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SUPERIOR COURT OF THE STATE OF CALIFORNIA

COUNTY OF CONTRA COSTA

Coordination Proceeding Special Title (Rule 3.350) PARAQUAT CASES This document relates to: All Coordinated Actions	Case No. JCCP 5031 MS 5031 **SYNGENTA DEFENDANTS' OPPOSITION TO ISAAK'S MOTION FOR TRIAL PREFERENCE**

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I. INTRODUCTION

Mr. Isaak's motion for trial preference should be denied. California Code of Civil Procedure Section 36 is not mandatory in coordinated proceedings, because the Judicial Counsel has empowered coordination judges to manage such proceedings in a manner that ensures the "just determination of the coordinated actions without delay." (Ca. Rule of Court 3.541.) Where, as here, expediting a case for trial would disrupt rather than facilitate the orderly disposition of coordinated cases, preference should be denied. (See, e.g., *In re Toyota Motor Cases*, JCCP 4621, 2012 WL 965830 (Super. Ct. L.A. County Mar. 5, 2012) [denying preference motions and holding that Section 36 is not mandatory in the context of coordinated proceedings].) Furthermore, Mr. Isaak has not demonstrated that he is entitled to trial preference because he lacks the requisite "substantial interest in the action as a whole." (Code Civ. Proc., § 36(a).) Mr. Isaak has presented no evidence regarding his alleged paraquat exposures, and his medical records and doctor's declaration cast doubt on whether he actually has Parkinson's disease. Because Mr. Isaak's case is not representative of the manner in which plaintiffs describe this litigation as a whole, he lacks a "substantial interest" in the coordinated proceeding that would justify granting trial preference. Finally, discovery in Mr. Isaak's case has not begun, and is likely to be complicated; to set his case for trial without providing Defendants adequate time to develop the evidence and mount a defense would be unfair, and would infringe upon Defendants' right to due process of law. For these reasons, the Syngenta Defendants respectfully request that the Court deny Mr. Isaak's motion for preference.

II. BACKGROUND

Plaintiff George Isaak filed his complaint on May 4, 2021, alleging that he was exposed to paraquat over a 40-year period during which he periodically sprayed paraquat and other agrichemicals on his farm. (See Isaak Compl. (May 4, 2021).) On August 2, 2021, this court added Mr. Isaak's case to Judicial Council Coordinated Proceeding (JCCP) No. 5301. On that same day, Mr. Isaak filed a motion for trial preference (See Isaak Mot. for Trial Preference (Aug 2, 2021)) and produced approximately 1200 pages of medical records from a single provider between 2019 and 2021. (See Ex. A, C. Hoke letter to Counsel re Medical Records (Aug. 2, 2021).)

At the same time, Plaintiffs have offered the Court competing plans for their leadership structure and for handling preference motions within the coordinated proceedings. On August 2, 2021, plaintiffs represented by the Walkup Firm filed Proposed Case Management Order No. 1, outlining their preferred leadership structure and preference protocol. (See Pls.' Proposed CMO No. 1 (Aug. 2, 2021); Pls.' Am. Proposed CMO No. 1 (Aug. 17, 2021).) Following a case management conference with the Court on August 23, 2021, the Walkup plaintiffs and counsel representing Mr. Isaak filed competing motions on those same subjects. (See Isaak Obj. to the Stipulated Order on Mots. for Trial Preference (Aug. 20, 2021); Isaak Mem. of Points and Authorities in Support of Proposed Am. CMO No. 1 and Proposed CMO No. 2 (Sept. 3, 2021); *Isaak* Pls.' Mot. to Enter Proposed CMO No. 1 (Sept. 3, 2021).) Defendants filed a Motion to Enter Defendants' Proposed Case Management Order No. 1, proposing that the Court take a "holistic approach to managing this litigation" that shepherds these coordinated cases through discovery to trial in an orderly, fair, and efficient way. (See Br. in Supp.of Defs.' Proposed CMO No. 1 (Sept. 3, 2021) at 2.) On September 7 and 8, 2021, two other groups of plaintiffs informed the court that they are considering filing an additional thirty-five preference motions for individual plaintiffs.

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(See Watts Guerra Firm's Joinder in Pls.' Mot. for CMO No. 1 and No. 2 [describing review of 15 potential California cases], and Pulaski Kherkher Firm's Joinder in Pls.' Mot. for CMO No. 1 and No. 2 [describing review of 20 potential California cases].) This Court is set to hear argument on Mr. Isaak's preference motion on September 30, 2021. The Court has not yet entered a CMO nor resolved the issue of Plaintiffs' leadership structure.

III. ARGUMENT

A. The Court Should Deny Isaak's Motion Because It Would Hinder Efficient Management Of These Proceedings

The Court should exercise its discretion under the California Rules of Court and Code of Civil Procedure to deny trial preference motions at this early stage in the coordinated proceedings. To allow individual, potentially non-representative cases to move forward to trial before the Court has determined how to approach common discovery and to select appropriate bellwether cases would upset the orderly management of the coordinated proceedings and would create a risk of prejudice to all parties.

The purpose of a coordinated proceeding is to advance "the ends of justice" by ensuring the fair and efficient resolution of a set of similar individual suits. (Code Civ. Proc., § 404.1.) The Judicial Council has the power to make procedural rules for coordinated civil actions "[n]otwithstanding any other provision of law." (*Indus. Indent. Co. v. Super Ct.* (1989) 214 Cal.App.3d 259, 263 [noting that the "practical effect" of the Judicial Council's "grant of power is to remove any restraints of statutory consistency on the Judicial Council's rules" for coordinated proceedings].) In fact, California law "vest[s] in the coordinating judge whatever great breadth of discretion may be necessary and appropriate" to manage coordinated proceedings, such that "the procedures which may be utilized by the coordinating judge are flexible." (*McGhan Med. Corp. v. Sup. Ct.* (1992) 11 Cal.App.4th 804, 812.) That includes the authority to evaluate preference motions in light of the needs of the

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coordination proceeding as a whole, and courts can and should deny preference motions where, as here, granting preference would hinder the Court's ability to manage the coordinated proceedings fairly and efficiently.

Specifically, the great discretion given to JCCP judges includes the ability to develop orderly processes by which trial preference motions can be evaluated and, if appropriate, accommodated within the structure of a JCCP. Contrary to Isaak's claim, California Code of Civil Procedure Rule 36(a) is *not mandatory* in the JCCP context, and several courts have determined that to hold otherwise would tie the coordinating judge's hands in a way the legislature could not have intended. (See, e.g., *In re Toyota Motor Cases*, 2012 WL 965830 [holding that the "coordinated power trumps the otherwise mandatory application of Cal. Civ. Proc. Section 36"]; see also Chevron's Br. in Opp'n to Isaak's Mot. for Trial Preference (Sept. 17, 2021) at 7-9 [collecting authority in support of the argument that Section 36 directly conflicts with, and therefore is superseded by, CRC 3.514].) For instance, in *Toyota Motor Cases* Judge Mohr denied motions for trial preference under Sections 36(b) and 36(d), explaining that "[w]hile Cal. Civ. Proc. section 36(b) is mandatory by its terms, special consideration is given to coordinated proceedings," and Section 36 is therefore "non-mandatory in coordinated cases due to its conflict [with] the California Rules of Court." (2012 WL 965830; *see also Abelson v. Nat'l Union Fire Ins. Co. of Pittsburgh* (1994) 28 Cal.App.4th 776, 788 [acknowledging that the statutory scheme "allow[s] the coordination judge to fashion schedules and procedures that do not precisely follow established procedure because of the unique nature of a coordinated proceeding"].) In that case, Judge Mohr held that because the court and counsel in that case had already selected bellwether cases for trial, the Court had discretion to deny the preference motion and "schedule trials in furtherance of justice and for the efficient use of judicial facilities and resources." (*Toyota Motor Cases*, 2012 WL

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965830, at *7 [citing Rule 3.541(b)(2)].) While this case is in a different posture, allowing preference trials now would be no less disruptive to the Court's ability to efficiently manage these proceedings.

Given the nature of this case—involving a disease that almost universally manifests in older individuals—allowing Mr. Isaak's case to proceed to an expedited trial will encourage a string of such filings from other plaintiffs. (See Br. in Supp. of Defs.' Proposed CMO No. 1 (Sept. 3, 2021) at 7; Pls.' Mem. of Points and Authorities in Support of Proposed Am. CMO No. 1 & Proposed CMO No. 2 (Sept. 3, 2021) at 11.) Indeed, certain groups of plaintiffs have recently informed the court that they are considering filing another thirty-five motions for trial preference. (See Watts Guerra Firm's Joinder in Pls.' Mot. for CMO No. 1 & No. 2 [describing review of 15 potential California cases], and Pulaski Kherkher Firm's Joinder in Pls.' Mot. for CMO No. 1 and No. 2 [describing review of 20 potential California cases].) An onslaught of litigation of individual claims would fundamentally impair this Court's ability to manage discovery on common issues and select appropriate bellwether cases for trial. The JCCP rules empower the Court to avoid this outcome, by giving the Court great discretion to manage that process, notwithstanding any other rules. For this reason (along with those below), the Court should deny Mr. Isaak's preference motion and use its discretion to set cases for trial in the order that best suits the needs of the coordinated proceedings as a whole.

B. Isaak's Section 36(a) Motion Should Be Denied Because He Lacks A "Substantial Interest" In The Proceeding As A Whole

Even if the Court were to take up the merits of Mr. Isaak's motion, it should still be denied. California Code of Civil Procedure Section 36(a) provides an avenue for a party over the age of 70 to seek an expedited trial if the court determines that the movant has a "substantial interest in the

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action as a whole," and that his or her state of health "is such that a preference is necessary to prevent prejudicing the party's interest in the litigation." (Code Civ. Proc., § 36(a).) In other words, on its face, Section 36 does not automatically grant trial preference to parties over 70 who are in poor health: "[t]he court has discretion to determine the *extent* of the party's interest" in the proceeding. (Weil & Brown, Cal. Practice Guide: Civil Procedure Before Trial (The Rutter Group 2021) ¶ 12:246 [emphasis in original].)

In a coordinated proceeding, "an individual plaintiff … does not have a '*substantial* interest in the action *as a whole*' simply by having a singular injury claim in the larger coordinated proceeding." (*Stevens v. Monsanto*, No. CIV SB 2104801, 2020 WL 10573310 (Cal. Super. Oct. 30, 2020) [emphasis in original] [denying motion for trial preference because plaintiff failed to meet burden of showing substantial interest in the coordinated proceeding as a whole].) Plaintiffs represented by the Walkup Firm evidently agree that, in the context of a JCCP, "substantial interest in the action as a whole" should be read to require a substantial interest in the *coordinated proceeding*. (See Pls.' Mem. of P. & A. in Supp. of Entry of CMO 1 & Proposed CMO 2 (Sept. 3, 2021) at 9 and n. 5 [collecting cases].) And as Chevron's brief explains, to read the phrase "the action as a whole" to refer only to an individual's own claims in the context of a coordinated proceeding would deprive that phrase of meaning and render it surplusage. (See Chevron's Br. in Opp'n to Isaak's Mot. for Trial Preference (Sept. 17, 2021) at 11-12.)

Instead, "the most persuasive interpretation of the phrase 'a substantial interest in the action as a whole' requires comparing the moving party's individual interest to the interests of every other party in the action." (*S. Ca. Fire Cases*, JCCP No. 4965, Ruling on Mot. for Trial Preference at *6 (L.A. Super. Ct. May 7, 2019).) In order to have a "substantial interest" in a coordinated proceeding

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like this one, a plaintiff's claims must be representative of all (or at least the great majority) of the coordinated cases, such that the resolution of his case would assist in the fair and efficient disposition of the remaining cases. This is because, on a practical level, granting trial preference makes the expedited case a bellwether trial. In complex coordinated litigation like these matters, courts choose bellwether cases with great care, knowing that "representative cases … will best produce information regarding value ascertainment for settlement purposes or to answer causation or liability issues common to the universe of plaintiffs." (*In re Hydroxycut Mktg. & Sales Practices Litig.*, No. 09-md-2087 BTM(KSC), 2012 WL 3637278, at *3 (S.D. Cal. Aug. 21, 2012); Manual for Complex Litigation (Fourth) § 22.315 (2004) [only if a "representative" set of bellwether cases are selected can "individual trials … produce reliable information about other mass tort cases."].) A plaintiff whose case is non-representative of plaintiffs' claims as a whole lacks a "substantial interest" in the coordinated proceeding that would weigh in favor of granting trial preference; in fact, as discussed below, if non-representative cases are permitted to jump the line, that might "compromise the rights of all remaining plaintiffs' interests in just and speedy resolution" of their suits. (Pls.' Mem. of P. & A. in Supp. of Entry of CMO 1 & Proposed CMO 2 (Sept. 3, 2021) at 9.)

Here, Mr. Isaak has not established that he has a "substantial interest" in the coordinated proceeding as whole. Isaak's interest in this lawsuit is limited to his as-yet unsubstantiated claim that he was exposed to paraquat and that such exposures caused him to develop Parkinson's disease ("PD"). Yet the "evidence" that Mr. Isaak has presented so far to support these allegations is thin, at best. For instance, Mr. Isaak has presented no evidence whatsoever related to his alleged paraquat exposures, and the allegations in his complaint are so broad as to be essentially

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meaningless—he alleges only that "at all relevant times," he "was a pesticide applicator who was exposed to Paraquat in California" but does not provide the most basic details on what paraquat products he allegedly used, or when and where he allegedly used them. (See Isaak Compl. ¶ 21.)

Perhaps more importantly, there is serious doubt that Mr. Isaak even has PD, as compared to another form of parkinsonism. (See generally Ex. B (Harrison's Principles of Internal Medicine, 20th ed. (2019), 427:6 [describing the differences between Parkinson's disease and other forms of parkinsonism].) Specifically, the medical records Mr. Isaak has produced to date show that he does not have certain key clinical signs of PD, such as a resting tremor, one of the "cardinal features" of the disease. (See *id.*) Indeed, the records from Mr. Isaak's July 2020 neurology evaluation indicate that his neurologist found no tremor, and noted that Mr. Isaak's condition did not present the typical hallmarks of PD. Notably, Dr. Oster—Isaak's hired expert who provided a declaration in support of his motion for trial preference—states his opinion "to a reasonable degree of medical certainty" that Mr. Isaak suffers from "*a Parkinsonian disorder*," rather than actual PD. (Oster Decl. (Aug. 1, 2021) at 1 [emphasis added].)

This is not mere hair-splitting. PD differs in significant ways from other parkinsonisms, both clinically and pathologically. Clinically, "[i]n comparison to PD, the atypical parkinsonisms are characterized [] by early involvement of speech and gait, absence of rest tremor, lack of motor asymmetry," among other differences. Ex. B (Harrison's Principles of Internal Medicine, 20th ed. (2019), 427:6.) Pathologically, PD involves localized damage to a part of the brain called the substantia nigra pars compacta ("SNc"), whereas other parkinsonisms are "usually associated with more widespread pathology than found in PD (potentially with degeneration of striatum, globus pallidus, cerebellum and brainstem as well as the SNc)." (*Id.*)

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Every complaint in this proceeding alleges a connection between *Parkinson's disease* and paraquat, and evidence on that alleged connection will surely play a key role in the determination of these cases. Given the very real differences between PD and other parkinsonisms, the question of whether paraquat may be related to other parkinsonisms sheds little or no light on the key questions in this coordinated proceeding. For this reason, Mr. Isaak's questionable diagnosis makes his case particularly unsuited to serving as a bellwether. Therefore, Mr. Isaak cannot be said to have a "substantial interest" in the coordination proceeding as a whole that would support granting trial preference.

C. Granting Isaak's Preference Motion Would Infringe Defendants' Due Process Rights

Finally, the Court should also deny Mr. Isaak's preference motion because expediting his trial would deny Defendants an opportunity to undertake the significant discovery necessary to mount an appropriate defense. Due process requires that defendants be afforded a reasonable opportunity for discovery and pretrial preparation, especially where, as here, plaintiff seeks punitive damages. (See, e.g., *Philip Morris USA v. Williams* (2007) 549 U.S. 346, 353 ["[T]he Due Process Clause prohibits a State from punishing an individual without first providing that individual with an opportunity to present every available defense."]; *San Bernardino City Unified Sch. Dist. v. Super. Ct.*, (1987) 190 Cal.App.3d 233, 240 [affirming trial court's denial of motion to set trial within 90 days in part because "some degree of prejudice would have resulted merely because of the relatively short period of time in which to actually prepare for trial"]; see also Weil & Brown, Cal. Practice Guide: Civil Procedure Before Trial (The Rutter Group 2021) ¶ 12:248.2 [if a court imposes a trial date "so early as to deprive defendant of [a] reasonable opportunity for discovery or pretrial preparation," that "may violate due process of law"] [citing *Roe v. Sup. Ct. (Sheldon)* (1990) 224 Cal.App.3d 642, n. 2].) Courts have acknowledged that "strong countervailing considerations—deriving from principles of efficient trial

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court management; from fairness and due process to other litigants; and from divergent public policy or statutory contexts" make it such that the "section 36(a) mandate may be difficult, impractical, or impossible to realize." (*Miller v. Super. Ct.*, (1990) 221 Cal.App.3d 1200, 1206; *see Roe v. Super. Ct.* (1990) 224 Cal.App.3d 642, 644 n.2 [recognizing that interests underlying preference motions must be balanced against due process, such that a court might determine that it cannot "bring the matter to trial within the technical limits of Code of Civil Procedure section 36, subdivision (f)")].)

The *Isaak* case is in its infant stages, and the necessary fact and expert discovery have yet to begin in earnest. For instance, although Mr. Isaak has represented that he has produced all of his medical records, those records are clearly incomplete. They only cover his most recent treatment (from 2019 to present) from one health system (Kaiser Permanente). Notably lacking are records relating to his long history of diabetes, his kidney transplant, or his pre-2019 history of falls and head trauma. Likewise, key records relating to his PD diagnosis, such as the actual images from Mr. Isaak's DaT brain scan, brain MRI, and brain CT scan, are missing entirely. Pushing forward with this case within the technical limits of Rule 36—at the expense of adequate time to obtain discovery from Mr. Isaak—would run the risk of infringing Defendants' due process rights. For this additional reason, the Syngenta Defendants respectfully request that the Court deny Mr. Isaak's motion for trial preference.

IV. CONCLUSION

For the foregoing reasons, and those advanced by Co-Defendant Chevron in its opposition, the Syngenta Defendants respectfully request that the Court exercise its discretion to deny Mr. Isaak's preference motion, and further request that the Court enter a protocol for preference motions to ensure that any future preference motions are evaluated in a manner that serves the needs of the JCCP as a

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whole.

Dated: September 17, 2021

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PROOF OF SERVICE

I am a resident of the State of California, over the age of eighteen years, and not a party to the within action. My business address is: Gordon Rees Scully Mansukhani, LLP, 1111 Broadway, Suite 1700, Oakland, CA 94607. On the date set forth below, I served the within documents:

SYNGENTA DEFENDANTS' OPPOSITION TO ISAAK'S MOTION FOR TRIAL PREFERENCE

☒	by electronically serving the document(s) described above via ***File & ServeXpress*** on the recipients designated on the Transaction Receipt that is located on the ***File & ServeXpress*** website and as set forth below:
☐	by placing the document listed above in a sealed envelope with postage thereon fully prepaid, in United States mail in the State of California at Oakland, addressed as set forth below.
☐	by transmitting via facsimile the documents listed above to the fax numbers set forth below on this date before 5:00 p.m.

I declare under penalty of perjury under the laws of the State of California that the above is true and correct.

Executed on September 17, 2021, at Vallejo, California.

Andrea Christie

ANDREA CHRISTIE

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EXHIBIT A

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Re: Paraquat JCCP 5031 – Medical Records on File for Plaintiff George Isaak

Dear Counsel,

Please see the enclosed medical records on file for Plaintiff George Isaak.

Very truly yours,

THE MILLER FIRM, LLC

Curtis G. Hoke, Esq.

EXHIBIT B

Chapter 427: Parkinson's Disease

C. Warren Olanow; Christine Klein; Anthony H.V. Schapira

CONTENT UPDATE

31 January 2019

Updated to reflect new findings on the use of Levadopa in Parkinson's disease.

PARKINSON'S DISEASE AND RELATED DISORDERS

Parkinson's disease (PD) is the second most common age-related neurodegenerative disease, exceeded only by Alzheimer's disease (AD). Its cardinal clinical features were first described by the English physician James Parkinson in 1817. It is noteworthy that James Parkinson was a general physician who captured the essence of this condition based on a visual inspection of a mere handful of patients, several of whom he only observed and did not formally examine. It is estimated that the number of people with PD in the most populous nations worldwide was ~4 million persons in 2005, and this number is expected to more than double to ~9 million by the year 2030 based on the aging of the population. The mean age of onset of PD is about 60 years, and the lifetime risk is ~2% for men and 1.3% for women. The frequency of PD increases with aging, but cases can be seen in individuals in their twenties and even younger, particularly in association with a gene mutation.

Clinically, PD is characterized by rest tremor, rigidity (stiffness), bradykinesia (slowing), and gait dysfunction with postural instability. These are known as the "cardinal features" of the disease. Additional clinical features can include freezing of gait, speech difficulty, swallowing impairment, autonomic disturbances, and a series of nonmotor features that include sensory alterations, mood disorders, sleep dysfunction, cognitive impairment, and dementia **(see Table 427-1 and discussion below)**.

TABLE 427-1

Clinical Features of Parkinson's Disease

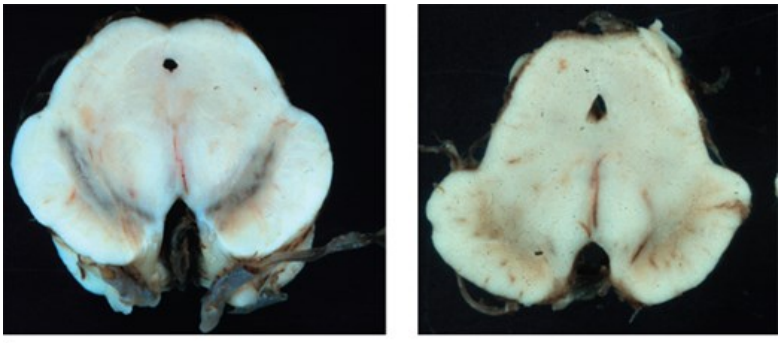
Cardinal Motor Features	Other Motor Features	Nonmotor Features
Bradykinesia	Micrographia	Anosmia
Rest tremor	Masked facies (hypomimia)	Sensory disturbances (e.g., pain)
Rigidity	Reduced eye blinking	Mood disorders (e.g., depression)
Postural instability	Drooling	Sleep disturbances (e.g., RBD)
	Soft voice (hypophonia)	Autonomic disturbances
	Dysphagia	Orthostatic hypotension
	Freezing	Gastrointestinal disturbances
		Genitourinal disturbances
		Sexual dysfunction
		Cognitive impairment/Dementia

Abbreviations: RBD, rapid eye movement behavior disorder.

Pathologically, the hallmark features of PD are degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc), reduced striatal dopamine, and intraneuronal proteinaceous inclusions known as Lewy bodies and Lewy neurites that primarily contain the protein α-synuclein **(Fig. 427-1)**. While interest has primarily focused on the dopamine system, neuronal degeneration with inclusion body formation can also affect cholinergic neurons of the nucleus basalis of Meynert (NBM), norepinephrine neurons of the locus coeruleus (LC), serotonin neurons in the raphe nuclei of the brainstem, and neurons of the olfactory system, cerebral hemispheres, spinal cord, and peripheral autonomic nervous system. This "nondopaminergic" pathology is likely responsible for the development of the nondopaminergic clinical features listed in Table 427-1. There is some evidence that Lewy body pathology can begin in the peripheral autonomic nervous system, olfactory system, and dorsal motor nucleus of the vagus nerve in the lower brainstem, and then spread in a predictable and sequential manner to affect the upper brainstem (SNc) and cerebral hemispheres (Braak staging). These studies suggest that the classic degeneration of SNc dopamine neurons and the cardinal motor features of PD develop at a mid-stage of the disease. Indeed, epidemiologic studies suggest that clinical symptoms reflecting early involvement of nondopaminergic neurons such as constipation, anosmia, rapid eye movement (REM) behavior sleep disorder, and cardiac denervation can precede the onset of the classic motor features of PD by several years if not decades. Based on these findings, efforts are underway to accurately define a premotor stage of PD.

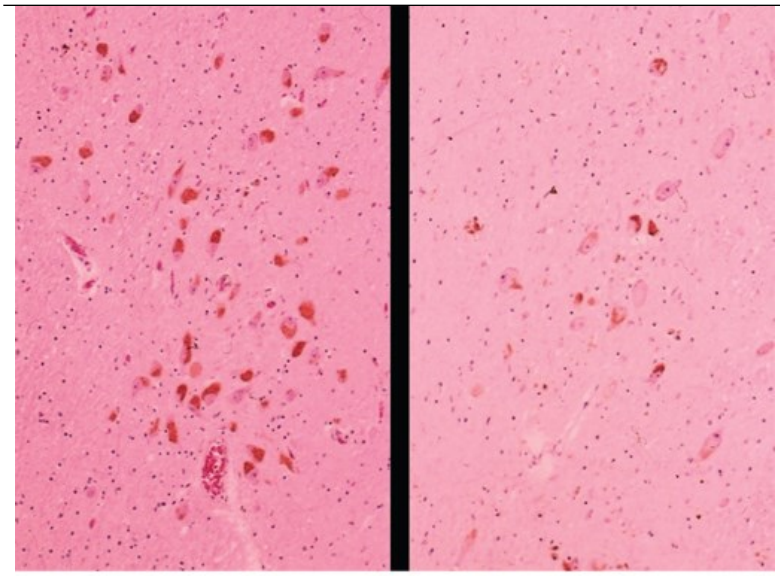
FIGURE 427-1

Pathologic specimens from a patient with Parkinson's disease (PD) compared to a normal control demonstrating (***A***) reduction of pigment in SNc in PD (*right*) versus control (*left*), (***B***) reduced numbers of cells in SNc in PD (*right*) compared to control (*left*), and (***C***) Lewy bodies (*arrows*) within melanized dopamine neurons in PD. SNc, substantia nigra pars compacta.



A

Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition



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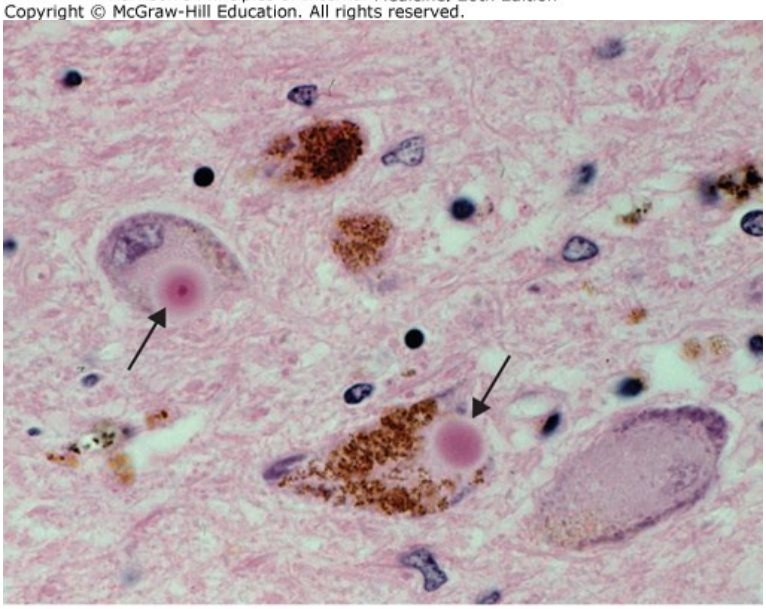


C

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Parkinsonism is a generic term that is used to define a syndrome manifest by bradykinesia with rigidity and/or tremor. It has a differential diagnosis **(Table 427-2)** that reflects differences in the site of damage and pathology in the various components of the basal ganglia. The basal ganglia comprise a group of subcortical nuclei that include the striatum (putamen and caudate nucleus), subthalamic nucleus (STN), globus pallidus pars externa (GPe), globus pallidus pars interna (GPi), and the SNc **(Fig. 427-2)**. Among the different forms of parkinsonism, PD is the most common (~75% of cases). Historically, PD was diagnosed based on the presence of two of three parkinsonian features (tremor, rigidity, bradykinesia). However, postmortem studies found a 24% error rate when diagnosis was based solely on these criteria. Clinicopathologic correlation studies subsequently determined that parkinsonism associated with rest tremor, asymmetry of motor impairment, and a good response to levodopa was more likely to

predict the correct pathologic diagnosis. With these revised criteria (known as the U.K. Brain Bank Criteria), a clinical diagnosis of PD could be confirmed pathologically in as many as 99% of cases. The International Parkinson's Disease and Movement Disorder Society (MDS) has recently suggested revised clinical criteria for PD (known as the MDS Clinical Diagnostic Criteria for Parkinson's disease) that are currently undergoing international validation. While motor parkinsonism has been retained as the core feature of the disease, the diagnosis of PD as the cause of parkinsonism relies on three additional categories of diagnostic features: supportive criteria (features that increase confidence in the diagnosis of PD), absolute exclusion criteria, and red flags (which must be counterbalanced by supportive criteria to permit a diagnosis of PD). Utilizing these criteria, two levels of certainty have been delineated; clinically established PD, and probable PD. The key diagnostic criteria for PD based on MDS criteria are illustrated in Table 427-2.

TABLE 427-2

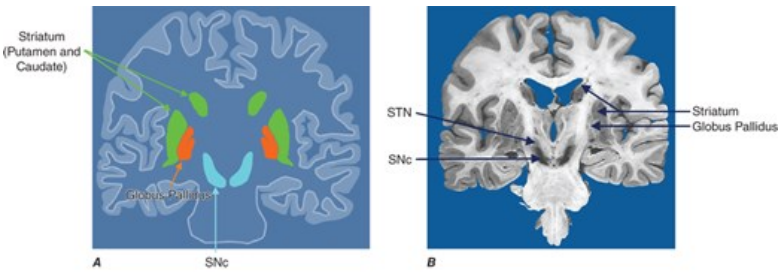
Differential Diagnosis of Parkinsonism

Parkinson's Disease Sporadic Genetic Dementia with Lewy bodies	Atypical Parkinsonism Multiple-system atrophy (MSA) Cerebellar type (MSA-c) Parkinson type (MSA-p) Progressive supranuclear palsy Parkinsonism Richardson variant Corticobasal Syndrome Frontotemporal dementia	Secondary Parkinsonism Drug-induced Tumor Infection Vascular Normal-pressure hydrocephalus Trauma Liver failure Toxins (e.g., carbon monoxide, manganese, MPTP, cyanide, hexane, methanol, carbon disulfide)	Neurodegenerative Disorders and other forms of parkinsonism Wilson's disease Huntington's disease Neurodegeneration with brain iron accumulation SCA 3 (spinocerebellar ataxia) Fragile X–associated ataxia-tremor-parkinsonism Prion disease X-linked Dystonia-parkinsonism Alzheimer's disease with parkinsonism Dopa-Responsive Dystonia

Abbreviations: MPTP, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine.

FIGURE 427-2

Basal ganglia nuclei. Schematic (***A***) and postmortem (***B***) coronal sections illustrating the various components of the basal ganglia. SNc, substantia nigra pars compacta; STN, subthalamic nucleus.

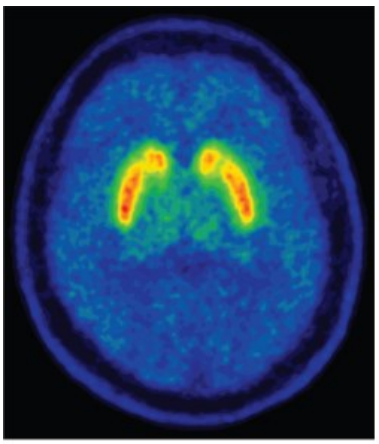


Imaging of the brain dopamine system in patients with PD can be performed using positron emission tomography (PET) or single-photon emission computed tomography (SPECT). These studies typically show reduced and asymmetric uptake of striatal dopaminergic biomarkers, particularly in the

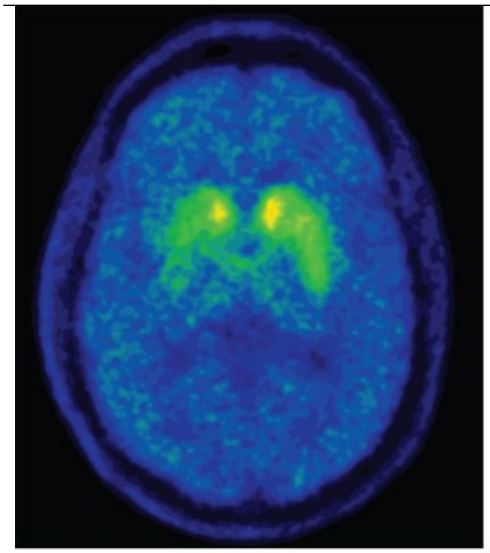
posterior putamen with relative sparing of the caudate nucleus **(Fig. 427-3)**. These findings reflect the degeneration of nigrostriatal dopaminergic neurons and the loss of striatal terminals. Imaging can be useful in patients where there is diagnostic uncertainty (e.g., essential tremor, dystonic tremor, psychogenic tremor) or in research studies, but is rarely necessary in routine practice because the diagnosis can usually be established on clinical criteria alone. This may change in the future when there is a disease-modifying therapy and it is critically important to make a correct diagnosis as early as possible. Genetic testing can be helpful for establishing a diagnosis, but is not routinely employed as monogenic forms are rare and likely account for no more than 5% of cases (see discussion below). A genetic form of PD should be considered in patients with a positive family history, early age of onset (<40 years), a specific clinical picture or a particular ethnic background, and in research studies. Mutations of the *LRRK2* gene have attracted particular interest because they are the most common known cause of familial PD and are responsible for ~1% of typical sporadic cases of the disease. Mutations in *LRRK2* are a particularly frequent cause (~25%) of PD in Ashkenazi Jews and North African Berber Arabs; however, there is considerable variability in penetrance and many carriers never develop clinical features of PD. Genetic testing is of particular interest to identify at-risk individuals in a research setting. There is also some evidence that diagnosis of PD, and even pre-PD, may possible based on the presence of increased iron accumulation in the SNc using transcranial sonography or special MRI protocols.

FIGURE 427-3

[^{11}C]Dihydrotetrabenazine positron emission tomography (a marker of VMAT2) in healthy control (*A*) and Parkinson's disease (*B*) patient. Note the reduced striatal uptake of tracer, which is most pronounced in the posterior putamen and tends to be asymmetric. *(Courtesy of Dr. Jon Stoessl.)*



A



B

Atypical, Secondary and Other Forms of Parkinsonism

Atypical parkinsonism refers to a group of neurodegenerative conditions that usually are associated with more widespread pathology than found in PD (potentially with degeneration of striatum, globus pallidus, cerebellum and brainstem as well as the SNc). These include Multiple System Atrophy (MSA), Progressive Supranuclear Palsy (PSP), and Corticobasal syndrome (CBS). As a group, they present with parkinsonism (rigidity and bradykinesia) but manifest clinical differences from PD reflecting the differences in their underlying pathology. In comparison to PD, the atypical parkinsonisms are characterized clinically by early involvement of speech and gait, absence of rest tremor, lack of motor asymmetry, poor or no response to levodopa, and a more aggressive clinical course. In the early stages, they may show a modest benefit from levodopa and can be difficult to distinguish from PD, but the diagnosis becomes clearer with disease evolution. Pathologically, neurodegeneration involves the SNc (typically without Lewy bodies) and has more extensive neurodegeneration than occurs in PD (see below for individual conditions). Neuroimaging of the dopamine system is usually not helpful, as striatal dopamine depletion can be seen in both PD and atypical parkinsonism. By contrast, metabolic imaging of the basal ganglia/thalamus network (using 2-F-deoxyglucose) may be helpful, showing a pattern of decreased activity in the GPi with increased activity in the thalamus, the reverse of what is seen in PD.

MSA manifests as a combination of parkinsonian, cerebellar, and autonomic features and can be divided into a predominant parkinsonian (MSA-p) or cerebellar (MSA-c) form. Clinically, MSA is suspected when a patient presents with features of atypical parkinsonism as described above in conjunction with cerebellar signs and/or prominent autonomic dysfunction, usually orthostatic hypotension **(Chap. 432)**. Pathologically, MSA is characterized by degeneration of the SNc, striatum, cerebellum, and inferior olivary nuclei coupled with characteristic glial cytoplasmic inclusions (GCIs) that stain positively for α-synuclein. Magnetic resonance imaging (MRI) can show pathologic iron accumulation in the striatum on T2-weighted scans, high signal change in the region of the external surface of the putamen (putaminal rim) in MSA-p, or cerebellar and brainstem atrophy (the pontine "hot cross bun" sign **[Fig. 432-2]**) in MSA-c. There is currently no established evidence for any gene mutation/genetic risk factor for MSA. Recent studies suggest the possibility that MSA may be a prion disorder (see discussion below).

PSP is a form of atypical parkinsonism that is characterized by slow ocular saccades, eyelid apraxia, and restricted vertical eye movements with particular impairment of downward gaze. Patients frequently experience hyperextension of the neck with early gait disturbance and falls. In later stages, speech and swallowing difficulty and cognitive impairment may become evident. There is usually little or no response to levodopa. Two clinical forms of PSP have been identified; a "Parkinson" form that can closely resemble PD in the early stages including a positive response to levodopa, and the more classic "Richardson" form that is characterized by the features described above. MRI may reveal a characteristic atrophy of the midbrain with relative preservation of the pons on midsagittal images (the so-called "hummingbird sign"). Pathologically, PSP is characterized by degeneration of the SNc, striatum, STN, midline thalamic nuclei, and pallidum, coupled with neurofibrillary tangles and inclusions that stain for the tau protein. Mutations

in the MAPT gene which encodes for the tau protein have been detected in some familial cases.

CBS is the least common of the three atypical parkinsonisms and usually presents with asymmetric dystonic contractions and clumsiness of one hand coupled with cortical sensory disturbances manifest as apraxia, agnosia, focal limb myoclonus, or alien limb phenomenon (where the limb assumes a position in space without the patient being aware of the position or recognizing that the limb belongs to him/her). Dementia may occur at any stage of the disease. Both cortical and basal ganglia features are required to make this diagnosis. MRI frequently shows asymmetric cortical atrophy but this must be carefully sought. Pathologic findings include achromatic neuronal degeneration with tau deposits. Considerable overlap may occur both clinically and pathologically between CBS and PSP, and they may be difficult to distinguish without pathologic confirmation.

Secondary parkinsonisms occur as a result of a variety of primary conditions including drugs, stroke, tumor, infection, or exposure to toxins such as carbon monoxide or manganese that can cause damage to specific regions of the basal ganglia. Clinical features reflect the region of the basal ganglia that has been damaged. For example, strokes or tumors that affect the SNc may have a clinical picture identical to PD, whereas toxins such as carbon monoxide or manganese that damage the globus pallidus more closely resemble atypical parkinsonism. Dopamine-blocking agents such as neuroleptics are the most common cause of secondary parkinsonism. These drugs are most widely used in psychiatry, *but medical physicians should be aware that drugs such as metoclopramide which are primarily used to treat gastrointestinal problems are also neuroleptic agents* and may induce secondary parkinsonism. These drugs can also cause acute and tardive dyskinesias **(see Chap. 428)**. Other drugs that can cause secondary parkinsonism include tetrabenazine, calcium channel blockers (flunarizine, cinnarizine), amiodarone, and lithium.

Parkinsonism can also be seen in Dopa-Responsive Dystonia, a condition that results from a mutation in the *GTP-Cyclohydrolase 1 gene* which can lead to a defect in a cofactor for tyrosine hydroxylase and the impaired manufacture of dopa and dopamine. While it typically presents as dystonia **(Chap. 428)**, it can present as a biochemically based form of parkinsonism (due to reduced synthesis of dopamine) which closely resembles PD and responds to levodopa, but is not associated with abnormalities on fluoro-dopa positron emission tomography (FD-PET) nor neurodegeneration. This diagnosis should be considered in individuals aged <20 years who present with a clinical picture resembling PD.

Finally, parkinsonism can be seen as a feature of a variety of other degenerative disorders such as Wilson's disease, Huntington's disease (especially the juvenile form known as the Westphal variant), certain forms of spinocerebellar ataxias, and neurodegenerative disorders with brain iron accumulation such as pantothenate kinase (PANK)–associated neurodegeneration (formerly known as Hallervorden-Spatz disease).

Some features that suggest that parkinsonism might be due to a condition other than PD are shown in **Table 427-3**.

TABLE 427-3

Features Suggesting an Atypical or Secondary Cause of Parkinsonism

Symptoms/Signs	Alternative Diagnosis to Consider
History	
Early speech and gait impairment (Lack of tremor, lack of motor asymmetry)	Atypical parkinsonism
Exposure to neuroleptics	Drug-induced parkinsonism
Onset prior to age 40	Genetic form of PD
Liver disease	Wilson's disease, non-Wilsonian hepatolenticular degeneration
Early hallucinations and dementia with later development of PD features	Dementia with Lewy bodies
Diplopia, impaired down gaze	PSP
Poor or no response to an adequate trial of levodopa	Atypical or secondary parkinsonism
Physical Examination	
Dementia as first or early feature	Dementia with Lewy bodies
Prominent orthostatic hypotension	MSA-p
Prominent cerebellar signs	MSA-c
Slow saccades with impaired down gaze	PSP
High-frequency (6–10 Hz) symmetric postural tremor with a prominent kinetic component	Essential tremor

Abbreviations: MSA-c, multiple-system atrophy–cerebellar type; MSA-p, multiple-system atrophy–Parkinson's type; PD, Parkinson's disease; PSP, progressive supranuclear palsy.

ETIOLOGY AND PATHOGENESIS

Most PD cases occur sporadically (~85–90%) and are of unknown cause. Gene mutations (see below) are the only known causes of PD. Twin studies performed several decades ago suggested that environmental factors might play an important role in patients with an age of onset ≥50 years, with genetic factors being more important in younger-onset patients. However, the demonstration of later onset genetic variants (e.g., *LRRK2* and *GBA*) argues against the emphasis on environmental factors, even in individuals >50 years of age. The environmental hypothesis received some support in the 1980s with the demonstration that MPTP (1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine), a by-product of the illicit manufacture of a heroin-like drug, caused a PD-like syndrome in addicts in northern California. MPTP is transported into the central nervous system, where it is oxidized to form MPP^+, a mitochondrial toxin that is selectively taken up by, and damages, dopamine neurons. However, MPTP or MPTP-like compounds have not been linked to sporadic PD. Epidemiologic studies have reported an increased risk of developing PD in association with exposure to pesticides, rural living, farming, and drinking well water. Dozens of other associations have also been reported in individual studies but results have been inconsistent, and

no environmental factor has yet been proven to be a cause or to contribute to the cause of PD. Some possible protective factors have also been identified in epidemiologic studies including caffeine, smoking, intake of nonsteroidal anti-inflammatory drugs, and calcium channel blockers. The validity of these findings and the responsible mechanism also remain to be established.

About 5–15% of cases are familial in origin, and mutations in several PD-linked genes have been identified **(Table 427-4)**. While monogenic mutations have been shown to be causative of PD, genetic risk factors that increase the risk of developing PD have also been identified. Large-size genome-wide association studies (GWASs) have identified 26 independent gene variants (single nucleotide polymorphisms) as PD risk factors including variants in the *SNCA, LRRK2, MAPT*, and *GBA* genes as well as in the HLA region on chromosome 6. It has been proposed that many cases of PD may be due to a "double hit" involving an interaction between (a) one or more genetic risk factors that induce susceptibility coupled with (b) exposure to a toxic environmental factor that may induce epigenetic or somatic DNA alterations or has the potential to directly damage the dopaminergic system. In this scenario, both factors are required for PD to ensue, while the presence of either one alone is not sufficient to cause the disease. Notably, however, even if a genetic or environmental risk factor doubles the risk to develop PD, this only results in a lifetime risk of 4% or lower, and thus cannot presently be used for individual patient counseling.

TABLE 427-4

Confirmed Genetic Causes of Parkinson's Disease*

Designation* and Reference	GeneReviews and OMIM Reference	Clinical Clues	Inheritance	Previous Locus Symbol
1. Classical PD				
PARK-*SNCA*	GeneReviews *http://www.ncbi.nlm.nih.gov/books/NBK1223/* OMIM 168601	Missense mutations cause classical parkinsonism. Duplication or triplication mutations in this gene cause early onset parkinsonism with prominent dementia.	AD	PARK1
PARK-*LRRK2*	GeneReviews *http://www.ncbi.nlm.nih.gov/books/NBK1208/* OMIM 607060	Clinically typical PD	AD	PARK8
PARK-*VPS35*	GeneReviews *http://www.ncbi.nlm.nih.gov/books/NBK1223/* OMIM 614203	Clinically typical PD	AD	PARK17
2. Early-onset PD				
PARK-*Parkin*	GeneReviews *http://www.ncbi.nlm.nih.gov/books/NBK1155/* OMIM 600116	Often presents with dystonia, typically in a leg	AR	PARK2
PARK-*PINK1*	GeneReviews *http://www.ncbi.nlm.nih.gov/books/NBK1223/* OMIM 605909	Often presents with psychiatric features	AR	PARK6
PARK-*DJ1*	GeneReviews *http://www.ncbi.nlm.nih.gov/books/NBK1223/* OMIM 606324		AR	PARK7
3. Parkinsonism				

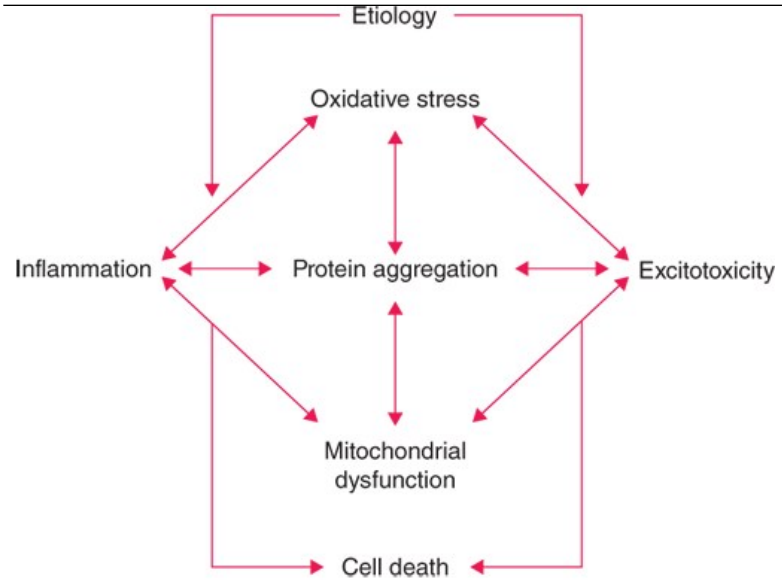
PARK-*ATP13A2*	GeneReviews *http://www.ncbi.nlm.nih.gov/books/NBK1223/* OMIM 606693	Kufor-Rakeb syndrome with parkinsonism and dystonia; additional features: Supranuclear gaze palsy, spasticity/pyramidal signs, dementia, facial-faucial-finger mini-myoclonus, dysphagia, dysarthria, olfactory dysfunction	AR	PARK9
PARK-*FBXO7*	GeneReviews *http://www.ncbi.nlm.nih.gov/books/NBK1223/* OMIM: 260300	Early onset parkinsonism with pyramidal signs	AR	PARK15
PARK-*DNAJC6*	GeneReviews: n/a OMIM 615528	May present with mental retardation and seizures	AR	PARK19
PARK-*SYNJ1*	GeneReviews: n/a OMIM 615530	May have seizures, cognitive decline, abnormal eye movements, and dystonia	AR	PARK20

*According to the recommendations of the International Parkinson's and Movement Disorder Society (C Marras: Mov Disord 31:436, 2016).

Several factors have been implicated in the pathogenesis of cell death in PD, including oxidative stress, inflammation, excitotoxicity, mitochondrial dysfunction, and the accumulation of misfolded proteins with consequent proteolytic stress. Recent studies have demonstrated that with aging, dopamine neurons switch from sodium to calcium pacing through calcium channels, potentially making these high-energy neurons vulnerable to calcium-mediated neurotoxicity. Whatever the pathogenic mechanism, cell death appears to occur, at least in part, by way of a signal-mediated apoptotic or "suicidal" process. Each of these mechanisms offers a potential target for putative neuroprotective drugs. However, it is not clear which of these factors is primary, if they are the same in all cases or specific to individual (genetic) patient subgroups, if they act by way of a network such that multiple insults are required for neurodegeneration to ensue, or if the findings to date merely represent an epiphenomenon unrelated to the true cause of cell death that still remains undiscovered **(Fig. 427-4)**.

FIGURE 427-4

Schematic representation of how pathogenetic factors implicated in Parkinson's disease interact in a network manner, ultimately leading to cell death. This figure illustrates how interference with any one of these factors may not necessarily stop the cell death cascade. *(Adapted from CW Olanow: Movement Disorders 22:S-335, 2007.)*



Although gene mutations cause only a minority of cases of PD, they may be helpful in pointing to specific pathogenic pathways and molecular mechanisms that are central to a neurodegenerative process that might be relevant to all forms of the disease. To date, most interest has focused on pathways implicated by mutations in *α-synuclein (SNCA)*, *GBA*, *LRRK2*, and *PINK1/Parkin*.

Although mutations in *SNCA* are an extremely rare cause of PD, *SNCA* was the first PD-linked and most intensely investigated PD gene, with respect to causative mutations but also risk variants, function of the gene and of the encoded protein. Shared clinical features of patients with *SNCA* mutations include earlier age of disease onset than in nongenetic PD, a faster progression of motor signs that are mostly levodopa-responsive, early occurrence of motor fluctuations, and presence of prominent nonmotor features. Intriguingly, SNCA constitutes the major component of Lewy bodies in patients with both monogenic and sporadic forms of PD (Fig. 427-1). Duplication or triplication of the wild-type *SNCA* gene also causes PD with triplication carriers being more severely affected than carriers of duplications. These findings indicate that increased production of the normal protein alone can cause the disease in a dose-dependent fashion. More recently, Lewy pathology was discovered to have developed in healthy embryonic dopamine neurons that had been implanted into the striatum of PD patients, suggesting that the abnormal protein had transferred from affected cells to healthy unaffected dopamine neurons. Based on these findings, it has been proposed that the SNCA protein may be a prion, and PD a prion disorder (**Chaps. 417 and 430**). Like the prion protein PrP^C, SNCA can misfold to form β-rich sheets, join to form toxic oligomers and aggregates, polymerize to form amyloid plaques (i.e., Lewy bodies), and cause neurodegeneration with spread to involve unaffected neurons. Indeed, injection of SNCA fibrils into the striatum of both transgenic and wild-type rodents leads to the development of Lewy pathology in host neurons, neurodegeneration, behavioral abnormalities, with spread of SNCA pathology to anatomically connected sites. Further support for this hypothesis comes from the demonstration that inoculation of SNCA derived from human Lewy bodies induces dopamine cell degeneration and widespread Lewy pathology in mice and primates. Collectively, this evidence supports the possibility that neuroprotective therapies for PD might be developed based on inhibiting the accumulation or accelerating the removal of SNCA aggregates, knocking down levels of host SNCA, or blocking the templating phenomenon whereby misfolded SNCA promotes misfolding of the native protein in a prion-like chain reaction.

Mutations in the glucocerebrosidase (*GBA*) gene represent the most important risk factor in terms of effect size for the development of PD, and experimentally there is a direct pathophysiological link between increased levels of SNCA and reduced levels of GBA. GBA encodes the enzyme glucocerebrosidase (GCase) which promotes lysosomal function and enhances the clearance of misfolded proteins. The identification of *GBA* as a risk gene for PD resulted from the clinical observation that patients with Gaucher's disease (GD) and their relatives commonly show signs of parkinsonism. This clinical observation of a link between GD and PD led to the discovery that several mutations in *GBA*, which cause Gaucher's disease in an autosomal recessive manner, confer risk for the development of PD, also in a heterozygous state. Further, reduced GCase activity due to GBA mutations impairs lysosomal function which results in the accumulation of SNCA. Accumulation of SNCA can also lead to inhibition of lysosomal function and a further reduction in levels of wild-type GBA by interfering with endoplasmic reticulum-to-Golgi trafficking. This in turn, leads to decreased GBA activity and a further increase in the accumulation of SNCA. In this regard, it is noteworthy that lysosomal function is impaired and

levels of GCase are reduced in patients with sporadic PD. These findings suggest that this molecular pathway may apply not only to patients with GD or with a *GBA* mutation, but also to patients with sporadic PD or other synucleinopathies who have two wild-type *GBA* alleles. These bidirectional effects of SNCA and GBA form a positive feedback loop that, after surpassing a theoretical threshold, could lead to self-propagating disease. Studies of drugs that enhance GCase activity are currently underway.

Seven different *LRRK2* mutations have now been clearly linked to PD, with p.G2019S being the most common due to a founder effect in the Ashkenazi Jewish and North African Arab populations. Mutations in *LRRK2* account for 3–41% of familial PD cases (depending on specific population) and are also found in apparently sporadic cases, albeit at a lower rate. The phenotype of LRRK2 p.G2019S mutations is indistinguishable from that of sporadic PD, although tremor appears to be more common, and leg tremor may be a useful diagnostic clue. The mechanism responsible for cell death with this mutation is not conclusively known but is thought to involve changes in kinase activity with altered phosphorylation of target proteins (including autophosphorylation) with possible impairment of lysosomal function. Kinase inhibitors can block toxicity associated with *LRRK2* mutations in laboratory models, and there has been much interest in developing drugs directed at this target. However, kinase inhibitors are potentially toxic, and the majority of PD patients do not carry a *LRRK2* mutation.

Mutations in *Parkin* and *PINK1* have also been identified as a cause of PD. *Parkin* mutations are the more common, and the major cause of autosomal recessive and early-onset PD, accounting for up to 77% of cases of juvenile PD with an age of onset <20 years, and for 10–20% of early-onset PD patients in general. The disease is slowly progressive, responds well to antiparkinsonian treatment, and is commonly complicated by dystonia, but very rarely by dementia. At pathology, neurodegeneration tends to be restricted to the SNc and LC in patients with *Parkin* mutations, and Lewy bodies are typically absent. The reason for these differences from classic PD are not known, but may related to impaired ubiquitination of damaged proteins (parkin is a ubiquitin ligase). The clinical phenotypes of *Parkin*- and *PINK1*-linked PD are similar. Recent studies suggest a role for Parkin and PINK1 proteins in the turnover and clearance of damaged mitochondria (mitophagy), and mutations in *Parkin* and *PINK1* cause mitochondrial dysfunction in transgenic animals that can be corrected with overexpression of Parkin or with drugs acting on the mitochondrial electron transfer chain, such as Vitamin K2. Improving mitochondrial function is a particularly attractive potential therapeutic target because postmortem studies in PD patients show a defect in complex I of the respiratory chain in SNc neurons.

Thus, evidence is accumulating that genetics plays an important role in both familial and “sporadic” forms of PD. It is anticipated that better understanding of the pathways responsible for cell death caused by these mutations will permit the development of more relevant animal models of PD and targets for the development of gene-specific neuroprotective drugs.

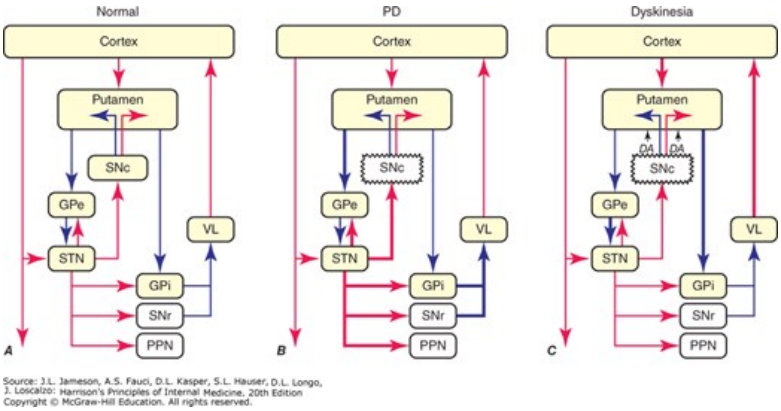
PATHOPHYSIOLOGY OF PD

The classic model of the organization of the basal ganglia in the normal and PD states is provided in **Fig. 427-5**. With respect to motor function, a series of neuronal circuits or loops link the basal ganglia nuclei with corresponding cortical motor regions in a somatotopic manner. The striatum is the major input region of the basal ganglia, while the GPi and SNr are the major output regions. The input and output regions are connected via direct and indirect pathways that have reciprocal effects on the activity of the basal ganglia output pathway. The output of the basal ganglia provides inhibitory (GABAergic) tone to thalamic and brainstem neurons that in turn connect to motor systems in the cerebral cortex and spinal cord that control motor function. An increase in neuronal activity in the output regions of the basal ganglia (GPi/SNr) is associated with poverty of movement or parkinsonism, while decreased output results in movement facilitation and involuntary movements. Dopaminergic projections from SNc neurons serve to modulate neuronal firing and to stabilize the basal ganglia network. Normal dopamine innervation thus serves to facilitate the selection of the desired movement and reject unwanted movements. Cortical loops integrating the cortex and the basal ganglia are now thought to also play an important role in regulating behavioral, emotional, and cognitive functions.

FIGURE 427-5

Basal ganglia organization. Classic model of the organization of the basal ganglia in the normal (***A***), Parkinson’s disease (PD) (***B***), and levodopa-induced dyskinesia (***C***) state. Inhibitory connections are shown as *blue arrows* and excitatory connections as *red arrows*. The striatum is the major input region and receives its major input from the cortex. The GPi and SNr are the major output regions, and they project to the thalamocortical and brainstem motor regions. The striatum and GPi/SNr are connected by direct and indirect pathways. This model predicts that parkinsonism results from increased neuronal firing in the STN and GPi and that lesions or DBS of these targets might provide benefit. This concept led to the rationale for surgical therapies for PD. The model also predicts that dyskinesia results from decreased firing of the output regions, resulting in excessive cortical activation by the thalamus. This component of the model is not completely correct because lesions of the GPi ameliorate rather than increase

dyskinesia in PD, suggesting that firing frequency is just one of the components that lead to the development of dyskinesia. DBS, deep brain stimulation; GPe, external segment of the globus pallidus; GPi, internal segment of the globus pallidus; PPN, pedunculopontine nucleus; SNc, substantia nigra, pars compacta; SNr, substantia nigra, pars reticulata; STN, subthalamic nucleus; VL, ventrolateral thalamus. *(Derived from JA Obeso et al: Trends Neurosci 23:S8, 2000.)*



In PD, dopamine denervation with loss of dopaminergic tone leads to increased firing of neurons in the STN and GPi, excessive inhibition of the thalamus, reduced activation of cortical motor systems, and the development of parkinsonian features (Fig. 427-5). The current role of surgery in the treatment of PD is based on this model, which predicted that lesions or high-frequency stimulation of the STN or GPi might reduce this neuronal overactivity and improve PD features.

TREATMENT

TREATMENT

Parkinson's Disease

LEVODOPA

Since its introduction in the late 1960s, levodopa has been the mainstay of therapy for PD. Experiments in the late 1950s by Carlsson and colleagues demonstrated that blocking dopamine uptake with reserpine caused rabbits to become parkinsonian; this could be reversed with the dopamine precursor, levodopa. Subsequently, Hornykiewicz demonstrated a dopamine deficiency in the striatum of PD patients, and suggested the potential benefit of dopamine replacement therapy. Dopamine does not cross the blood-brain barrier (BBB), so clinical trials were initiated with levodopa, the precursor of dopamine. Studies over the course of the next decade confirmed the value of levodopa and revolutionized the treatment of PD.

Levodopa is routinely administered in combination with a peripheral decarboxylase inhibitor to prevent its peripheral metabolism to dopamine and the development of nausea, vomiting, and orthostatic hypotension due to activation of dopamine receptors in the area postrema that are not protected by the BBB. In the United States, levodopa is combined with the decarboxylase inhibitor carbidopa (Sinemet®), whereas in many other countries it is combined with benserazide (Madopar®). Levodopa plus a decarboxylase inhibitor is also available in a methylated formulation, a controlled-release formulation (Sinemet CR® or Madopar HP®) and in combination with a catechol-*O*-methyltransferase (COMT) inhibitor (Stalevo®). A long-acting formulation of levodopa (Rytary®) has also recently been approved. An inhaled form of levodopa that is rapidly and reliably absorbed is currently in late stage investigation as a rescue therapy for the treatment of individual "off" episodes (see below).

Levodopa remains the most effective symptomatic treatment for PD and the gold standard against which new therapies are compared. No current medical or surgical treatment provides antiparkinsonian benefits superior to what can be achieved with levodopa. Levodopa benefits the classic motor features of PD, prolongs independence and employability, improves quality of life, and increases life span. Almost all PD patients experience improvement, and failure to respond to an adequate trial of levodopa should cause the diagnosis to be questioned. Levodopa has not been demonstrated to have any disease-modifying or neuroprotective effect, so it should be primarily used as a symptomatic treatment.

There are, however, important limitations of levodopa therapy. Acute dopaminergic side effects include nausea, vomiting, and orthostatic hypotension as indicated above. These are usually transient and can generally be avoided by starting with low doses and gradual titration. If they persist, they can be treated with additional doses of a peripheral decarboxylase inhibitor (e.g., carbidopa), administering with food, or adding a

peripheral dopamine-blocking agent such as domperidone (not available in the United States). More important are motor complications (see below) that develop in the majority of patients treated long-term with levodopa. In addition, the disease continues to progress, and features such as neuropsychiatric problems, falling, freezing, autonomic dysfunction, sleep disorders, and dementia may emerge that are not adequately controlled by levodopa. Indeed, these nondopaminergic features (especially falling and dementia) are the primary source of disability and the main reason in the present era for nursing home placement for patients with advanced PD.

Levodopa-induced motor complications consist of fluctuations in motor response ("on" episodes when the drug is working and "off" episodes when parkinsonian features return) and involuntary movements known as dyskinesias which typically complicate "on" periods **(Fig. 427-6)**. When patients initially take levodopa, benefits are long-lasting (many hours) even though the drug has a relatively short half-life (60–90 min). With continued treatment, however, the duration of benefit following an individual dose becomes progressively shorter until it approaches the half-life of the drug. This loss of benefit is known as the *wearing-off effect*. In more severe cases, the response to a given dose may be variable with patients potentially experiencing a delay in turning on (delayed-on) or no response at all (no-on). Peak-dose dyskinesias occur at the time of levodopa peak plasma concentration and maximal clinical benefit. They are usually choreiform, but can manifest as dystonic movements, myoclonus, or other movement disorders. They are not troublesome when mild, but can be disabling when severe, and can limit the ability to use higher doses of levodopa to better control PD motor features. In more advanced states, patients may cycle between "on" periods complicated by disabling dyskinesias and "off" periods in which they suffer from severe parkinsonism and painful dystonic postures. Patients may also experience "diphasic dyskinesias," which occur as the levodopa dose begins to take effect and again as it wears off. These dyskinesias typically consist of transient, stereotypic, rhythmic movements that predominantly involve the lower extremities and are frequently associated with parkinsonism in other body regions. They can be relieved by increasing the dose of levodopa, although higher doses may induce more severe peak-dose dyskinesia. Long-term double blind studies show that motor complications are dose related, and can be minimized by using the lowest dose of levodopa that provides satisfactory benefit and through the use of polypharmacy to avoid raising the dose of levodopa.

The cause of levodopa-induced motor complications is not precisely known. They are more likely to occur in females, younger individuals with more severe disease, and with the use of higher doses of levodopa. The classic model of the basal ganglia has been useful for understanding the origin of motor features in PD, but has proved less valuable for understanding levodopa-induced dyskinesias (Fig. 427-5). The model predicts that dopamine replacement might excessively inhibit the pallidal output system, thereby leading to increased thalamocortical activity, enhanced stimulation of cortical motor regions, and the development of dyskinesia. However, lesions of the pallidum are associated with amelioration rather than induction of dyskinesia as would be suggested by the classic model. It is now thought that dyskinesia results from alterations in the GPi/SNr neuronal firing pattern (pauses, bursts, synchrony, etc.) and not simply the firing frequency alone. This in turn leads to the transmission of "misinformation" from pallidum to thalamus/cortex, resulting in dyskinesia. Surgical lesions or high-frequency stimulation targeted at the GPi or STN can ameliorate dyskinesia by interfering with (blocking or masking) this abnormal neuronal activity and preventing the transfer of misinformation to motor systems. There has also been recent interest in the use of ultrasound to lesion these target regions in a relatively noninvasive manner.

Current information suggests that altered neuronal firing patterns and motor complications develop in response to nonphysiologic levodopa replacement. Striatal dopamine levels are normally maintained at a relatively constant level. In PD, dopamine neurons degenerate and striatal dopamine is dependent on the peripheral availability of levodopa. Intermittent oral doses of levodopa result in fluctuating plasma levels because of variability in the transit of the drug from the stomach to the duodenum where it is absorbed and the short half-life of the drug. This variability is translated to the brain and results in exposure of striatal dopamine receptors to alternating high and low concentrations of dopamine. It has been hypothesized that more continuous delivery of levodopa might prevent the development of motor complications. Indeed, a recent double-blind, double-dummy, double titration study demonstrated that continuous intraintestinal infusion of levodopa/carbidopa is associated with significant improvement in "off" time and in "on" time without dyskinesia in advanced PD patients compared with optimized standard oral levodopa. These benefits are superior to what has been observed in double blind controlled studies with other dopaminergic agents, and this therapy is now approved in the United States and Europe (Duodopa®, Duopa®). The treatment is, however, complicated by potentially serious adverse events related to the surgical procedure and the tubing, and the inconvenience of the infusion system. New approaches are currently being tested in which levodopa is continuously administered by subcutaneous infusion or by long-acting oral levodopa formulations in an effort to avoid the need for a surgical procedure. An inhaled formulation of levodopa is in late stage development as an acute rescue therapy for individual off episodes.

Behavioral complications can also be encountered in levodopa-treated patients. A dopamine dysregulation syndrome has been described where patients have a craving for levodopa and take frequent and unnecessary doses of the drug in an addictive manner. PD patients taking high doses of levodopa can also develop purposeless, stereotyped behaviors such as the assembly and disassembly or collection and sorting of objects. This is

known as punding, a term taken from the Swedish description of the meaningless behaviors seen in chronic amphetamine users. Hypersexuality and other impulse-control disorders are occasionally encountered with levodopa, although these are more commonly seen with dopamine agonists.

DOPAMINE AGONISTS

Dopamine agonists are a diverse group of drugs that act directly on dopamine receptors. Unlike levodopa, they do not require metabolic conversion to an active product and do not undergo oxidative metabolism. Initial dopamine agonists were ergot derivatives (e.g., bromocriptine, pergolide, cabergoline) and were associated with potentially serious ergot-related side effects such as cardiac valvular damage and pulmonary fibrosis. They have largely been replaced by a second generation of nonergot dopamine agonists (e.g., pramipexole, ropinirole, rotigotine). In general, dopamine agonists do not have comparable efficacy to levodopa. They were initially introduced as adjuncts to levodopa to enhance motor function and reduce "off" time in fluctuating patients. Subsequently, it was shown that dopamine agonists are less prone than levodopa to induce dyskinesia, possibly because they are relatively long-acting. For this reason, many physicians initiate therapy with a dopamine agonist particularly in younger patients, although supplemental levodopa is eventually required in virtually all patients. This view has been tempered by the recognition that dopamine agonists are associated with potentially serious adverse effects such as unwanted sleep episodes and impulse control disorders (see below). Both ropinirole and pramipexole are available as orally administered immediate (tid) and extended-release (qd) formulations. Rotigotine is administered as a once-daily transdermal patch, and may be useful in managing surgical patients who are NPO. Apomorphine is a dopamine agonist with efficacy comparable to levodopa, but it must be administered parenterally as it is rapidly and extensively metabolized if taken orally. It has a short half-life and duration of activity (45 min). It can be administered by subcutaneous injection as a rescue agent for the treatment of severe "off" episodes, but can also be administered by continuous subcutaneous infusion where it has been demonstrated to reduce both "off" time and dyskinesia in advanced patients. This latter approach has not been approved in the United States. A sublingual bilayer formulation of apomorphine is in late stage development as a rapid and reliable therapy for individual "off" periods that avoids the need for a subcutaneous (SC) injection.

Dopamine agonist use is associated with a variety of side effects. Acute side effects are primarily dopaminergic and include nausea, vomiting, and orthostatic hypotension. As with levodopa, these can usually be avoided by starting with low doses and using slow titration. Side effects associated with chronic use include hallucinations and cognitive impairment. Sedation with sudden unintended episodes of falling asleep that can occur in dangerous situations such as while driving a motor vehicle have been reported. Patients should be informed about this potential problem and should not drive when tired. Dopamine agonists can also be associated with impulse-control disorders, including pathologic gambling, hypersexuality, and compulsive eating and shopping. Patients should also be advised of these risks and specifically questioned for their occurrence at follow-up examinations. The precise cause of these problems, and why they appear to occur more frequently with dopamine agonists than levodopa, remains to be resolved, but reward systems associated with dopamine and alterations in the ventral striatum and orbitofrontal regions have been implicated. In general, chronic side effects are dose-related and can be avoided or minimized with lower doses. Injections of apomorphine can be complicated by skin lesions at sites of administration, but this has not been a problem with the sublingual bilayer formulation.

MAO-B INHIBITORS

Inhibitors of monoamine oxidase type B (MAO-B) block central dopamine metabolism and increase synaptic concentrations of the neurotransmitter. Selegiline and rasagiline are relatively selective suicide inhibitors of the MAO-B isoform of the enzyme. Clinically, these agents provide antiparkinsonian benefits when used as monotherapy in early disease stages and reduced "off" time when used as an adjunct to levodopa in patients with motor fluctuations. MAO-B inhibitors are generally safe and well tolerated. They may increase dyskinesia in levodopa-treated patients, but this can usually be controlled by down-titrating the dose of levodopa. Inhibition of the MAO-A isoform prevents metabolism of tyramine in the gut, leading to a potentially fatal hypertensive reaction known as a "cheese effect" because it can be precipitated by foods rich in tyramine such as some cheeses, aged meats, and red wine. Selegiline and rasagiline do not functionally inhibit MAO-A and are not associated with a cheese effect with doses used in clinical practice. There are theoretical risks of a serotonin reaction in patients receiving concomitant selective serotonin reuptake inhibitor (SSRI) antidepressants, but these are rarely encountered. Safinamide (Xadago®) is a reversible MAO-B inhibitor that has recently been approved as an adjunct to levodopa in advanced PD patients with motor fluctuations. The drug also acts to block activated sodium channels and inhibit glutamate release, and is currently being studied as a possible antidyskinetic agent.

Interest in MAO-B inhibitors has also focused on their potential to have disease-modifying effects. MPTP toxicity can be prevented experimentally by coadministration of an MAO-B inhibitor that blocks its conversion to the toxic pyridinium ion MPP^+ that selectively damages dopamine neurons. MAO-B inhibitors also have the potential to block the oxidative metabolism of dopamine and prevent oxidative stress. In addition, both selegiline and rasagiline incorporate a propargyl ring within their molecular structure that provides antiapoptotic effects in laboratory models. The DATATOP

study showed that selegiline significantly delayed the time until the emergence of disability necessitating the introduction of levodopa in untreated PD patients. However, it could not be definitively determined whether this was due to a neuroprotective effect that slowed disease progression or a symptomatic effect that masked ongoing neurodegeneration. More recently, the ADAGIO study used a two-period delayed-start design and demonstrated that early treatment with rasagiline 1 mg/d, but not 2 mg/d, provided benefits that could not be achieved when treatment with the same drug was initiated at a later time point. This benefit is consistent with a disease-modifying effect; however, the long-term significance of these findings is uncertain.

COMT INHIBITORS

When levodopa is administered with a decarboxylase inhibitor, it is primarily metabolized in the periphery by the catechol-O-methyl transferase (COMT) enzyme. Inhibitors of COMT increase the elimination half-life of levodopa and enhance its brain availability. Combining levodopa with a COMT inhibitor reduces "off" time and prolongs "on" time in fluctuating patients while enhancing motor scores. Two COMT inhibitors, tolcapone and entacapone, have been approved for use. More recently, opicapone (a long-acting, once daily COMT inhibitor) has been approved in Europe. There is also a combination tablet of levodopa, carbidopa, and entacapone (Stalevo®).

Side effects of COMT inhibitors are primarily dopaminergic (nausea, vomiting, increased dyskinesia) and can usually be controlled by down-titrating the dose of levodopa by 20–30%. Severe diarrhea has been described with tolcapone, and to a lesser degree with entacapone, and necessitates stopping the medication in 5–10% of individuals. Cases of fatal hepatic toxicity have been reported with tolcapone. It is still used because it is the most effective of the COMT inhibitors, but periodic monitoring of liver function is required. This problem has not been encountered with entacapone. Discoloration of urine can be seen with COMT inhibitors due to accumulation of a metabolite, but it is of no clinical concern.

It has been proposed that initiating levodopa in combination with a COMT inhibitor to enhance its elimination half-life could provide more continuous levodopa delivery and reduce the risk of motor complications if administered at frequent intervals. While this result has been demonstrated in a preclinical MPTP model, and continuous infusion reduces both "off" time and dyskinesia in advanced PD patients, no benefit of initiating levodopa with a COMT inhibitor compared to levodopa alone was detected in early PD patients in the STRIDE-PD study. This may have been because the combination was not administered at frequent enough intervals to provide continuous levodopa availability. For now, the main value of COMT inhibitors continues to be in patients who experience motor fluctuations.

OTHER MEDICAL THERAPIES

Centrally acting anticholinergic drugs such as trihexyphenidyl and benztropine were used historically for the treatment of PD, but they lost favor with the introduction of dopaminergic agents. Their major clinical effect is on tremor, although it is not certain that this benefit is superior to what can be obtained with agents such as levodopa and dopamine agonists. Still, they can be helpful in individual patients with severe tremor. Their use is limited particularly in the elderly, due to their propensity to induce a variety of side effects including urinary dysfunction, glaucoma, and particularly cognitive impairment.

Amantadine was originally introduced as an antiviral agent, but was appreciated to also have antiparkinsonian effects that are thought to be due to *N*-methyl-D-aspartate (NMDA) receptor antagonism. While some physicians use amantadine in patients with early disease for its mild symptomatic effects, it is most widely used as an antidyskinesia agent in patients with advanced PD. Indeed, it is the only oral agent that has been demonstrated in controlled studies to reduce dyskinesia without worsening parkinsonian features, although benefits may be relatively transient. Cognitive impairment is a major concern. Other side effects include livedo reticularis and weight gain. Amantadine should always be discontinued gradually because patients can experience withdrawal-like symptoms. An extended release formulation of amantadine has recently been approved in the United States.

The anticonvulsant zonisamide has also been shown to have antiparkinsonian effects and is approved for use in Japan. Its mechanism of action is unknown.

Several new classes of drugs are currently being investigated in an attempt to enhance antiparkinsonian effects, reduce off time, and treat or prevent dyskinesia. These include adenosine A_{2A} antagonists, nicotinic agonists, glutamate antagonists, and 5-HT_{1A} agonists. The A_{2A} antagonist Istradefylline is approved in Japan.

A list of the major drugs and available dosage strengths currently available to treat PD is provided in **Table 427-5**.

NEUROPROTECTION

Despite the many therapeutic agents available for the treatment of PD, patients continue to progress and to develop intolerable disability. A neuroprotective therapy that slows or stops disease progression remains the major unmet therapeutic need. Numerous trials have shown positive results (e.g., selegiline, rasagiline, pramipexole, ropinirole) consistent with a disease-modifying effect. However, it has not been possible to determine with certainty if the positive results were due to neuroprotection with slowing of disease progression or confounding symptomatic or pharmacologic effects that mask disease progression. There is a flurry of clinical activity testing interventions targeting etiopathogenic factors; these include calcium channel blockers, urate, and agents that enhance glucocerebrocidase (GCase) or interfere with SNCA or LRRK2 in the hope that they might provide disease-modifying effects. A major limitation is the uncertainty as to a specific clinical development plan and trial design that will prove acceptable to both clinicians and regulatory authorities.

SURGICAL TREATMENT

Surgical treatments for PD have been used for more than a century. Lesions were initially placed in the motor cortex and improved tremor but were associated with motor deficits, and this approach was abandoned. Subsequently, it was appreciated that lesions placed into the ventral intermediate (VIM) nucleus of the thalamus reduced contralateral tremor without inducing hemiparesis, but these lesions did not meaningfully help other more disabling features of PD. In the 1990s, it was shown that lesions placed in the posteroventral portion of the GPi (motor territory) improved rigidity and bradykinesia as well as tremor. Importantly, pallidotomy was also associated with marked improvement in contralateral dyskinesia. This procedure gained favor with greater understanding of the pathophysiology of PD (see above). However, this procedure is not optimal, because bilateral lesions are associated with side effects such as dysphagia, dysarthria, and impaired cognition. Lesions of the STN are associated with antiparkinsonian benefit and reduced levodopa requirement, but there is a concern about the risk of hemiballismus, and this procedure is not commonly performed.

Most surgical procedures for PD performed today use deep brain stimulation (DBS). Here, an electrode is placed into the target area and connected to a stimulator inserted subcutaneously over the chest wall. DBS simulates the effects of a lesion without necessitating making a brain lesion. The precise mechanism whereby DBS works is not fully resolved but may act by disrupting the abnormal neurophysiological signals associated with PD and motor complications. The stimulation variables can be adjusted with respect to electrode configuration, voltage, frequency, and pulse duration in order to maximize benefit and minimize adverse side effects. The procedure does not require making a lesion in the brain and is thus suitable for performing bilateral procedures with relative safety. In cases with intolerable side effects, stimulation can be stopped and the system removed.

DBS for PD primarily targets the STN or the GPi. It provides dramatic results, particularly with respect to tremor and reducing both “off” time and dyskinesias, but does not provide superior clinical benefits or improve features that do not respond to levodopa such as freezing, falling, and dementia. The procedure is thus primarily indicated for patients who suffer disability resulting from severe tremor, or levodopa-induced motor complications that cannot be satisfactorily controlled with drug manipulation. In such patients, DBS has been shown to provide benefits in comparison to best medical therapy. Side effects can be seen with respect to the surgical procedure (hemorrhage, infarction, infection), the DBS system (infection, lead break, lead displacement, skin ulceration), or the stimulation (ocular and speech abnormalities, muscle twitches, paresthesias, depression, and rarely suicide). Recent studies indicate that benefits following DBS of the STN and GPi are comparable, but that GPi stimulation may be associated with a reduced frequency of depression. Although not all PD patients are candidates, the procedure can be profoundly beneficial for many. Long-term studies demonstrate continued benefits with respect to the classic motor features of PD, but DBS does not prevent the development of nondopaminergic features, which continue to evolve and to be a source of disability. Studies continue to evaluate the optimal way to use DBS (low- vs high-frequency stimulation, closed loop systems, etc.). Studies of DBS in early PD patients show benefits in comparison to medical therapy, but this must be weighed against the cost of the procedure and the risk of side effects in patients who might otherwise be well controlled with medical therapies. Controlled studies comparing DBS to other therapies aimed at improving motor function without causing dyskinesia, such as Duodopa® and apomorphine infusions, remain to be performed. The utility of DBS may also be reduced in future years if new medical therapies are developed that provide the benefits of levodopa without motor complications. New targets for DBS that might benefit gait dysfunction, depression, and cognitive impairment are being actively explored **(Chap. 477)**.

MRI-guided ultrasound is also now being used as a means of damaging critical target regions such as the GPi in PD patients with motor complications in a noninvasive manner that avoids the needs for a surgical procedure. Preliminary results suggest good target localization and safety.

EXPERIMENTAL THERAPIES FOR PD

There has been considerable scientific and public interest in a number of novel interventions that are being investigated as possible treatments for

PD. These include cell-based therapies (such as transplantation of fetal nigral dopamine cells or dopamine neurons derived from stem cells), gene therapies, trophic factors, and therapies directed against gene-specific targets. Transplant strategies are based on the concept of implanting dopaminergic cells into the striatum to replace degenerating SNc dopamine neurons. Fetal nigral mesencephalic cells have been demonstrated to survive implantation, re-innervate the striatum in an organotypic manner, and restore motor function in PD models. However, two double-blind studies failed to show significant benefit of fetal nigral transplantation in comparison to a sham operation with respect to their primary endpoints. Additionally, grafting of fetal nigral cells is associated with a previously unrecognized form of dyskinesia (graft-induced dyskinesia) that persists after lowering or even stopping levodopa. This has been postulated to be related to suboptimal release of dopamine from grafted cells leading to a sustained form of diphasic dyskinesia. In addition, there is evidence that after many years, transplanted healthy embryonic dopamine neurons from unrelated donors develop PD pathology and become dysfunctional, suggesting transfer of α-synuclein from affected to unaffected neurons in a prion-like manner (see discussion above). Perhaps most importantly, it is not clear how replacing dopamine cells alone will improve nondopaminergic features such as falling and dementia, which are the major sources of disability for patients with advanced disease. While stem cells, and specifically induced pluripotent stem cells derived from the recipient, may overcome problems related to immunity, type and number of cells, and physiologic integration, many of these same concerns still apply. To date, stem cells have not yet been properly tested in PD patients and bear the additional concern of tumors and other unanticipated side effects. While there remains a need for scientifically based studies attempting to evaluate the potential role of cell-based therapies in PD, there is no scientific basis to warrant routine treatment of PD patients with stem cells as is being marketed in some countries.

Trophic factors are a series of proteins that enhance neuronal growth and restore function to damaged neurons. There are several different trophic factors that have been demonstrated to have beneficial effects on dopamine neurons in laboratory studies. Glial-derived neurotrophic factor (GDNF) and neurturin have attracted particular attention as possible therapies for PD. However, double-blind trials of intraventricular and intraputaminal infusions of GDNF failed to show benefits compared to placebo in PD patients, possibly because of inadequate delivery of the trophic molecule to the target region.

Gene therapy offers the potential of providing long-term expression of a therapeutic protein with a single procedure. Gene therapy involves placing the DNA of a therapeutic protein into a viral vector that can then be taken up and incorporated into the genome of host cells and then synthesized and released on a continual basis. The AAV2 virus has been most often used as the vector because it does not promote an inflammatory response, is not incorporated into the host genome, and is associated with long-lasting transgene expression. Clinical trials of AAV2 delivery of the trophic factor neurturin showed promising results in open label trials but failed in double-blind trials, even when injected into both the putamen and the SNc. This likely reflects α-synuclein-mediated downregulation of Nurr1 and RET receptors, thereby limiting the potential of the trophic factor to interact with its receptor and induce upregulation of repair genes. Gene delivery is also being explored as a means of delivering aromatic amino acid decarboxylase with or without tyrosine hydroxylase to the striatum to facilitate the conversion of orally administered levodopa to dopamine. Animal studies suggest that this approach can provide antiparkinsonian benefits with reduced motor complications, and clinical trials in PD patients are underway. Although gene delivery technology has great potential and will likely be used to deliver novel therapies in the future (e.g. Parkin), current approaches carry the risk of unanticipated side effects and do not address the nondopaminergic features of the illness.

MANAGEMENT OF THE NONMOTOR AND NONDOPAMINERGIC FEATURES OF PD

Although PD management has primarily focused on dopaminergic features, management of the nondopaminergic features should not be ignored. Some nonmotor features, although not thought to reflect dopaminergic pathology, nonetheless benefit from dopaminergic drugs. For example, problems such as anxiety, panic attacks, depression, pain, sweating, sensory problems, freezing, and constipation all tend to be worse during “off” periods and have been reported to improve with better dopaminergic control. Approximately 50% of PD patients suffer depression during the course of the disease, and depression is frequently underdiagnosed and undertreated. Antidepressants should not be withheld, particularly for patients with major depression, although dopaminergic agents such as pramipexole may prove helpful for both depression and PD motor features. Serotonin syndromes have been a theoretical concern with the combined use of SSRIs and MAO-B inhibitors but these problems are rarely encountered. Anxiety is also a common problem, and if not adequately controlled with better antiparkinsonian drugs can be treated with short-acting benzodiazepines.

Psychosis can be a problem for some PD patients, and is often a harbinger of developing dementia. In contrast to AD, hallucinations are typically visual, formed, and nonthreatening. Importantly, they can limit the use of dopaminergic agents necessary to obtain satisfactory motor control. They can be associated with dopaminergic drugs, and the first approach is typically to withdraw agents that are less effective than levodopa such as anticholinergics, amantadine, and dopamine agonists followed by lowering the dose of levodopa if possible. Psychosis in PD often responds to low

doses of atypical neuroleptics and may permit higher doses of levodopa to be tolerated. Clozapine is an effective drug, but it can be associated with agranulocytosis, and regular monitoring is required. Quetiapine avoids these problems but it has not been established to be effective in placebo-controlled trials. Pimavanserin (Nuplazid®) differs from other atypical neuroleptics in that it is also an inverse agonist of the serotonin 5-HT_{2A} receptor. It has been shown to be effective in double-blind trials with a relatively good safety profile. It was recently approved for use in the United States.

Dementia in PD (PDD) is common, ultimately affecting as many as 80% of patients. Its frequency increases with aging and, in contrast to AD, primarily affects executive functions and attention, with relative sparing of language, memory, and calculation domains. When dementia precedes or develops within 1 year after the onset of motor dysfunction, it is by convention referred to as dementia with Lewy bodies (DLB; **Chap. 426**). These patients are particularly prone to have hallucinations and diurnal fluctuations. Pathologically, DLB is characterized by Lewy bodies distributed throughout the cerebral cortex (especially the hippocampus and amygdala) and is often also associated with AD pathology. It is likely that DLB and PD with dementia represent a spectrum of PD rather than separate disease entities. Mild cognitive impairment (MCI) frequently precedes the onset of dementia and is a more reliable index of impending PDD than in the general population. Dopaminergic drugs can worsen cognitive function in demented patients and should be stopped or reduced to try and provide a compromise between antiparkinsonian benefit and preserved cognitive function. Drugs are usually discontinued in the following sequence: anticholinergics, amantadine, dopamine agonists, COMT inhibitors, and MAO-B inhibitors. Eventually, patients with cognitive impairment should be managed with the lowest dose of standard levodopa that provides meaningful antiparkinsonian effects and does not worsen mental function. Anticholinesterase agents such as memantine, rivastigmine, and donepezil reduce the rate of deterioration of measures of cognitive function and can improve attention in PD, but do not typically improve cognitive function in any meaningful way. More effective therapies that treat or prevent dementia are a critical unmet need in the therapy of PD.

Autonomic disturbances are common and frequently require attention. Orthostatic hypotension can be problematic and contribute to falling. Initial treatment should include adding salt to the diet and elevating the head of the bed to prevent overnight sodium natriuresis. Low doses of fludrocortisone (Florinef) or midodrine provide control for most cases. The norepinephrine precursor 3-0-methylDOPS (Droxidopa®) has been shown to provide mild and transient benefits for patients with orthostatic hypotension, and was recently approved by the U.S. Food and Drug Administration. Vasopressin and erythropoietin can be used in more severe or refractory cases. If orthostatic hypotension is prominent in early parkinsonian cases, a diagnosis of MSA should be considered **(Chap. 432)**. Sexual dysfunction can be helped with sildenafil or tadalafil. Urinary problems, especially in males, should be treated in consultation with a urologist to exclude prostate problems. Anticholinergic agents, such as oxybutynin (Ditropan), may be helpful. Constipation can be a very important problem for PD patients. Mild laxatives or enemas can be useful, but physicians should first ensure that patients are drinking adequate amounts of fluid and consuming a diet rich in bulk with green leafy vegetables and bran. Agents that promote gastrointestinal (GI) motility can also be helpful.

Sleep disturbances are common in PD patients, with many experiencing fragmented sleep with excess daytime sleepiness. Restless leg syndrome, sleep apnea, and other sleep disorders should be treated as appropriate. REM behavior disorder (RBD) is a syndrome composed of violent movements and vocalizations during REM sleep, possibly representing acting out of dreams due to a failure of motor inhibition that typically accompanies REM sleep **(Chap. 27)**. Low doses of clonazepam (0.5–1 mg at bedtime) are usually effective in controlling this problem. Consultation with a sleep specialist and polysomnography may be necessary to identify and optimally treat sleep problems. Many PD patients have a history of RBD preceding the onset of the classic motor features of PD, and most cases of RBD go on to develop an α-synucleinopathy (PD or MSA).

NONPHARMACOLOGIC THERAPY

Gait dysfunction with falling is an important cause of disability in PD. Dopaminergic therapies can help patients whose gait is worse in “off” time, but there are currently no specific therapies for gait dysfunction. Canes and walkers may become necessary to increase stability and reduce the risk of falling. An effective therapy for gait impairment is an important unmet need in PD.

Freezing, where patients suddenly become stuck in place for seconds to minutes as if their feet were glued to the ground, is a major cause of falling. Freezing may occur during “on” or “off” periods. Freezing during “off” periods may respond to dopaminergic therapies, but there are no specific treatments for “on” period freezing. Some patients will respond to sensory cues such as marching in place, singing a song, or stepping over an imaginary line.

Speech impairment is another source of disability for many advanced PD patients. Speech therapy programs may be helpful, but benefits are generally transient.

Exercise has been shown to maintain and even improve function for PD patients, and active and passive exercises with full range of motion reduce the risk of arthritis and frozen joints. Some laboratory studies suggest the possibility that exercise might also have neuroprotective effects, but this has not been confirmed in PD. Exercise is generally recommended for all PD patients. It is less clear that physical therapy or specific exercise programs such as tai chi or dance offer any specific advantage. It is important for patients to maintain social and intellectual activities to the extent possible. Education, assistance with financial planning, social services, and attention to home safety are important elements of the overall care plan. Information is available through numerous PD foundations and on the web, but should be reviewed with physicians to ensure accuracy. The needs of the caregiver should not be neglected. Caring for a person with PD involves a substantial work effort and there is an increased incidence of depression among caregivers. Support groups for patients and caregivers may be useful.

CURRENT MANAGEMENT OF PD

The management of PD should be tailored to the needs of the individual patient, and there is no single treatment approach that is universally accepted and applicable to all individuals. Clearly, if an agent could be demonstrated to have disease-modifying effects, it should be initiated at the time of diagnosis. Indeed, recent studies suggest that dopamine terminal degeneration may be complete within 4 years of diagnosis. Epidemiologic and pathologic studies suggest that constipation, RBD, and anosmia may represent premotor features of PD and could permit diagnosis and the initiation of a disease-modifying therapy even prior to the onset of the classical motor features of the disease. However, no therapy has yet been conclusively proven to be a disease-modifying agent. For now, physicians must use their judgment in deciding whether or not to introduce a drug such as rasagiline (see above) for its possible disease-modifying effects based on available preclinical and clinical information.

The next important issue to address is when to initiate symptomatic therapy. Several studies suggest that it may be best to start therapy at the time of diagnosis in order to preserve beneficial compensatory mechanisms and possibly provide functional benefits even in the early stage of the disease. Levodopa remains the most effective symptomatic therapy for PD, and some recommend starting it immediately using low doses (≤400 mg/d), as motor complications have now clearly been shown to be dose-related. Others, however, prefer to delay levodopa treatment, particularly in younger patients, in order to reduce the risk of inducing motor complications entirely. An alternate approach is to begin with a MAO-B inhibitor and/or a dopamine agonist, and reserve levodopa for later stages when these drugs no longer provide satisfactory control. In making this decision, the age, degree of disability, and side effect profile of the drug must all be considered. In patients with more severe disability, the elderly, those with cognitive impairment, those with significant comorbidities, or those in whom the diagnosis is uncertain, most physicians would initiate therapy with levodopa. Regardless of initial choice, most patients ultimately require polypharmacy (combination of levodopa, an MAO-B inhibitor, and a dopamine agonist). While it is important to use low doses of each agent in order to reduce the risk of side effects, it is important not to deny patients levodopa when they cannot be adequately controlled with alternative medications.

If motor complications develop, patients can initially be treated by manipulating the frequency and dose of levodopa or by combining lower doses of levodopa with a dopamine agonist, a COMT inhibitor, or a MAO-B inhibitor. Amantadine is the only drug that has been demonstrated to treat dyskinesia without worsening parkinsonism, but benefits may be short-lasting, and there are important side effects related to cognitive function. In advanced cases, it may be necessary to consider a surgical therapy such as DBS or Duodopa® if the patient is a suitable candidate, but as described above, these procedures have their own set of complications. The use of DBS in early PD patients has been advocated by some, but there is considerable skepticism about this approach considering the costs and potential side effects, when inexpensive, well tolerated, and effective medical alternatives are available. Continuous intraintestinal infusion of levodopa/carbidopa intestinal gel (Duodopa) appears to offer similar benefits to DBS, but also requires a surgical intervention with potentially serious complications. Continuous infusion of apomorphine is a treatment option that does not require surgery but is associated with potentially troublesome skin nodules. Comparative studies of these approaches in more advanced patients are awaited. There are ongoing efforts aimed at developing a long-acting oral or subcutaneous formulation of levodopa that mirrors the pharmacokinetic properties of a levodopa infusion. Such a formulation might provide all of the benefits of levodopa without motor complications and avoid the need for polypharmacy and surgical intervention.

A decision tree that considers the various treatment options and decision points for the management of PD is provided in **Fig. 427-7**.

FIGURE 427-6

Changes in motor response associated with chronic levodopa treatment. Levodopa-induced motor complications. Schematic illustration of the gradual shortening of the duration of a beneficial motor response to levodopa (wearing off) and the appearance of dyskinesias complicating “on”

time. PD, Parkinson's disease.

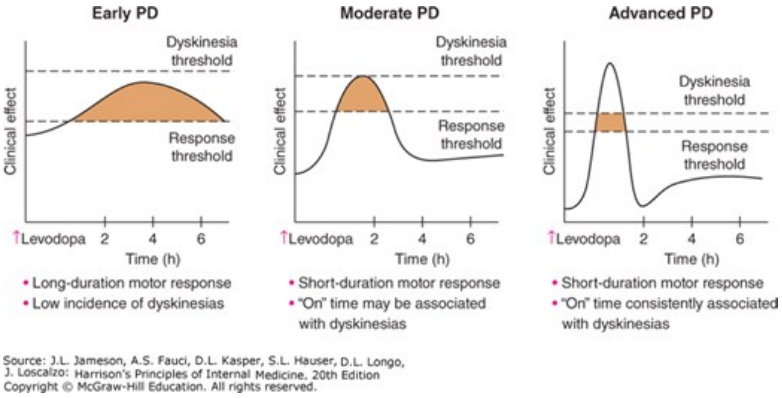
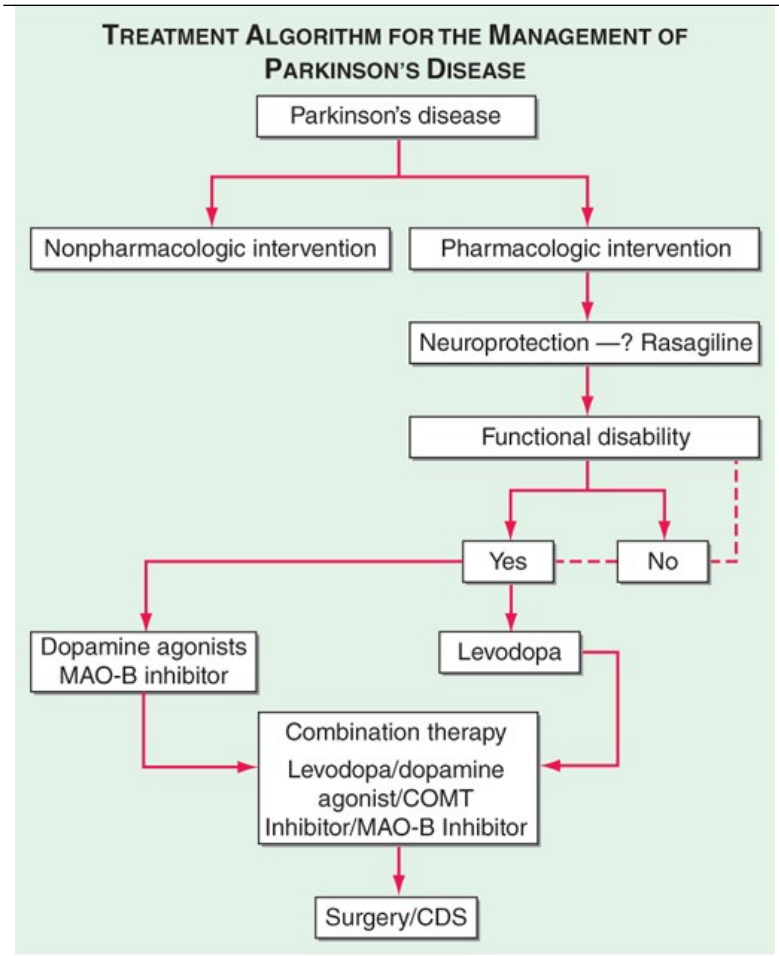


FIGURE 427-7

Treatment options for the management of Parkinson's disease (PD). Decision points include: (1) Introduction of a neuroprotective therapy: no drug has been established to have or is currently approved for neuroprotection or disease modification, but there are several agents that have this potential based on laboratory and preliminary clinical studies (e.g., rasagiline 1 mg/d, coenzyme Q10 1200 mg/d, the dopamine agonists ropinirole, and pramipexole). (2) When to initiate symptomatic therapy: There is a trend toward initiating therapy at the time of diagnosis or early in the course of the disease because patients may have some disability even at an early stage, and there is the possibility that early treatment may preserve beneficial compensatory mechanisms; however, some experts recommend waiting until there is functional disability before initiating therapy. (3) What therapy to initiate: many experts favor starting with a monoamine oxidase type B (MAO-B) inhibitor in mildly affected patients because of the good safety profile of the drug and the potential for a disease-modifying effect; dopamine agonists for younger patients with functionally significant disability to reduce the risk of motor complications; and levodopa for patients with more advanced disease, the elderly, or those with cognitive impairment. Recent studies suggest the early employment of polypharmacy using low doses of multiple drugs to avoid side effects associated with high doses of any one agent. (4) Management of motor complications: motor complications are typically approached with combination therapy to try and reduce dyskinesia and enhance the "on" time. When medical therapies cannot provide satisfactory control, surgical therapies such as DBS or continuous infusion of levodopa/carbidopa intestinal gel can be considered. (5) Nonpharmacologic approaches: interventions such as exercise, education, and support should be considered throughout the course of the disease. CDS, continuous dopaminergic stimulation; COMT, catechol-*O*-methyltransferase. *(Adapted from CW Olanow et al: Neurology 72:S1, 2009.)*



Source: J.L. Jameson, A.S. Fauci, D.L. Kasper, S.L. Hauser, D.L. Longo, J. Loscalzo: Harrison's Principles of Internal Medicine, 20th Edition

TABLE 427-5

Drugs Commonly Used for Treatment of Parkinson's Disease[a]

Agent	Available Dosages	Typical Dosing
Levodopa[a]		
Carbidopa/levodopa	10/100, 25/100, 25/250 mg	200–1000 mg levodopa/day
Benserazide/levodopa	25/100, 50/200 mg	
Carbidopa/levodopa CR	25/100, 50/200 mg	
Benserazide/levodopa MDS	25/200, 25/250 mg	
Parcopa	10/100, 25/100, 25/250	
Rytary (carbidopa/levodopa)	23.75/95, 36.25/145, 48.75/195, 61.25/245	See conversion tables
Carbidopa/levodopa/entacapone	12.5/50/200, 18.75/75/200, 25/100/200, 31.25/125/200, 37.5/150/200, 50/200/200 mg	
Dopamine agonists		
Pramipexole	0.125, 0.25, 0.5, 1.0, 1.5 mg	0.25–1.0 mg tid
Pramipexole ER	0.375, 0.75, 1.5. 3.0, 4.5 mg	1–3 mg/d
Ropinirole	0.25, 0.5, 1.0, 3.0 mg	6–24 mg/d
Ropinirole XL	2, 4, 6, 8 mg	6–24 mg/d
Rotigotine patch	2-, 4-, 6-, 8-mg patches	4–24 mg/d
Apomorphine SC	2-8 mg	2–8 mg
COMT inhibitors		
Entacapone	200 mg	200 mg with each levodopa dose
Tolcapone	100, 200 mg	100–200 mg tid
Opicapone	50 mg	50 mg HS
MAO-B inhibitors		
Selegiline	5 mg	5 mg bid
Rasagiline	0.5, 1.0 mg	mg QAM
Safinamide	100 mg	100 mg QAM

[a]Treatment should be individualized. Generally, drugs should be started in low doses and titrated to optimal dose.

Note: Drugs should not be withdrawn abruptly but should be gradually lowered or removed as appropriate.

Abbreviations: COMT, catechol-*O*-methyltransferase; MAO-B, monoamine oxidase type B; QAM, every morning.

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