Current understanding and management of Parkinson disease

Five new things

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A PubMed query for "Parkinson disease" yields more than 2,000 articles per year for each of the last 5 years. That is a daunting pile of bedside reading for even the most diligent neurologist. This review highlights 5 emerging topics that are changing our current understanding and management of Parkinson disease (PD). When using the term PD, we mean Lewy body parkinsonism as defined by the clinical criteria of the United Kingdom Parkinson's Disease Society Brain Bank. Other parkinsonian syndromes, such as progressive supranuclear palsy and multiple system atrophy, are beyond the scope of this review.

GENETICS OF PD Clinicians are frequently faced with the question, posed by a newly diagnosed patient or family member: "Is Parkinson's genetic?" This apparently simple question has a complex answer. In a small minority of cases, there are defined genes that, when mutated, cause PD. For example, mutations in α-synuclein (*SNCA*), leucine-rich repeat kinase-2 (*LRRK2*), *Parkin*, PTEN-induced kinase-1 (*PINK1*), and *DJ-1* have been convincingly demonstrated to cause familial PD but often without a typically Mendelian pattern of inheritance. Families with clear autosomal recessive and dominant patterns are rare. Yet the relative risk of developing PD is more than 3 times higher for an asymptomatic individual when a first-degree relative is affected with sporadic PD.[1] Even where there is clear familial clustering of cases, a causative gene may not be identified.

What is the source of this "missing heritability"? Some insight has come from recent genome-wide association studies[2,3] of large numbers of patients. These analyses—essentially case-control studies where "exposures" are defined by genotyping individuals over a large number of sites of variation in the genome—have identified a number of novel "risk genes" that contribute to the overall chance of developing PD. Importantly, some of these were loci already implicated in familial PD (*SNCA, LRRK2*), supporting the notion that common mechanisms underlie both the common sporadic and rare inherited forms. However, in all cases, the individual contribution of any given locus was small (odds ratios [OR] <1.5).

Another particularly interesting risk gene has recently emerged from the convergence of several lines of evidence. Clinicians have long observed that patients with type III Gaucher disease (a recessive lysosomal storage disorder, caused by mutations in the glucocerebrosidase *GBA* gene, resulting in bone, spleen, and liver pathology) sometimes developed a parkinsonian syndrome. Further studies have demonstrated a higher than expected incidence of PD in Gaucher families, including obligate heterozygote carriers of *GBA* mutations. Recently, Sidransky et al.[4] synthesized these observations and conducted an analysis on patients from 16 clinical sites, demonstrating that GBA mutations were highly associated (OR ~5–6) with the development of PD. Phenotypic characteristics differed (earlier age at onset, higher proportion with cognitive dysfunction) in patients with PD with *GBA* mutations compared to those without. While the mechanism by which altered GBA function might influence the onset and evolution of parkinsonian symptoms is not known, some speculate that compromised lysosomal function from glucocerebroside accumulation may interfere with the normal disposal of degraded cellular protein, leading to cell death. Overall, these data implicate the GBA locus as one

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of the most common and powerful influences on the risk of sporadic PD and suggest that better understanding the link between *GBA* mutations and PD will lead to etiologic insights and a new model for the development of more effective treatments.

These studies highlight a remarkable advance in understanding the genetics of PD, but it is certain that genetics alone do not determine development of disease and its clinical expression. For example, LRRK-2, the most common monogenic determinant of PD, accounts for only 1%–2% of sporadic PD cases (despite pockets of higher prevalence in some parts of the world, specifically Northern Africa), and penetrance among carriers is incomplete.[5] Additionally, numerous toxic and environmental exposures may play a causative (MPTP, pesticides) or protective (caffeine, nicotine) role in the development of PD.[6] Thus, the majority of PD cases likely have a multifactorial etiology, and an effort to understand both genetic and environmental causes will be key to defining what leads to the first of a presumed cascade of stages of neurodegeneration.

PREMOTOR DIAGNOSIS Development of disease-modifying therapies for neurodegenerative disorders, including PD, is hindered by the substantial burden of pathology that has already accumulated by the time clinical signs appear. Although recent clinical trials suggest that one currently available drug may have neuroprotective properties, convincing proof may be difficult to demonstrate simply because therapeutic intervention may be too late to slow or halt progression of neurodegeneration after symptoms have become apparent, given the long preclinical evolution of the underlying neuropathology.[7]

Many agents exhibiting neuroprotective effects in animal models ultimately fail in clinical trials. One possible explanation is that in laboratory experiments, animals typically receive drug at the same time as or prior to the pathogenic insult, whereas patients are not treated until diagnosis and the disease process has been long underway. One currently popular and preoccupying strategic approach to detection of preclinical PD is to identify reliable biomarkers in people who are genetically or otherwise predisposed to developing the disease at a later time.

How can a disease be diagnosed before symptoms appear? The search for molecular biomarkers of premotor PD in blood, CSF, and urine has been active but nonproductive at the present time. On the other hand, the search for a biomarker in the brain, using the neuroimaging techniques of PET and SPECT, has shown more promise. For example, visualization at nigrostriatal nerve terminals of dopamine synthesis with fluorodopa PET or of the presynaptic dopamine transporter (DAT) with SPECT are sensitive and specific methods for showing presymptomatic pathology affecting nigral neurons and their striatal projections. Additionally, PET and SPECT imaging can be used as investigative tools to study a potentially enriched population of asymptomatic first-degree relatives of patients with PD who may be genetically susceptible to the later development of clinically evident PD. Some premotor symptoms of PD, particularly decreased olfaction (hyposmia) and REM sleep behavior disorder (vivid dreams and dream enactment), are found randomly in the general population and have been found to be risk factors for PD.[8] Screening for such individuals who may be at a higher risk of developing PD may yield an even more enriched population worthy of longitudinal study to clarify the nature of the predisposition and the positive predictive value of these factors as biomarkers. However, while hyposmia is a relatively sensitive marker for PD, it is not specific, since hyposmia is common in early AD, and in normal elderly. Therefore, these early markers must be combined with additional, more specific methods to identify early pathology peculiar to PD.

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An economically practical model for conducting this type of clinical research is the Parkinson At Risk Study, which uses an inexpensive but sensitive screening test of olfaction (the University of Pennsylvania Smell Identification Test) to select hyposmic but asymptomatic people at risk for PD to undergo further testing with the more expensive and more specific SPECT-DAT neuroimaging procedure. Those that show abnormally reduced uptake of DAT are being followed to determine the probability of developing overt motor signs of PD. The results of this study will have important implications for the feasibility of such multi-tiered approaches to identifying PD in presymptomatic stages.

The role these advanced neuroimaging methods should play in current clinical practice is still unclear. Additionally, many of the techniques are available

only on a research basis, but protocols to make dopamine terminal imaging commercially available are under consideration for approval by the US Food and Drug Administration. One scenario where these studies would be immediately helpful to the general practitioner is in the differential diagnosis of parkinsonism and essential tremor (where dopamine imaging would be normal). Although these conditions most often can be distinguished on clinical grounds, there may be overlap in difficult cases, and making the correct diagnosis has important implications for prognosis and treatment.

DEEP BRAIN STIMULATION SURGERY Dopamine replacement therapy provides significant and relatively durable improvement in the motor symptoms of PD in a majority of patients. However, most ultimately experience medication-related complications including drug-induced involuntary movements (dyskinesia) and fluctuations between medication "on" and "off" states. Additionally, some patients experience refractory tremor despite an otherwise favorable response to medical therapy. Deep brain stimulation (DBS) was introduced in the early 1990s as an effective treatment for select patients with PD and other tremor disorders. Briefly, DBS for PD involves stereotactic surgical implantation of an electrode with 4 contacts into deep gray nuclei (globus pallidus interna [GPi] or subthalamic nucleus [STN]). Chronic high-frequency stimulation is then provided through an implantable pulse generator residing in the anterior chest wall. This method is preferable to prior ablative surgical methods in that electrical stimulation is both reversible and programmable. DBS has been increasingly affirmed in a variety of clinical trials, but questions have remained regarding the most prudent timing of the procedure, the best anatomic target for stimulation, ways to mitigate perioperative and postoperative adverse effects, and which patients should be selected to have the procedure.

The ideal surgical candidate is young (<70), cognitively and medically healthy, robustly responsive to levodopa and other optimally managed antiparkinson medications, but with motor fluctuations, dyskinesia, or medication-refractory tremor. However, the average patient with PD tends to be older with more medical comorbidities and a greater likelihood of having surgically unresponsive midline symptoms such as postural instability and speech and swallowing problems. Therefore, the ideal candidate is relatively uncommon, but a sufficient number of patients meet or come close to meeting strict inclusion criteria for consideration of DBS in practice for it to be an important therapeutic option for patients with advanced disease and declining quality of life. The most reliable estimate is that approximately 10%–15% of all patients with PD are candidates to undergo DBS.

Two recent reports from a large, multicenter study (Veterans Affairs Cooperative Studies Program [VA-CSP]) have addressed many of these issues. This multipart study eventually examined DBS in more than 300 patients with PD who were carefully selected to meet strict inclusion criteria that predicted a good outcome. In the first phase of the study, patients were randomized to DBS (GPi or STN) or best medical therapy (BMT) and followed for 6 months.[9] The DBS group fared better on motor outcomes, gaining an average of 4.6 hours per day of "on" time without dyskinesia (0 hours/day for BMT). Quality of life measures also improved significantly in the DBS group. Adverse events were significantly higher for the first 3 months postsurgery in the DBS group (mostly related to mechanical or infectious problems with the implanted hardware), but similar after 6 months with the exception of a higher incidence of falls. There was a small but significant decrease in several cognitive measures in the DBS group. A similar large trial comparing DBS to BMT is ongoing in the United Kingdom (PD-SURG) and a recent report of the 1-year follow-up data describes improvement in quality of life (judged by the PDQ39 questionnaire).[10]

The second phase of the VA-CSP trial[11] compared outcomes of stimulation of each of the 2 targets: GPi and STN. Motor and quality of life outcomes did not differ significantly. The STN group had slightly lower scores on measures of cognitive processing speed and higher self-reported depression. STN stimulation allowed greater reduction in the amount of PD medications required to control symptoms after surgery. Adverse effects were frequent (~50%) but similar in the 2 groups. The suggestion of a differential effect of target on nonmotor symptoms (NMS) was also seen in the COMPARE trial,[12] particularly when more ventral stimulation was used in STN.

Together, these reports provide strong evidence for the efficacy of DBS in improving motor symptoms and quality of life in appropriately selected patients with PD. Additionally, choice of target need not be made on the basis of motor outcomes, but may take into account individual patient features (such as depression or the desire to lower medication levels). Overall, the benefits of DBS must be balanced with the risk of adverse events, particularly an increased risk of falls and cognitive dysfunction. Fur-

thermore, patients should understand that DBS treats a fairly specific set of symptoms (mostly levodopa-induced), has no effect on other important problems, such as postural instability, and does not alter the natural history of PD. At best, it can "turn back the clock" for an indeterminate period of time and thereby decrease some aspects of parkinsonian disability.

NEUROPROTECTION While medical and surgical therapy can provide long-lasting symptomatic benefit, the holy grail of therapeutics in PD (and other neurodegenerative disorders) is the development of drugs that slow or halt progression of disease—so-called neuroprotection or disease modification. Ideally, a neuroprotective agent would modify the underlying pathophysiology that causes neurodegeneration and cell death. To that end, a variety of agents, targeted at hypothesized pathogenic or protective mechanisms including excitotoxicity (riluzole), apoptosis/programmed cell death (TCH346, CEP-1347, minocycline), oxidative stress/mitochondrial dysfunction (vitamin E, coenzyme Q_{10}, creatine), and neurotrophic factors (glial-derived neurotrophic factor, neurturin) have been tested in clinical trials in PD. None has had a clear impact on clinical outcomes in initial studies, although some agents (creatine, CoQ_{10}) have shown sufficient promise to warrant larger, currently ongoing, phase III trials. Additionally, a recent meta-analysis of epidemiologic studies suggested that nonaspirin nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of incident PD by 15%, possibly by inhibiting a neuroinflammatory pathway.[13] This finding is intriguing given the wide availability, low cost, and well-characterized safety profile of NSAIDs, but it needs to be explored in prospective trials.

Though considered mainstays of symptomatic therapy, drugs that directly (levodopa, dopamine agonists) or indirectly (monoamine oxidase [MAO-B] inhibitors) influence dopamine signaling have also been evaluated for neuroprotective activity but with controversial results. A comprehensive analysis of these studies is beyond the scope of this discussion, but they have been recently reviewed.[14] Central to the controversy is the use of clinical measures, such as change in score on the Unified Parkinson's Disease Rating Scale (UPDRS), as primary outcome measures, making it difficult to distinguish pure symptomatic benefit from bona fide neuroprotection, as both would be reflected in improved scores.

One potential answer to the conflict between a symptomatic vs neuroprotective effect of a drug is to use an independent and objective biomarker of disease progression, such as PET or SPECT imaging of nigrostriatal dopamine terminals. This approach was taken in CALM-PD (Comparison of the dopamine Agonist pramipexole vs Levodopa on Motor complications of Parkinson's Disease, using the DAT ligand ^{123}I-β-CIT SPECT) and REAL-PET (Requip as Early therapy vs L-dopa Positron Emission Tomography, using ^{18}F-DOPA-PET). While patients treated with either dopamine agonist showed relatively less radiotracer uptake loss over time than levodopa-treated groups (implying slower loss of dopamine neurons in the pramipexole group), the lack of placebo groups and the possible greater regulatory influence of the agonists on the expression of the tracer binding molecules themselves make the results difficult to interpret. Additionally, the apparent effect on neuronal survival represented by the imaging findings was in opposition to clinical outcomes (which favored levodopa in both cases), calling into question the utility of these methods as biomarkers for clinical trials.

The recently reported clinical trial ADAGIO (Attenuation of Disease progression with Azilect Given Once daily)[15] used a novel delayed-start trial design in an attempt to separate symptomatic from neuroprotective or disease-modifying effects of the MAO-B inhibitor rasagiline (Azilect). Patients with early, untreated PD were randomized to receive 1 or 2 mg of rasagiline daily for the entire 72-week study (early start) or placebo for 36 weeks (phase I) followed by rasagiline (delayed start) for the second 36-week period (phase II). To prove disease modification attributable to rasagiline, the investigators used 3 hierarchical endpoints in their primary analysis, based on magnitude and rate of change of UPDRS scores during different periods of the study. Despite the novel design and successful execution, the study's results were mixed. The 1-mg daily dose fulfilled all 3 criteria, suggesting a disease-modifying effect. However, the 2-mg dose failed to meet all 3 of the predetermined criteria for disease modification.

One possible explanation for the discordant findings is a "U-shaped" dose-response curve of rasagiline observed in preclinical models where lower doses confer neuroprotection but higher doses do not.[16] However, those changes were observed as concentration of drug varied over orders of magnitude, whereas the change in ADAGIO was only 2-fold. An alternative explanation, as proposed by the authors of ADAGIO, is that larger symptomatic benefits of rasagiline at 2 mg daily may have masked relatively smaller disease-modifying effects in the time period examined. The authors concluded their discussion of the results of ADAGIO with this caveat: "From a

practical point of view, the study findings suggest a possible benefit of the early use of rasagiline at a dose of 1 mg per day; however, given the negative findings for the 2 mg dose, we cannot definitively conclude that rasagiline at a dose of 1 mg per day has disease modifying effects." A similar delayed-start clinical trial of the dopamine agonist pramipexole in early PD (the PROUD PD study) has been completed. Although the results have not been published, presentations at meetings indicate that pramipexole does not have disease-modifying properties.

Despite these disappointments, disease modification remains in sharp focus as a worthy objective in the overall search for PD therapeutics. Clearly, the answers are still elusive and more research is necessary for the next stage of clarification to materialize. The ambiguity of the ADAGIO study underscores the need for more precise biomarkers in conducting clinical research, but its tentative support for disease modification is also a tantalizing hint that improved research methodology will bring us closer to actually finding the holy grail.

NONMOTOR SYMPTOMS: IMPACT AND MANAGEMENT Although PD is a clinically defined movement disorder characterized by tremor, rigidity, bradykinesia, and postural instability, numerous NMS including cognitive, mood, behavioral, sleep, and olfactory disturbances have attracted the attention of clinical investigators in recent years because of their growing importance. The PRIAMO Study[17] examined over 1,000 patients with PD for the prevalence and types of NMS experienced by patients with a diagnosis of PD. More than 98% of patients had at least one NMS, and the average number per patient was 7.8. The most common NMS were psychiatric (68%, anxiety most common), fatigue (58%), leg pain (38%), insomnia (37%), urinary (35%), drooling (31%), and difficulty concentrating (31%). Dementia was not specifically addressed. Pain, fatigue, and psychiatric symptoms were significantly more common in women than in men. NMS significantly influenced quality of life (measured by the PDQ39), with apathy, autonomic symptoms, fatigue, and cognitive dysfunction having the most negative impact.

Not surprisingly, the number and impact of NMS increase with disease duration and severity. The Sydney Multicenter study on PD[18] has followed 136 incident cases over an unprecedented 20 years of follow-up. In this population, the prevalence of NMS increased dramatically over time with some, such as dementia, becoming "inevitable" by 20 years. Similar results were observed in the cross-sectional PRIAMO study, as the number and severity of NMS increased with disease stage and duration. Unfortunately, many NMS, such as hallucinations, fatigue, and orthostatic hypotension, are not responsive to dopaminergic therapy and in some cases may be worsened, leading to further disability in advanced PD.

The high impact of NMS on the management of PD led the American Academy of Neurology's Quality Standards Subcommittee to review the literature and issue a set of guidelines for practitioners.[19] Evidence-based recommendations included consideration of sildenafil (Viagra) for erectile dysfunction, polyethylene glycol (MiraLax) for constipation, methylphenidate (Ritalin), for fatigue, modafinil (Provigil) for excessive daytime somnolence, and carbidopa/levodopa (Sinemet) for periodic limb movements of sleep. A prior Practice Parameter supported the use of cholinesterase inhibitors such as donepezil (Aricept) and rivastigmine (Exelon) (Exelon is the only one approved by the Food and Drug Administration) for the treatment of cognitive dysfunction associated with PD. The table provides a sample of available treatments for NMS based on this analysis summarizing the available literature but should not be viewed as a specific endorsement of any treatment. Perhaps the most salient finding from the Subcommittee's review of NMS was a lack of evidence to

Table Treatments for nonmotor symptoms in Parkinson disease[a]

Nonmotor symptoms domain	Symptom	AAN recommendation	Used based on clinical experience
Autonomic	Erectile dysfunction	Sildenafil	
	OH	Insufficient evidence	Midodrine, droxidopa, fludrocortisone
	Incontinence	Insufficient evidence	Anticholinergics[b]
	Constipation	Polyethylene glycol	Water, fiber, stool softeners
	Drooling	Botulinum toxin glycopyrrolate	
Sleep	EDS	Modafinil	
	Insomnia	Insufficient evidence	Melatonin
	RBD	Insufficient evidence	Clonazepam
	PLMS	Carbidopa/levodopa	
Psychiatric	Depression	Insufficient evidence	SSRIs, TCAs[c]
	Anxiety	Insufficient evidence	Benzodiazepines[c]
Cognitive	Dementia	Rivastigmine	Donepezil, memantine
Miscellaneous	Fatigue	Methylphenidate	

Abreviations: AAN = American Academy of Neurology; ED = erectile dysfunction; EDS = excessive daytime somnolence; OH = orthostatic hypotension; PLMS = periodic limb movements of sleep; RBD = REM sleep behavior disorder; SSRI = serotonin-specific reuptake inhibitor; TCA = tricyclic antidepressant.
[a] This summary is not meant to endorse specific treatment modalities.
[b] Monitor for confusion.
[c] See reference 19.

support or refute treatments for orthostatic hypotension, incontinence, insomnia, REM sleep behavior disorder, and anxiety, highlighting the urgent need for controlled clinical trials for management of these debilitating symptoms.

CONCLUSION In this brief review of 5 new things, we have highlighted only a few of the many areas of active investigation that are shaping contemporary thinking on the pathogenesis and treatment of PD. While this list represents our own selection bias and could have been completely different if compiled by others, we know that these topics have important practical value for neurologists challenged to keep up with the rapidly expanding knowledge base on the pathophysiology, clinical manifestations, and management of PD.

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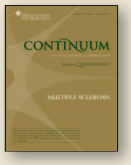

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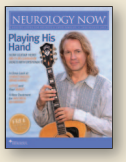

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