stores in neurons; may have	Parkinson disease: Adjunctive to levodopa • smooths levodopa response	Oral • *Toxicity & interactions:* May cause serotonin syndrome with meperidine, and theoretically also with selective serotonin reuptake inhibitors, tricyclic antidepressants

		neuroprotective effects		
• *Selegiline: Like rasagiline, adjunctive use with levodopa; may be less potent than rasagiline* • *Safinamide: Also used as adjunct to levodopa in patients with response fluctuations*				
COMT INHIBITORS				
• Entacapone	Inhibits COMT in periphery • does not enter CNS	Reduces metabolism of levodopa and prolongs its action	Parkinson disease	Oral • *Toxicity:* Increased levodopa toxicity • nausea, dyskinesias, confusion
• *Tolcapone: Like entacapone but enters CNS; some evidence of hepatotoxicity, elevation of liver enzymes* • *Opicapone: Taken once daily; not yet available in the USA*				
ANTIMUSCARINIC AGENTS				
• Benztropine	Antagonist at M receptors in basal ganglia	Reduces tremor and rigidity • little effect on bradykinesia	Parkinson disease	Oral • *Toxicity:* Typical antimuscarinic effects—sedation, mydriasis, urinary retention, constipation, confusion, dry mouth
• *Biperiden, orphenadrine, procyclidine, trihexyphenidyl: Similar antimuscarinic agents with CNS effects*				
DRUGS USED IN HUNTINGTON DISEASE				
• Tetrabenazine, deutetrabenazine, reserpine	Deplete amine transmitters, especially dopamine, from nerve endings	Reduce chorea severity	Huntington disease • other applications, see Chapter 11	Oral • *Toxicity:* Hypotension, sedation, depression, diarrhea • deutetrabenazine is the least toxic
• *Haloperidol, fluphenazine, other neuroleptics, olanzapine: Dopamine receptor blockers, sometimes helpful*				
DRUGS USED IN TOURETTE SYNDROME				
• Pimozide, haloperidol	Block central D_2 receptors	Reduce vocal and motor tic frequency, severity	Tourette syndrome • other applications, see Chapter 11	Oral • *Toxicity:* Parkinsonism, other dyskinesias • sedation • blurred vision • dry mouth • gastrointestinal disturbances • pimozide may cause cardiac rhythm disturbances
• *Clonidine, guanfacine: Effective in ~50% of patients; see Chapter 11 for basic pharmacology* • *Phenothiazines, atypical antipsychotics, tetrabenazine, deutetrabenazine, clonazepam, carbamazepine, topiramate: Often of value*				

PREPARATIONS AVAILABLE

GENERIC NAME	AVAILABLE AS
Amantadine	Generic, Gocovri, Osmolex ER, Symmetrel
Apomorphine	Apokyn
Benztropine	Generic, Cogentin
Biperiden	Akineton
Bromocriptine	Generic, Parlodel
Carbidopa	Lodosyn
Carbidopa/levodopa	Generic, Parcopa, Rytary, Sinemet
Carbidopa/levodopa/entacapone	Generic, Stalevo
Deutetrabenazine	Austedo
Entacapone	Generic, Comtan
Levodopa	Dopar, others
Opicapone*	Ongentys
Orphenadrine	Generic, various
Penicillamine	Cuprimine, Depen
Pergolide*	Permax, other
Pramipexole	Generic, Mirapex
Procyclidine	Kemadrin
Rasagiline	Azilect
Ropinirole	Generic, Requip, Requip XL
Safinamide	Xadago
Selegiline (deprenyl)	Emsam
Tetrabenazine	Xenazine
Tolcapone	Tasmar
Trientine	Syprine

Trihexyphenidyl	Generic, Artane, others
Valbenazine	Ingrezza

*Not available in the USA.

CASE STUDY ANSWER

The history is suggestive of parkinsonism, but the inconspicuous tremor and early cognitive changes raise the possibility of atypical parkinsonism rather than classic Parkinson disease. The prognosis of these disorders is worse than that of classic Parkinson disease. Given the cognitive changes and his age, the use of a dopamine agonist was unwise, as these agents are more likely than levodopa to exacerbate or precipitate behavioral and cognitive disturbances. Sleep attacks may occur spontaneously but are especially noted in patients receiving dopamine agonists. The patient has also developed punding, which is a recognized adverse effect of dopaminergic medication. Surgical treatment (deep brain stimulation) is contraindicated in patients with cognitive changes or atypical parkinsonism.

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