REVIEW ARTICLE

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Parkinson's Disease

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N Engl J Med 2024;391:442-52.
DOI: 10.1056/NEJMra2401857

CME

The global burden of Parkinson's disease is projected to increase in future decades as the number and proportion of older adults increases. This review addresses research advances since 1998, when the disorder was last reviewed in the *Journal*, and includes recently introduced concepts relevant to clinical practice.[1,2] For two centuries, Parkinson's disease has been diagnosed clinically on the basis of the characteristic motor syndrome of bradykinesia accompanied by resting tremor, rigidity, and postural reflex impairment, all largely the result of dopaminergic dysfunction in the nigrostriatal system.[3] Advances in our understanding of the disease suggest that a biologic definition may be possible, but many questions remain.[4,5] In this review, we use the clinical definition of Parkinson's disease.

Epidemiology

The incidence and prevalence of Parkinson's disease increase with age,[6,7] with a male:female ratio of approximately 2:1. In various studies, incidence rates range from 47 to 77 cases per 100,000 persons 45 years of age or older and from 108 to 212 cases per 100,000 persons 65 years of age or older. The incidence of Parkinson's disease has generally been higher among White persons than among Black or Asian persons,[8] but the frequency of Lewy bodies detected at autopsy — a hallmark of Parkinson's disease, as described below — has been similar among Black persons and White persons.[9] The prevalence of the disorder is approximately 572 cases per 100,000 persons 45 years of age or older.[7] Mortality adjusted for age and sex has been estimated to be approximately 60%, which is higher than the mortality in the general population. The economic burden of Parkinson's disease in the United States is predicted to increase from $52 billion in 2017 to $79 billion in 2037.[10]

Defining Parkinson's Disease

Although the motor syndrome of parkinsonism that is attributable to the loss of dopaminergic neurons remains the cornerstone of diagnosis, Parkinson's disease is a multisystem neurologic disorder. Nonmotor symptoms include sleep disorders, cognitive impairment, altered mood and affect, autonomic dysfunction (constipation, urogenital disorders, and orthostatic hypotension), and sensory symptoms (hyposmia and pain). Nonmotor symptoms — particularly hyposmia and rapid-eye-movement (REM) sleep behavior disorder, which is characterized by loss of normal atony during REM sleep and limb movements that simulate running or flailing — often predate the onset of motor symptoms by many years, which suggests that such symptoms may be prodromal. The burden of symptoms progresses, contributing to increasing disability and functional decline.

The International Parkinson and Movement Disorder Society has published

KEY POINTS

PARKINSON'S DISEASE

- Parkinson's disease is a progressive disorder of later life, defined clinically by motor features (asymmetric bradykinesia, rigidity, tremor, and imbalance) and pathologically by neuronal degeneration and intraneuronal misfolded α-synuclein (Lewy bodies) in specific central and peripheral nervous system regions, including dopaminergic brain-stem neurons.
- Disorders of mood, sleep, sensation, cognition, and autonomic function are common, often preceding motor signs by years (prodromal Parkinson's disease) and increasing with the duration of the disease.
- Gene variants are causative in approximately 20% of cases. Nongenetic risk factors that increase risk (toxicants and head injury), plus small contributions of common variants, probably cause most cases. Exercise may decrease risk.
- No therapy has been proved to slow progression. Dopaminergic therapies improve motor function, but loss of efficacy and side effects are common. Deep-brain stimulation surgery is effective for motor fluctuations.
- Nonmotor symptoms cause substantial morbidity, but evidence for treatment is sparse. Off-label medications are commonly used. Comprehensive multidisciplinary care is helpful.
- Biomarker research suggests that a biologic definition of Parkinson's disease is possible.

clinical diagnostic criteria for Parkinson's disease[3] and research diagnostic criteria for prodromal Parkinson's disease.[11] These criteria rely on clinical features and are supplemented by special imaging techniques. Although no imaging technique can confirm the diagnosis of Parkinson's disease, visualization of the striatal dopamine system (mainly with the use of ^{123}I-ioflupane single-photon-emission computed tomography [SPECT] or ^{18}F-labeled fluorodopa positron-emission tomography) can differentiate between Parkinson's disease and disorders such as essential tremor. The sensitivity and specificity of ^{123}I-ioflupane SPECT imaging are 90% or higher, and a systematic review showed that the use of these techniques led to changes in diagnosis in 31% of study participants and changes in management in 54%.[12]

Magnetic resonance imaging (MRI) of the brain can identify changes in basal ganglia or infratentorial structures that are characteristic of other neurodegenerative disorders involving parkinsonism but distinct from Parkinson's disease, such as progressive supranuclear palsy[13] and multiple-system atrophy.[14] Advances in MRI techniques are also being explored for the purpose of refining the diagnosis of Parkinson's disease and distinguishing it from other movement disorders.[15]

At autopsy, intraneuronal accumulation of misfolded α-synuclein protein (Lewy bodies and Lewy neurites, collectively termed "Lewy pathology") is present in up to 90% of clinically defined cases of Parkinson's disease, selectively affecting brain-stem nuclei (dorsal motor nucleus of the vagus, locus coeruleus, and substantia nigra), the peripheral autonomic region (myenteric plexus, sympathetic ganglia, and skin autonomic nervous system), and the limbic and neocortical regions.[16] The loss of pigmented neurons, particularly substantia nigra neurons producing dopamine, is considered to be another highly characteristic feature of the disease. Although the clinical diagnostic criteria remain useful, they have limitations. In one cohort, the agreement between the clinical diagnosis and the findings at autopsy was only 28% at the time of the initial diagnosis but increased to 89% with a long disease duration.[17] Agreement between diagnostic and postmortem findings is most likely when the diagnosis is made by movement-disorder experts.[18]

CAUSES

Parkinson's disease is considered to have multiple causes, resulting from both genetic and nongenetic factors. Genetic variants with large effect sizes have been identified in approximately 20% of persons with Parkinson's disease (monogenic Parkinson's disease). Autosomal dominant Parkinson's disease with incomplete penetrance includes variants in *LRRK2* (present in approximately 1 to 2% of all cases and up to 40% of familial cases); *GBA1*, encoding glucocerebrosidase (present in 5 to 15% of cases and most common in populations with Ashkenazi Jewish or North African ancestry); and *VPS35* and *SNCA*, which are even less common (present in <1% of cases).[19,20] Recessively

inherited Parkinson's disease variants include *PRKN*, *PINK1*, and *DJ1*, which account for most cases that develop at a young age. Although all the variants are infrequent, in some populations, they are the most common genetic causes. Abnormal α-synuclein is found in Parkinson's disease associated with *SNCA* or *GBA1* and in approximately half of cases associated with *LRRK2* but is rare in Parkinson's disease associated with recessive variants; recessively inherited Parkinson's disease has fewer nonmotor features and more prominent dystonia than the typical disorder.[19]

Genomewide association studies have identified more than 90 genetic risk loci with small independent effects, many of which are located near the causative genes noted above.[20,21] Most genetic studies have focused on White persons with European ancestry. As global initiatives expand, new genetic associations may be identified. An example is the report of a novel variant in *GBA1* that accounts for 39% of cases of Parkinson's disease in persons of African ancestry.[21]

In persons without a strong genetic risk factor for Parkinson's disease, heritability is estimated to be 20 to 30%,[20,22] which suggests a contribution of nongenetic factors. The identification of risk factors has been limited to observations in specific populations, which are subject to several types of bias. In contrast to studies of genetic risk, most epidemiologic studies have investigated only a few risk factors, although people generally have many potential exposures throughout life, and from what is currently known, it is likely that the combination of these exposures plus genetic susceptibility, rather than a single factor, determines risk. Furthermore, many environmental and lifestyle-associated risks are not easily measured. Almost all the work in this field has focused on populations in Europe and North America.

Residential or occupational exposure to pesticides (e.g., paraquat, rotenone, 2,4-dichlorophenoxyacetic acid, and several organochlorines and organophosphates) or chlorinated solvents (e.g., trichloroethylene and perchloroethylene) has been associated with a dose-dependent, 40% or greater risk of Parkinson's disease in most studies.[23-25] In laboratory studies, these toxicants can cause experimental analogues of Parkinson's disease — for example, by interfering with mitochondrial function, which causes selective dopaminergic neuron loss, motor dysfunction, and other changes. In a prospective cohort study, high consumption of dairy products was associated with an increased risk of a clinical or pathological diagnosis of Parkinson's disease and with increased brain concentrations of heptachlor, an organochlorine pesticide, possibly resulting from bioconcentration of this compound in milk.[26]

Some but not all studies have shown an association between a mild-to-moderate head injury and the onset of Parkinson's disease or REM sleep behavior disorder decades later, with the disease risk increased by 31% to more than 400%.[27,28] Less consistently, exposure to metals, type 2 diabetes mellitus, certain inflammatory disorders, and infections have putatively increased the risk of Parkinson's disease.[28,29] A decreased risk of Parkinson's disease has been associated with cigarette smoking, caffeine consumption, and increased physical activity.[28] Studies of the mechanisms associated with genetic variants and laboratory investigations of toxicant exposures have identified putative abnormalities that are common to genetic and sporadic disease, including inflammation, immune dysregulation, oxidative stress, mitochondrial dysfunction, protein aggregation, impaired autophagy, and dysfunction of the endolysosomal system.[30]

NATURAL HISTORY AND CLINICAL COURSE

Motor symptoms of slowness and tremor tend to be asymmetrical. Eventually, bilateral bradykinesia, rigidity, tremor, and gait and balance disorders lead to functional impairment and loss of independence, often from the combined effects of motor and cognitive decline, falls, and fractures. The time course of progression is quite variable. Nonmotor symptoms, including hyposmia, autonomic dysfunction, and REM sleep behavior disorder, precede motor and cognitive dysfunction in most people with Parkinson's disease, often by decades.[11] Other autonomic abnormalities, including orthostatic hypotension, impaired gastrointestinal motility, urinary dysfunction, erectile dysfunction, and impaired thermoregulation, may develop early and often progress.

Cognitive changes, such as visuospatial or executive dysfunction, may be subjective symptoms, sometimes preceding motor symptoms, and can be identified by means of neuropsycho-

logical tests as Parkinson's disease progresses. Cognitive decline associated with mild cognitive impairment or Parkinson's disease dementia [31,32] develops in approximately 10% of patients annually.[33] The allied entity of dementia with Lewy bodies has predominantly cognitive and psychiatric features, such as visual hallucinations, and includes parkinsonism; it may represent an alternative phenotypic presentation of Parkinson's disease or an overlapping entity with different etiologic underpinnings. Approximately 38% of clinically diagnosed cases of Parkinson's disease and 89% of cases of dementia with Lewy bodies have Alzheimer's-associated pathological features.[34]

Identification of clinical subtypes with characteristic patterns of disease progression has not been reproducible across populations.[35] Biologic characterization of subgroups of clinical Parkinson's disease is expected to improve individual prognostication and patient counseling. For example, cognitive decline is common in patients with variants in *GBA1* but infrequent in those with variants in *PRKN*.[19]

TREATMENT

Regular exercise, a healthy diet, high-quality sleep, and avoidance of adverse exposures have been associated with reduced mortality and provide a foundation for advising persons with Parkinson's disease at any stage.[36] No available pharmacologic therapy definitely slows the progression of Parkinson's disease, despite nearly four decades of clinical trials to identify such agents. For example, although initial trials of monoamine oxidase B (MAO-B) inhibitors were considered promising, further study of these agents did not show a protective effect that was independent of their effect on symptoms.[37] Trials of treatments to slow disease progression, which have enrolled persons after Parkinson's disease has been diagnosed, may have failed because up to 75% of substantia nigra dopaminergic neurons have lost function even in the early stages of disease. Intervention before motor symptoms occur, or when only biomarker evidence of disease is present, may increase the potential for neuroprotection.[38,39] Trials that have been focused on mechanisms for clearing alpha-synuclein aggregates have had mixed results to date,[40,41] as have trials targeting genetically defined subpopulations with pathogenic variants in *GBA1* or *LRRK2*.[38] Provocative but early investigations of glucagon-like peptide receptor agonist have evinced interest in the field.[42]

Symptom management must understandably be individualized to achieve the best results, since Parkinson's disease manifests and evolves differently from person to person. A multidisciplinary approach, guided by the patient's input and implemented by a team that includes a neurologist, mental health professional, neurosurgeon, and physical, occupational, and speech therapists, among others, is ideally introduced early. The needs of the patient, family members, and caregivers should be reassessed regularly, including advanced care planning and, in some severe cases, referral to hospice.[43]

PHARMACOTHERAPY

Motor Symptoms

Oral formulations of levodopa are the main treatment for motor symptoms (Table 1), although tremor may be less responsive than bradykinesia and rigidity in some patients.[44] If patients do not have a motor response to levodopa, the diagnosis may need to be reconsidered. The duration of effect after a levodopa dose ("on" time), typically several hours, starts to shorten, on average, after 4 years. "On" time is interspersed with periods of reduced symptomatic benefit ("off" time). These motor fluctuations are probably due to the short half-life of levodopa, inconsistent gastrointestinal absorption, and progressive degeneration of dopaminergic neurons. Strategies such as increasing the overall dose, increasing the frequency of administration, or adding or switching to extended-release formulations are often used to address these fluctuations. Common dose-related side effects include dyskinesia (hyperkinetic involuntary movements), development or worsening of hallucinations or behavioral problems, orthostatic hypotension, and nausea.

Other strategies to ameliorate motor symptoms and fluctuations involve the use of dopamine agonists either as monotherapy or in combination with levodopa, providing the added benefit of a longer half-life than levodopa. Dopamine agonists are currently used less commonly than in the past because of their unfavorable side-effect profile; side effects include dose-dependent

Table 1. Medications Used for Motor Symptoms of Parkinson's Disease (PD).*

Drug Class and Medication	Formulation	Motor Indications or Clinical Applications
Levodopa		
Carbidopa–levodopa IR and CR formulations, carbidopa–entacapone–levodopa	Generic	Broad indication for PD
Carbidopa–levodopa ER	New	Early monotherapy (symptomatic); for wearing-off episodes and motor fluctuations
Carbidopa–levodopa enteral suspension	New	For wearing-off episodes and motor fluctuations
Levodopa inhaled powder	New	Adjunct to levodopa for wearing-off episodes and motor fluctuations
Carbidopa–levodopa functionally scored tabs	New	Broad indication for PD
Nonergot dopamine agonist		
Pramipexole IR and ER	Generic	Broad indication for PD
Ropinirole IR and ER	Generic	Broad indication for PD
Rotigotine transdermal system	Generic	Broad indication for PD
Apomorphine hydrochloride injectable, subcutaneous	Generic	For wearing-off episodes and motor fluctuations
MAO-B inhibitor		
Selegiline	Generic	Adjunct to levodopa
Rasagiline	Generic	Broad indication for PD
Zonisamide	Generic	Off-label use as adjunct to levodopa for wearing-off episodes and motor fluctuations
Safinamide	New	Adjunct to levodopa for wearing-off episodes and motor fluctuations
Selegiline oral disintegrating tablets	New	For wearing-off episodes and motor fluctuations
Catechol-*O*-methyltransferase inhibitor		
Entacapone	Generic	Adjunct to levodopa for wearing-off episodes and motor fluctuations
Opicapone	New	Adjunct to levodopa for wearing-off episodes and motor fluctuations
Adenosine A2A receptor antagonist: istradefylline	New	Adjunct to levodopa for wearing-off episodes and motor fluctuations
Anticholinergic agent		
Trihexyphenidyl	Generic	Adjunct to levodopa
Benztropine	Generic	Adjunct to levodopa
NMDA receptor antagonist		
Amantadine IR	Generic	Broad indication for PD, off-label use for dyskinesia
Amantadine ER capsules	New	Adjunct to levodopa for wearing-off episodes, motor fluctuations, and dyskinesia
Amantadine ER tablets	New	Broad indication for PD, off-label use for dyskinesia

* The listed medications are approved by the Food and Drug Administration (FDA) and require a prescription in the United States. Drugs that do not have established generic formulations are listed as new formulations. CR denotes controlled release, ER extended release, IR immediate release, MAO-B monoamine B, and NMDA *N*-methyl-D-aspartate.

nausea, somnolence, sleep attacks, impulse-control disorders, and peripheral edema. The effect of levodopa can be enhanced by adding catechol-*O*-methyltransferase (COMT) inhibitors, or MAO-B inhibitors, which block synaptic dopamine metabolism.[45] Other, nondopaminergic medications, such as amantadine and istradefylline, can sometimes ameliorate motor fluctuations and reduce

dyskinesia when used as adjunctive therapy. Anticholinergic drugs targeting tremor are less commonly used now than in the past because they may cause worsening cognition in older patients.[46]

On-demand strategies for dopaminergic therapies for severe or frequent off episodes include subcutaneous injection or sublingual apomorphine and inhaled levodopa. Continuous enteral delivery of levodopa through an intrajejunal pump, subcutaneous delivery of apomorphine, or delivery of levodopa by means of a subcutaneous pump has also been used in advanced cases of Parkinson's disease.[47] No approach is universally beneficial.

Nonmotor Symptoms

Nonmotor symptoms contribute greatly to the burden of Parkinson's disease, as mentioned above, but evidence-based studies to guide treatment are lacking, and use of off-label medications is common (Table 2). Many nonmotor symptoms worsen with advancing disease or with dopaminergic therapy. Parkinson's disease–related dementia may decrease modestly in response to treatment with acetylcholinesterase inhibitors or memantine, but only rivastigmine is classified as clinically useful according to the evidence-based review conducted by the International Parkinson and Movement Disorder Society.[48] Depression and anxiety can be treated with selective serotonin-reuptake inhibitors, selective serotonin–norepinephrine reuptake inhibitors, or less commonly, dopamine agonists, with careful attention to drug interactions and the potential development of the serotonin syndrome. Psychiatric symptoms of hallucinations and delusions can be treated with pimavanserin[49] or with atypical antipsychotic medications (clozapine or quetiapine). Other dopamine D2 receptor–blocking antipsychotic agents are not used because they can worsen parkinsonism.[50] Cognitive behavioral therapy and counseling have been useful nonpharmacologic strategies for managing psychiatric symptoms.[51]

Autonomic symptoms, including orthostatic hypotension, can be addressed with increased fluid intake, additional dietary salt, compression stockings, and medications to increase blood pressure, such as fludrocortisone, midodrine, or droxidopa.[48] Pain, which is typically multifactorial, may be managed by optimization of dopaminergic therapy, but evidence supporting pain management in Parkinson's disease remains a key unmet need.[48] Drooling can be managed with sublingual atropine drops or salivary-gland botulinum toxin injections. Constipation is managed with increased dietary fiber, stool softeners, or laxatives. Disrupted sleep or REM sleep behavior disorder may be ameliorated with cognitive behavioral therapy, melatonin, or low-dose clonazepam.[48,49]

SURGICAL THERAPEUTIC APPROACHES

Deep-brain stimulation (DBS) therapy entails intracranial placement of thin leads (on one side or both sides of the brain), typically into the subthalamic nucleus or globus pallidus, which are connected through extension leads to a neurostimulator placed subcutaneously in the subclavicular region. Electrical stimulation delivered through the leads can be adjusted and tailored to target an individual patient's symptoms over time.[52] The mechanism of the effect is not known but is considered to be due in part to interruption of aberrantly functioning basal ganglia circuits that are responsible for the main motor features of the disease. Determination of candidacy for DBS, implantation of the system, and ongoing patient care and device management are typically performed at specialized centers. Most patients undergoing DBS therapy have motor fluctuations that are poorly controlled by medication, which justifies performing the procedure.

DBS improves the quality of life and alleviates motor fluctuations (average increase in "on" time, 3 to 4 hours a day) and symptoms that occur in the absence of medication (average improvement in off-medication UPDRS III [Unified Parkinson's Disease Rating Scale, part III] score of 30 to 50%); it also allows for a reduction in medication (average dose reduction, 50%), especially when the subthalamic nucleus is targeted after programming of stimulation parameters has been optimized to best address the patient's symptoms, which typically occurs within the first 3 to 6 months after surgery.[47] Given the low procedural risks (i.e., stroke and infection) with modern procedures and its effectiveness, DBS is approved for use when motor fluctuations begin.[53] The motor benefit may persist for up to 15 years.

Current DBS neurostimulator options include single- and dual-channel systems with either nonrechargeable batteries (battery life, 3 to 5 years)

Table 2. Treatment of Nonmotor Symptoms.*

Drug Class and Medication	Formulation	Nonmotor Indications or Clinical Applications
Acetylcholinesterase inhibitor		
Rivastigmine tablets or transdermal system	Generic	Mild-to-moderate dementia associated with PD
Donepezil	Generic	Dementia of Alzheimer's type, off-label use for cognitive impairment or dementia in PD
NMDA antagonist: memantine	Generic	Dementia of Alzheimer's type, off-label use for cognitive impairment or dementia in PD
Serotonin-reuptake inhibitor: citalopram, escitalopram, paroxetine, fluoxetine, or sertraline	Generic	General depression or anxiety, off-label use for PD-specific indication
Serotonin–norepinephrine reuptake inhibitor: venlafaxine	Generic	General depression or anxiety, off-label use for PD-specific indication
Tricyclic antidepressant		
Desipramine	Generic	General depression or anxiety, off-label use for PD-specific indication
Nortriptyline	Generic	General depression or anxiety; off-label use for PD-specific indication
Atypical antipsychotic		
Clozapine	Generic	Treatment-resistant schizophrenia, off-label use for PD-related psychosis
Quetiapine	Generic	Schizophrenia, bipolar I disorder, manic episodes, bipolar disorder, depressive episodes; off-label use for PD-related psychosis
Serotonin 5-HT 2A/C inverse agonist and antagonist: pimavanserin	New	Hallucinations and delusions in patients with PD-associated psychosis
Benzodiazepine: clonazepam	Generic	Seizure and panic disorder; off-label use for PD-associated REM sleep behavior disorder
Hormone and dietary supplement: melatonin	Available over the counter	PD-associated REM sleep behavior disorder
Stimulant		
Methylphenidate	Generic	Attention deficit disorder, off-label use for PD-associated fatigue
Modafinil	Generic	Excessive sleepiness associated with narcolepsy, obstructive sleep apnea symptoms, or shift work disorder; off-label use for PD-associated fatigue
Prokinetic agent: domperidone	Available only through FDA investigational drug protocol	Nausea and vomiting
Mineralocorticoid: fludrocortisone	Generic	Partial replacement therapy for primary or secondary adrenocortical insufficiency in Addison's disease and salt-losing adrenogenital syndrome; off-label use for orthostatic hypotension

Alpha-1 adrenergic agonist and vasopressor: midodrine	Generic	Orthostatic hypotension
Acetylcholinesterase inhibitor: pyridostigmine	Generic	Myasthenia gravis; off-label use for orthostatic hypotension
Norepinephrine prodrug: droxidopa	Generic	Orthostatic dizziness, lightheadedness, symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure PD, multiple system atrophy, and pure autonomic failure
Acetylcholine release inhibitor and neuromuscular blocking agent		
OnabotulinumtoxinA injection	Generic	Overactive bladder, urinary incontinence due to detrusor overactivity, chronic migraine, adult upper-limb spasticity, cervical dystonia, severe axillary hyperhidrosis, blepharospasm, strabismus, glabellar lines; off-label use for PD-associated sialorrhea and focal dystonia
IncobotulinumtoxinA injection	Generic	Adult upper-limb spasticity, cervical dystonia, blepharospasm, glabellar lines; off-label use for PD-associated sialorrhea and focal dystonia
AbobotulinumtoxinA injection	Generic	Cervical dystonia, glabellar lines, adult upper-limb spasticity; off-label use for PD-associated sialorrhea and focal dystonia
RimabotulinumtoxinB injection	Generic	Cervical dystonia; off-label use for PD-associated sialorrhea and focal dystonia
Anticholinergic agent: glycopyrrolate		Uses related to anesthesia and peptic ulcer disease; off-label use for PD-associated sialorrhea
Antimuscarinic agent		
Oxybutynin	Generic	Bladder instability associated with voiding in patients with uninhibited neurogenic or reflex neurogenic bladder
Trospium	Generic	Overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency
Beta-3 adrenergic agonist: mirabegron	New	Overactive bladder with symptoms of urge urinary incontinence, urgency, and urinary frequency
Alpha-blocker: tamsulosin	Generic	Signs and symptoms of benign prostatic hyperplasia
Alpha-1–selective adrenoceptor antagonist: terazosin	Generic	Symptomatic benign prostatic hyperplasia and hypertension
Phosphodiesterase-5 inhibitor: sildenafil	Generic	Erectile dysfunction

* The listed medications require a prescription in the United States and have FDA approval, with one exception that is available over the counter. Drugs that do not have established generic formulations are listed as new formulations. REM denotes rapid eye movement.

or rechargeable batteries (battery life, >15 years). Some DBS systems include image-based software allowing visualization of the leads relative to the targeted brain structure and simulation of the volume of tissue activation to facilitate programming. Sensing systems capable of measuring local field potentials from DBS leads also can aid in programming and may soon allow for adaptive stimulation, in which the intensity of stimulation is adjusted on the basis of a neuronal feedback signal. Most nonmotor symptoms of Parkinson's disease (cognitive impairment, mood changes, apathy, and autonomic symptoms) and some motor symptoms (impaired balance and freezing of gait) typically do not improve with the use of DBS, but future neuromodulation strategies may better address these symptoms. Potential complications of DBS include dyskinesia and worsening of speech, gait, and balance. In rare cases, off-target stimulation causes changes in mood, cognition, or behavior, which are usually modifiable with DBS programming changes.

Older techniques involving direct lesioning with a heated probe (unilateral thalamotomy or pallidotomy) are now used only in rare cases. An incisionless lesioning approach involving MRI-guided, high-frequency, focused ultrasonography[54] targeting the ventral intermediate nucleus of the thalamus on one side is increasingly being used to treat tremor in patients with Parkinson's disease, but this approach may have a limited benefit over time and does not treat other symptoms of Parkinson's disease. Pallidal and subthalamic nucleus targets are also being explored with the use of ultrasonography.[55]

Previous and ongoing gene therapies have included stereotactic infusion of gene-mediated viral vectors into the putamen or substantia nigra to enhance the production of neurotrophic factors (glial-derived neurotrophic factor and neurturin), γ-aminobutyric acid delivered into the subthalamic nucleus to modify the motor circuitry, or aromatic L-amino acid decarboxylase delivered into the putamen to increase the synthesis of dopamine. So far, none of these therapies have received regulatory approval. Despite the disappointing results of previous efforts to transplant dopamine-producing cells into the putamen,[56] newer approaches, with the use of cells derived from human induced pluripotent stem cells, allogeneic cells, and human embryonic stem cell–derived graft lines, are still in development. These approaches focus on improving motor symptoms and reducing the medication burden through a one-time surgical procedure but face the challenges of unproven safety, feasibility, and efficacy.[57]

FUTURE DIRECTIONS

Prevention of Parkinson's disease remains an important focus of research. Attempts to address existing disparities across sex, race, ethnic group, economic status, and geographic location, combined with a global effort to reduce exposure to environmental toxicants and improve lifestyle behaviors, will be needed. Identification of genetic changes, especially in understudied populations, will provide new insights. Advances in technology, including telemedicine, can improve access to care, and artificial intelligence, digital assessments, wearable devices, and virtual reality may one day improve screening, monitoring, and treatment.[58,59] Biomarkers for abnormal α-synuclein can distinguish persons with clinically defined Parkinson's disease, dementia with Lewy bodies, or REM sleep behavior disorder from healthy controls and from persons with other neurologic diseases, with high sensitivity and specificity; these markers can also be detected in persons with hyposmia alone (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).[60,61] Testing of α-synuclein may allow early detection of neuronal α-synuclein disease, which would provide a path to early intervention and a foundation for precision medicine.[4,38,60,61]

CONCLUSIONS

Parkinson's disease causes progressive motor and nonmotor symptoms and signs. Advances in the past two decades in identifying genetic variants that confer a risk of the disorder and different phenotypic and pathological presentations, biomarker characterization, refinement in medical and surgical treatment, and a renewed emphasis on lifestyle have allowed for a framework to individualize treatment, reduce symptoms, and improve quality of life for patients with this condition.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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