AN UPDATE ON PARKINSON'S DISEASE

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The Clinical Picture of Parkinson's Disease

Parkinson's disease (PD) is a progressive neurodegenerative disease that results in slowly increasing physical difficulties in multiple arenas. Peak onset is age 55-65 years old, but some cases are classified as Early Onset PD (onset < 41 years old) or juvenile parkinsonism (onset < 21 years old). The prevalence of PD is now estimated to be approximately 1% in individuals over 60 years of age, with 4.1 to 4.6 million affected, a number predicted to more than double by 2030 as populations age.[1]

Specific movement disturbances, the so-called "cardinal signs" of PD include: bradykinesia, rest tremor (in the majority), rigidity, and postural instability (later in the disease). These features are typically asymmetric and respond to PD medications. However, Langston in 2006 described parkinsonism as the "tip of the iceberg" of PD, with non-motor symptoms including mood disorders, cognitive dysfunction, sleep disorders, autonomic dysfunction, and pain or sensory syndromes co-existing alongside motor symptoms.[2] A number of non-motor features are now well described, and these together with motor features are listed in Table 1.

TABLE 1: MOTOR AND NON-MOTOR SYMPTOMS OF PD

MOTOR DISTURBANCES	NON-MOTOR DISTURBANCES
hypophonia	mild cognitive impairment, dementia
hypomimia	depression, anxiety
dysphagia	sialorrhea
hand incoordination	orthostatic hypotension
dystonia	gastrointestinal dysmotility, constipation
generalized slowing	bladder dysfunction
gait impairment	sexual dysfunction
imbalance and falls	hyposmia
freezing (gait, speech uncommon)	sleep disorders: RBD; RLS, sleep fragmentation
micrographia	visual impairment: impaired contrast discrimination
	pain syndromes
	weight loss
	peripheral neuropathy?
	hearing loss?

RBD: Rapid eye movement (REM) sleep behavior disorder; RLS: restless legs syndrome

Emerging Concept of Pre-Motor PD

There is now increasing recognition that non-motor symptoms, although commonly seen alongside the motor symptoms of PD, might in many cases arise prior to the characteristic motor symptoms. There is now strong evidence for the existence of a pre-motor syndrome. Recently, features identifying individuals at risk for developing PD have been proposed as a "Parkinson's associated risk syndrome" (PARS).[3] While these are being carefully evaluated, examples of published findings to date are provided in Table 2.

TABLE 2: CLINICAL STUDIES ADDRESSING POSSIBLE PRE-MOTOR PD FEATURES

Premotor feature	Clinical studies
Cardiac autonomic dysfunction	Reduced MIBG uptake of (^{123}I-meta-iodobenzylguanidine) prior to motor symptoms and in early PD;[4] abnormal cardiac R-R interval variability[5]
Gastrointestinal symptoms -constipation -gastroparesis	4-fold increased PD risk in men with < 1 daily bowel movement versus men with 2-3 daily bowel movements;[6] constipation presented before motor symptoms in ~45% PD (average 18 years prior);[7] abnormal ^{13}C sodium octanoate breath test, transit time measurement[8]
Neurobehavioural symptoms -anxiety and depression -apathy -cognitive alteration -mood disorders -personality type	Affective changes;[9] cognitive disorders;[10] neurobehavioural alterations[11, 12]
Olfactory sense dysfunction	Odor discrimination testing: 5-fold increased PD risk for 4th versus 1st/2nd quartiles;[13] association of decreased odor discrimination with dopamine transporter density;[14] abnormal anterior olfactory region MRI DTI signal[15]
Sexual dysfunction	Sexual dysfunction in 22-23% prior to PD[16]
Sleep disturbance -REM Sleep Behavior Disorder (RBD)	Predicts PD/DLB in 45% at 11.5 years follow up;[17] predicts any neurodegenerative disorder in 18% at 5 years, 52% at 12 years follow up;[18] 38% men aged >50 years were diagnosed with a parkinsonian disorder at mean 12.7 years after RBD onset[19]

Pathophysiology of Parkinson's Disease

PD symptoms have long been attributed to substantia nigra (SN) pathology, with loss of pigmented dopaminergic neurons observed at autopsy, and mechanisms of pathogenesis have been well reviewed by Hirsch and colleagues.[20] Surviving SN neurons often contain Lewy Bodies (LB), intracytoplasmic proteinaceous inclusions. These comprise multiple proteins including α-synuclein recognized as key to PD pathogenesis. LB, as well as dystrophic α-synuclein-containing Lewy neurites, have now been widely described in other tissues. PD pathology has now been detected not only in widespread regions of the CNS, but also in other sites, for example in autonomic nerves innervating the heart,[21] gut,[22] prostate,[23] and immunoreactivity in skin tissue is observed in autopsy-identified cases with Lewy Body disease.[24] Some of these findings may therefore correlate with non-motor and pre-motor features described above.

A staging system has been proposed based on > 125 autopsy cases selected for α-synuclein pathology (and not specifically for PD clinical diagnosis).[25] Six neuropathological stages have been proposed, originating in nondopaminergic structures of the brainstem and olfactory bulb, with progression to more caudal CNS. These stages are:

1. caudal medulla, including the dorsal motor nucleus of the vagus, and the olfactory bulb
   medulla oblongata and adjoining portions of the pontine tegmentum (locus ceruleus and other "gain setting nuclei")
2. substantia nigra
3. forebrain and temporal mesocortex

5/6. widespread regions of cerebral cortex.

It must be emphasized, however, that this is a hypothesis. The presence of LB and Lewy neurites may not fully define regions of cellular dysfunction. Moreover, axonal loss may occur earlier than cell body degeneration.[26,27,28] This is important since axonal loss, occurring as a distinct process prior to neuronal cell body loss in PD, has implications regarding target choices for neuroprotection. Despite limitations of such cross-sectional studies, the Braak hypothesis of PD pathology progression has stimulated interest in exactly how this spread occurs at a molecular level,[29] and recently a mechanism similar to spread of prions has been proposed.[30] The role of exosomes as vesicular intercellular carriers transporting alpha-synuclein has recently been proposed, and might represent another step for intervention in treatment. Other mechanisms involved in PD pathogenesis have also gained increasing attention, including inflammatory processes and the role of oxidative stress and mitochondrial dysfunction. [29,31]

Risk Factors for Parkinson's Disease

Genetic determinants

Genes that lead to, or are associated with risk of, PD are summarized in Table 3. Corresponding PARK loci are provided in cases in which they have been designated.

TABLE 3: PD GENETICS

Locus	Gene	Function	Notes
PARK1	α-synuclein	normal function poorly understood; aggregates important in pathogenesis	AD; A30P like typical PD; A53T younger onset, faster progression
PARK2	parkin	ubiquitin ligase active in protein degradation by proteasomal pathways	AR; early onset; dystonia can be prominent; usually no LB (see below)
PARK3	2p13		AD; usually typical PD-like; some families w/ dementia
PARK4	α-synuclein (increased gene dose)	normal function poorly understood; aggregates important in pathogenesis	AD; early onset; ± dystonia, myoclonus, early weight loss, seizures, fast progression; triplication more associated with PDD, DLB
PARK5	UCH-L1	protein degradation (UPS pathway)	AD; resembles typical PD
PARK6	PINK1	PTEN-induced kinase 1; mitochondrial protein kinase	AR; early onset (see below)
PARK7	DJ-1	Oxidative stress sensor, chaperone	AR; early onset; slow progression
PARK8	LRRK2	Leucine-rich repeat kinase	AD (see below)
PARK9	ATP13A2	Lysosomal ATPase	AR; juvenile onset; spasticity, supranuclear gaze palsy, dementia (Kufor-Rakeb syndrome)
PARK10	1p32		Late onset sporadic
PARK11	GIGYF2	IGF signaling	Associated with PD, also DLB
PARK12	Xq21-25		
PARK13	Omi/HtrA2	Anti-apoptotic serine protease	Not yet well-confirmed
PARK14	PLA2G6	Phospholipase A2 group 6	AR; early onset
PARK15	FBX07	F-box protein; component of E3 ubiquitin protein ligases	AR; early onset; Parkisonian Pyramidal Syndrome (Pallidopyramidal syndrome; PKPS)
PARK16	1q32		
PARK17	GAK	cyclin G-associated kinase	Association locus
PARK18	HLA-DRA		Association locus
	7p15-21.1		AD; late onset (one family)
	NURR1	transcription factor	Rare, mutations found in late onset PD
	SCA3		Usually presents with ataxia (Macahdo-Joseph)
	SCA8		Usually presents with ataxia Repeat expansion in some with PD – significance?
	SCA17		Usually presents with ataxia Repeat expansion in some with PD – significance?
	Synphilin 1		Role not well understood
	GBA	β-glucocerebrosidase, lysosomal	Modifies risk
	MAPT	tau (microtubule associated proein)	Modifies risk
	α-synuclein		Modifies risk
	BST-1	bone marrow stromal cell antigen	Modifies risk
	LRRK2	leucine-rich repeat kinase	Modifies risk (also PARK7 locus)

Abbreviations: AD: autosomal dominant; AR: autosomal recessive; DLB: Dementia with Lewy Bodies; PDD: Paarkinson's Disease Dementia; UPS: ubiquitin proteasomal system

In a recent meta-analysis of PD risk studies, the most important risk factor was any family member with PD. [32] Although monogenic forms of PD account for about 30% of familial and 3%-5% of sporadic cases, [33,34,35,36] multiple susceptibility loci are now identified that not only contribute to appreciation of the strength of genetic contribution to PD, but may shed light upon pathogenesis (see below).

How best to use genetic testing as a predictor of PD ion the clinic remains to be established. Gene testing is commercially available in the US to detect sequence variants in the following PD genes:

- parkin
- PINK1
- LRRK2 (codons 1441, 2019, 2020)

Individuals may also obtain testing by "23andMe" (codon 2019, LRRK2), a service that can be ordered online for a fee, and without referral by a physician.

Parkin-associated PD is characterized by generally younger onset with slow progression, and is typically without Lewy body pathology. In a study of 73 PD families (autosomal recessive pattern, ≥ one individual with onset < 45 years old), parkin mutations occurred in almost 50% of cases.[37] Parkin mutations also lead to sporadic young onset PD: of 246 individuals with YOPD, parkin mutations led to 15% cases total, and 70% cases < 20 years old.[38] Genetic testing may therefore be helpful in such cases, when combined with clinical judgment.

PINK1 is the second most common monogenetic cause of autosomal recessive PD, accounting for 1-8% of sporadic early onset cases. As for parkin-associated PD, these cases are usually early onset and only slowly progressive, but in contrast seem to be associated with Lewy body pathology.[39]

Mutations in the LRRK2 gene account for ~10-15% familial PD cases and ~1-2% sporadic PD cases in white populations[40,41] Prevalence varies by population, however, and in certain groups LRRK2 mutations are much more common. In Ashkenazi Jewish and North African Arab populations, the G2019S mutation may account for up to 30-40% familial PD cases.[42,43] Although genetic testing is available, its predictive use in the clinical realm is complicated by incomplete penetrance (in one large study, penetrance was 30% at 60 years old, and almost 75% at 80 years old.[44] LRRK2 mutations also lead to phenotypic heterogeneity. The role of other modifying genes is being elucidated, for example GBA (present in ~20% of the Ashkenazi Jewish population).[43,44,45,46]

Identification of genetic risk loci and use of genome wide association studies (GWAS)

Recent large genome wide association studies (GWAS) have expanded our understanding of genetic risk in PD.[47,48] Several moderate genetic risk factors for sporadic PD have now been proposed, including polymorphisms in the α-synuclein and LRRK2 genes. *REP1* variants (variants in length of a dinucleotide repeat near the SNCA promoter) affect α-synuclein expression levels and PD risk: a meta-analysis of > 2500 PD cases versus controls revealed an odds ratio of 1.4 for PD associated with presence of an expanded 263bp *REP1* allele.[49] Microtubule-associated protein Tau (MAPT) mutations are known as a cause of frontotemporal dementia with parkinsonism linked to chromosome 17 (FTDP-17) but recently the MAPT H1 haplotype has been recognized as a PD risk factor, with H1 homozygosity associated with an approximately 50% increased risk of PD.[50]

Environmental and Lifestyle Risk Factors for Parkinson's Disease

Certain environmental and lifestyle associations have been well described in PD for some time: these include coffee consumption and tobacco use (lower risk) and drinking well water and rural location (higher risk). However, recently large studies have determined a broader range of potentially important exposures that not only enhance our understanding of PD epidemiology, but also seem in many cases to tie in with mechanisms of PD pathogenesis, in particular those of oxidative stress and mitochondrial dysfunction.

<u>Environmental exposures and PD risk</u>

There is increasing concern based upon the growing literature linking toxic environmental exposures to PD, and multiple specific agents have been implicated, for example:

- 2,4-diphenoxyacetic acid: OR 2.6 (95% CI 1.03-6.48) in case-control USA/Canada study of exposures based upon job- and task-based occupational history (permethrin, paraquat also suggested in this study) [51]
- trichloroethylene: OR 6.1 (95% CI = 1.2–33; p = 0.034)[52]
- rotenone: OR = 10.0 (95% CI = 2.9-34.3) in case-control East Texas study (paraquat - trend for association)[53]
- manganese-associated parkinsonism[54]
- welding-related parkinsonism[55]

Of note, paraquat (increases oxidative stress) and rotenone (mitochondrial toxin) have been used to generate animal models of PD.

Lifestyle factors and PD risk

Diet and exercise may represent modifiable risk factors, and lower risk of PD has been associated with:

- diets associated with increased urate levels[56] *men only
- "healthy diet" high in vegetables, seaweed, pulses, mushrooms, fruit, fish (odds ratio 0.54 for highest versus lowest quartile, 95% CI = 0.32–0.92)[57]
- "prudent" dietary pattern: high in fruit, vegetables, legumes, whole grains, nuts, fish, poultry, low intake of saturated fat, and moderate intake of alcohol (Health Professionals Follow-Up Study; Nurses' Health Study)[58]
- moderate-to-vigorous exercise [59,60]
- medication use, including calcium channel blockers and NSAIDS [32]

Other modifiable risk factors may also turn out to be important but have yet to be studied more extensively. For example, hypertension in women has been associated with higher PD risk.[61]

Improving PD Diagnosis

PD remains a clinical diagnosis, and when ancillary testing is performed (such as brain MRI) it is almost always to test for other possible diagnoses that may explain parkinsonism (for example if normal pressure hydrocephalus (NPH) or vascular Parkinsonism (VP) are suspected as possibilities). However, clinical diagnosis can be challenging. For example PD symptoms/signs may overlap with other neurodegenerative disorders, such as Progressive Supranuclear Palsy (PSP), Multiple System Atrophy (MSA), Corticobasal Degeneration (CBD), or DLB. This is particularly true in early PD, when only subtle motor signs are present. Diagnosis based upon clinical features is therefore not fully accurate. For example in a clinicopathological study of 100 clinically diagnosed PD cases, just 90/100 satisfied neuropathological criteria for PD, with PSP, MSA, and vascular parkinsonism accounting for the remainder.[62] Misdiagnosis of non-PD conditions (essential tremor, VP, MSA, PSP) as PD means that an estimated 5–25% of patients diagnosed with PD are receiving treatment that may be of marginal or no help[63,64,65] At the same time, failure to diagnose PD also occurs, with an estimated 20% of patients with PD not diagnosed despite medical evaluation.[64] Although long-term clinical follow-up improves diagnostic accuracy, it is desirable to make the most accurate possible diagnosis early in the disease course: this will help avoid inappropriate treatment and testing, aid in assessing prognosis, and is important in offering the possibility of participation in clinical trials. AAN guidelines regarding diagnosis and prognosis have been published in 2006 (see below).

Recently, in order to identify PD earlier and more accurately, a number of biomarker-based approaches are being tested. Potential markers include neuroimaging and sophisticated biochemical and molecular techniques, and major research initiatives are now underway including the Parkinson's Progression Markers Initiative (PPMI, including the Parkinson's Progression Markers Initiative (PPMI, http://www.ppmi-info.org),[66] and BioFIND (https://www.michaeljfox.org/page.html?biofind-clinical-study).

Neuroimaging as a diagnostic tool in PD

PD neuroimaging has focused largely on ligand binding detected either by single photon emission computed tomography (SPECT) or by position emission tomography (PET). [^{123}I]FP-CIT SPECT (DaTscan) is now available for clinical use in many countries, including as of 2011 the USA, but a number of ligands have been investigated that bind to presynaptic targets in the nigrostriatal pathway, as follows:

- dopamine transporter (DAT)
  - [^{123}I]FP-CIT [N-fluoropropyl-2β-carbmethoxy-3β-(4-[^{123}I]iodophenyl)nortoprane, ioflupane]
  - [^{99m}Tc]TRODAT-1
  - [^{123}I]β-CIT [2β-carbomethoxy-3β-(4-[^{123}I]iodophenyl)tropane, iometopane].
- vesicular monoamine transporter (VMAT)
  - [^{11}C]DTBZ
- dopa decarboxylase activity (reflecting dopamine synthesis)
  - [^{18}F]Dopa
  - [^{11}C]Dopa

Such techniques show promise in facilitating earlier detection and improving diagnostic accuracy as they reflect nigrostriatal tract integrity.[67] Dopaminergic imaging, however, has not been considered helpful in differentiating PD from MSA, CBD, or PSP, and approaches using alternative ligands may be of more utility in such cases (for example [^{18}F]fluorodeoxyglucose (FDG) PET.[68]

Other imaging techniques including MRI, magnetic resonance spectroscopy, and ultrasound imaging are also being actively investigated. In particular, ultrasound imaging appears to show promise as a PD biomarker, and demonstrates hyperechogenicity of the SN in PD. Moreover, an ultrasound study of 102 subjects with PD, 34 with MSA, and 21 with PSP, found that the combination of SN hyperechogenicity with normal lentiform nucleus echogenicity, versus moderate or less SN echogenicity with lentiform hyperechogenicity yielded a positive predictive value of 0.91 for PD versus atypical parkinsonism.[69]

Genetic, molecular and biochemical biomarker development
Approaches focused upon specific protein measures in CSF (e.g. α-synuclein, DJ-1),[70] genomic, proteomic, transcriptomic and metabolomic analyses,[71,72,73] markers of oxidative stress, inflammatory markers and others are not yet close to clinical application, although are an exciting avenue of research (see review[74]).

Pharmacologic Treatment of Parkinson's Disease
Medications commonly used in the USA for treatment of motor symptoms of PD are listed in Table 4, and Fox and colleagues for the Movement Disorder Society have provided a recent evidence-based update on their use in PD.[75]

TABLE 4: MEDICATIONS FOR MOTOR SYMPTOMS OF PD

Medication	Mechanism of action	Comments
Anticholinergic agents o trihexyphenidyl, other	Anticholinergic activity	Improves tremor Care regarding cognitive side effects
Dopamine agonists o bromocriptine o pramipexole (IR, ER) o ropinirole (IR, ER) o rotigotine o apomorphine	Direct binding to dopamine receptors	Monotherapy and adjunctive therapy Counsel patient about driving, ICD side effects Apomorphine is injectable Rotigotine is transdermal delivery
levodopa o carbidopa/levodopa o carbidopa/levodopa orally dissolving o carbidopa/levodopa extended release o carbidopa/levodopa/entacapone	Dopamine precursor	Risk of motor complications Use of extended release not recommended for reducing off time (decreased bioavailability)
COMT-Inhibitors o entacapone o tolcapone	Inhibit peripheral breakdown of levodopa	Adjunct therapy only Tolcapone use requires monitoring for hepatic toxicity
Selective MAO-B inhibitors o rasagiline o selegiline o Zydis-selegline	Inhibit dopamine breakdown	Monotherapy and adjunctive therapy Long term benefits suggested
Other o amantadine o carbidopa	NMDA receptor antagonist, other Inhibits peripheral levodopa breakdown	Monotherapy and adjunctive therapy; decreases dyskinesias Administer with carbidopa/levodopa to reduce nausea side effect

Abbreviations: COMT: catechol-O-methyl transferase; MAO-B: monoamine oxidase B: ICD: impulse control disorders

Pharmacologic Treatment of Early Motor Symptoms
Medications approved for use in early motor PD are aimed at controlling motor symptoms. Their pharmacology and use in the clinical realm have been well reviewed,[76] and the available drugs are therefore only briefly described here. In general, there is still a trend to initiate treatment with medications other than levodopa where appropriate, due to concerns over developing motor complications of wearing off at end of levodopa dose, and of dyskinesias (see American Academy of Neurology guidelines on treatment of motor symptoms in early PD, see below).

Although the properties of these drugs are well known to practitioners, a subset of recent studies of interest, categorized by medication, are briefly discussed bellow:

Levodopa
Levodopa has been the mainstay of PD treatment since the 1960's, and is orally administered in combination with aromatic amiinoacid decarboxylase (AADC) inhibitors (carbidopa in the USA) to inhibit peripheral breakdown. Side effects include nausea (in which case carbidopa 25 mg administered prior to each dose may help); orthostatic hypotension; drowsiness; hallucinations (rare in early PD) and others.

The Early versus Later Levodopa in Parkinson's Disease study (ELLDOPA) phase III clinical trial examined levodopa efficacy versus placebo over a range of doses, but additionally employed a drug washout phase to determine any potential effect upon PD progression.[77] Subjects were randomized to receive placebo, 150 mg, 300 mg or 600 mg levodopa daily over 40 weeks. Motor benefit was clearly dose-related, although motor complications occurred in a significant proportion (17% in the highest dose group experienced dyskinesias by 40 weeks). Following a 2-week washout period, despite predicted lack of symptomatic effect, a significant motor benefit persisted in those who received the highest daily dose of levodopa persisted. What this means is as yet unclear, as SPECT imaging in a subset of subjects demonstrating less decline in [^{123}I]beta-CIT uptake in the placebo versus levodopa group. Finally, in a post hoc analysis, broad variability was described in individual response, with overlap between individual responses to placebo and active drug.[78] While this is consistent with clinical experience, its basis remains to be understood.

Although the combination of carbidopa/levodopa/entacapone (Stalevo) is indicated for wearing off, not early PD, it was recently tested in early PD in the multi-center STRIDE-PD trial (STalevo Reduction In Dyskinesia Evaluation). The trial aimed to evaluate whether carbidopa/levodopa/entacapone as initial therapy would delay time to onset of dyskinesia, compared with carbidopa/levodopa, based upon the concept of continuous dopaminergic stimulation. Carbidopa/levodopa or carbidopa/levodopa/entacapone (100 mg levodopa per dose) were administered four times daily. Contrary to predictions, dyskinesias were more frequent and time to dyskinesia was shorter in the carbidopa/levodopa/entacapone versus carbidopa/levodopa groups (hazard ratio 1.29; p=0.04).[79] More events of myocardial infarction were observed in the carbidopa/levodopa/entacapone group, and there were more cases of prostate and skin cancer in the carbidopa/levodopa/entacapone group. This combination is not generally used in clinical practice in early PD, but these results suggest appropriate counseling during its use in moderate-advanced PD, until these data are better understood.

Dopamine Agonists
Ropinirole, pramipexole, bromocriptine, and rotigotine (a transdermal preparation unavailable in the US at the time of writing) may all be used as monotherapy to alleviate motor symptoms. Multiple clinical trials have now been conducted comparing dopamine agonists with levodopa, and find that they are less likely to lead to motor complications during early PD (note, this benefit is not sustained in advanced PD). For example, 28% of subjects assigned to pramipexole (supplemental levodopa allowed) experienced wearing off, dyskinesias, or on-off motor fluctuations versus 51% of subjects assigned to levodopa. [80,81] This has led to preferential use of dopamine agonists in patients deemed at higher risk of developing debilitating motor complications. However, their use must be balanced with side effects including those seen with levodopa, but seemingly a higher risk of sudden onset of sleep (potentially dangerous in drivers), and impulse control disorders (see below).

More recent studies have attempted to dissect out other potential benefits of dopamine agonists (although not all limited to early monotherapy). For example effects upon mood are now well documented. In a 12-week randomized, double-blind, placebo-controlled trial of pramipexole (0.125 mg–1 mg three times daily) depression improved significantly.[82] There have been efforts to determine whether this class of drugs might slow disease progression, based upon pre-clinical studies demonstrating neuroprotective properties. A delayed-start study was employed to determine whether pramipexole has detectable disease modifying activity using this trial design.

Although results have been presented in abstract form only at the time of writing, it seems that no support for a disease modifying benefit of 1.5mg dose of pramipexole could be demonstrated.[83,84] Use of these drugs in early PD therefore remains based upon symptomatic motor benefits.

Finally, extended release formulations of pramipexole[85] and ropinirole[86,87] are now available, as well as a rotigotine transdermal patch (available in the US in 2012) allowing once daily dosing.[88]

A note on impulse control disorders (ICDs) and dopamine agonist withdrawal syndrome (DAWS)
Behavioral alterations have been increasingly recognized in association with anti-PD medications, and were first recognized for dopamine agonists. This has been best investigated in the DOMINION study (Impulse Control Disorders in Parkinson's Patients Treated with Pramipexole and Other Agents). Of 3090 subjects with PD asked about problem/pathologic gambling, compulsive buying, binge-eating, and sexual behavior, a greater incidence of ICDs was evident in those treated with any dopamine agonist versus no dopamine agonist (17.1% versus 6.9%, p<0.001). However, this problem was not confined to agonists: use of both levodopa and agonists were independently associated with ICD occurrence (odds ratio 1.51, p=0,01 and 2.72, p<0.001 respectively). For this reason, patients starting these medications must be appropriately counseled on these in addition to other potential side effects.[89]

Recently a pattern of symptoms akin to drug withdrawal, termed the dopamine agonist drug withdrawal syndrome (DAWS) has been described.[90] Symptoms including anxiety, panic attacks, agoraphobia, depression, dysphoria, diaphoresis, fatigue, pain, orthostatic hypotension, and drug cravings were described as dopamine agonists were tapered, and degree of motor impairment did not seem to associate with these symptoms. Patients therefore need to be monitored and counseled when these medications are reduced.

Selective monoamine oxidase (MAO)-B inhibitors
Rasagiline and selegiline are irreversible and specific MAO-B inhibitors used in PD treatment. Symptomatic benefit has long been known for selegiline. More recently, the TEMPO trial Rasagiline mesylate (TVP-1012) in Early Monotherapy for Parkinson's Disease Outpatients) tested 1 mg and 2 mg rasagiline daily versus placebo in early PD. Both doses demonstrated improvement in total UPDRS scores at 6 months (-4.20 units for 1 mg rasagiline versus placebo; -3.56 units for a 2 mg rasagiline versus placebo).[91] These drugs both have excellent tolerability profiles,[92] although attention needs to be paid to potential drug interactions (note: dietary restriction of tyramine is not required at recommended medication doses).

There has been longstanding interest in whether MAO-B inhibitors could modify disease progression, and both selegiline and rasagilnie have neuroprotective properties in pre-clinical PD models. The DATATOP study (Deprenyl and α-Tocopherol Antioxidative Treatment of Parkinsonism) attempted to detect whether selegiline, might slow PD progression.[93] Its symptomatic benefit confounded attribution of patient benefit to neuroprotection, but further studies have reopened the question of whether it could modify disease progression. Subjects who reached endpoint in DATATOP were allowed to enroll in an open-label extension, BLIND-DATE,[94] in which they received selegiline for a further eighteen months, then were re-randomized to treatment with selegiline versus placebo. Those assigned to selegiline developed less freezing of gait (16% versus 29%; p<0.0003). A potential effect beyond symptomatic benefit has been supported by additional studies.[95]

Recent studies of rasagiline have specifically addressed effects upon disease progression, distinct from short-term symptomatic benefit. At the end of the first 6-month placebo-controlled phase of the TEMPO study (see above), those taking rasagiline continued at their assigned doses, and those taking placebo were now reassigned to rasagiline 2mg daily.[96] By the end of the trial at 12 months, total UPDRS score had worsened by 3.01 ± 8.26 for the early start 1 mg group, by 1.97 ± 7.49 for the early start 2 mg group, and by 4.17 ± 8.83 for the delayed 2 mg group, supporting an advantage for early start versus delayed start. Moreover, an open label extension study followed subjects for up to 6.5 years total, with additional anti-parkinsonian medications allowed according to standard clinical treatment,[97] supporting sustained benefit. In a delayed start design trial of 1176 patients with early untreated PD, nicknamed ADAGIO (Attenuation of Disease Progression with Azilect Given Once-Daily) subjects were assigned to rasagiline 1 mg or 2 mg daily versus placebo for 9 months. They then either continued assigned rasagiline doses, or switched from placebo to rasagiline 1 mg or 2 mg daily. Rasagiline 1mg daily early-start met all end points: (1) a slower rate of worsening in UPDRS score during the placebo-controlled (first) phase of the trial; (2) less worsening from baseline to end of study (2.82 ± 0.53 UPDRS points, early-start, versus 4.52 ± 0.56 UPDRS points, delayed-start group, P=0.02); (3) non-inferiority between groups in rate of change in UPDRS

score in the second phase of the trial (all subjects taking active drug). However, rasagiline at a dose of 2 mg per day did not meet all endpoints, since the change in the UPDRS score between baseline and week 72 was not significantly different in the two groups (3.47+/-0.50 points in the early-start group and 3.11+/-0.50 points in the delayed-start group, P=0.60).[98] Since then, post hoc analyses have been published that help shed further light on the complexities of this trial.[99]

Agents that modulate glutamate activity

Amantadine, with action at the NMDA receptor, is used for therapeutic benefit in early and advanced motor PD, and its use has been associated in one study with improved 10 year survival rates.[100] A 2-year placebo-controlled, double-blind multi-center trial of riluzole (approved for amyotrophic lateral sclerosis treatment) was terminated after meeting predefined futility criteria.[101] Attention is now turning to agents acting at the AMPA receptor, and the metabotropic glutamate receptors (mGluR) in drug development.[102]

Pharmacologic Treatment of Advanced PD Motor Symptoms

As PD advances, the vast majority of patients require levodopa treatment, and with time motor fluctuations (wearing off and on-off fluctuations) and dyskinesias develop. Off periods are typically characterized by re-emergence of motor symptoms, but may also comprise distressing non-motor symptoms including anxiety, shortness of breath, diaphoresis, paresthesias and pain, and other symptoms that are less easily recognized. Symptoms of freezing and postural instability may also occur in later disease, and are often resistant to dopamine-based therapies.

Medications useful in treating wearing off and dyskinesias are summarized in Table 3 (also see review[103]), and AAN guidelines have been published in 2006 (see below). Briefly, management strategies for wearing off include:

1. Fragmentation of levodopa dosing

This strategy is commonly used, and can be very effective, with levodopa administration up to 7-8 times per day (or more in some cases). However, not only is it is burdensome for patient and caregiver, but this approach may be limited by dyskinesias, and lower individual doses of levodopa may fail. Therefore other strategies should be considered where appropriate.

2. Adjunctive use of COMT-inhibitors, entacapone and tolcapone

These medications increase half-life of single levodopa doses, thereby extending duration of effect. In patients with wearing off, clinical trials have demonstrated reduction in off time between approximately 1-2.5 hours. Although tolcapone seems more efficacious,[104] it is less widely used due to the requirement for monitoring hepatic function. Use can be limited by occurrence of dyskinesias, and other increased levodopa-associated side effects.

3. Adjunctive use of dopamine agonists

Multiple clinical trials have provided convincing evidence to support the use of adjunctive dopamine agonists, including bromocriptine, ropinirole and pramipexole in treating wearing off. For example, ropinirole extended release provided a reduction of -30% off time versus -4% for placebo over the period of a 24-week randomized, placebo-controlled, double blind study of 393 subjects with advanced PD.[86] The newly available (in the US) transdermal rotigotine preparation also provides relief of off time,[105] and in a double-blind, double dummy, randomized controlled trial was comparable in efficacy to pramipexole.[106] A third route of administration is provided by apomorphine, which, injected subcutaneously provides rapid relief of off symptoms.[107] Trimethobenzamide is routinely administered to individuals receiving this treatment in order to avoid nausea.

4. Adjunctive use of MAO-B inhibitors

Both rasagiline and selegiline may be used to extend duration of levodopa action. Two large phase III clinical trials have demonstrate efficacy of rasagiline as a levodopa adjunct, although dyskinesias may be increased as for other adjunctive therapies. In the Parkinson's Rasagiline: Efficacy and Safety in the Treatment of "Off" study (PRESTO), rasagiline 1 mg daily led to 0.94 hours less off time per day than placebo, and rasagiline 0.5 mg per day led to 0.49 hours less “off” time.[108] In the Lasting effect in Adjunct therapy with Rasagiline Given Once daily study (LARGO),[109] which employed entacapone as a comparator, reduction in off time was similarly demonstrated.. A randomized, placebo-controlled, multicenter trial of Zydis-selegiline, an orally dissolving sublingually absorbed selegiline formulation included 140 subjects with advanced PD (at least 3 hours off time daily). Zydis-selegiline demonstrated significant reduction in “off” time, from 6.9±2.0 hours (41.5±11.6%) at baseline, to 4.7±2.7 hours (28.3±15.8%) versus reduction from 7.0±2.2 hours (42.1±12.5%) at baseline to 6.4±2.7 hours (28.3±15.8%) for placebo, associated with increased no time without dyskinesias of 12% versus 3% for placebo (and no significant increase in on time with dyskinesias).[110]

All of the above interventions risk increasing dyskinesias, which can become bothersome or even disabling. At present, only amantadine is useful in treating dyskinesias. There is, however, recent evidence that memantine, which also possesses NMDA-receptor antagonist properties, may be helpful in some patients (although this remains at present an "off-label" use).[111]

Selected drugs in the pipeline

Some of the new approaches being actively studied include:

- Rytary © (IPX066) levodopa formulation (Phase III: more sustained clinical benefit with fewer doses than optimal current therapy – under review by FDA at time of writing) [112]
- Methyl-ester levodopa (prodrug)
- Levodopa intestinal gel (clinically available but not in USA at time of writing)
- Apomorphine infusion
- Adenosine A2A antagonists (e.g. tozadenant: Phase II trial of SYN115 decreased "off" time – information publicly available but unpublished at time of writing)
- Alpha 2-adrenergic antagonists (e.g. fipamezole: Phase II trial suggests may reduce dyskinesias)
- Safinamide (reversible MAO-B inhibitor, reduces dopamine reuptake, antiglutamatergic)
- Cogane, potential neuroprotectant (PYM50028) (NCT01060878)
- Anti-alpha-synuclein vaccine (NCT01568099)

Note, this is not a complete list –please refer to www.clinicaltrials.gov as well as review of drugs in the pipeline.[113]

Treatment-related symptoms

Although discussion above has focused upon positive benefits of anti-PD medications, Table 5 summarizes briefly some of the adverse events that must be balanced into treatment decisions and discussion with patients,

TABLE 5 TREATMENT-RELATED SIGNS AND SYMPTOMS

Motor and Non-motor medication-related symptoms	Comments
development of dyskinesias, wearing off, other motor complications	Levodopa > others
worsening of dyskinesias	"dopaminergic" side effects
confusion	
hallucinations	
nausea	
orthostatic hypotension	
somnolence	sleep attacks reported with dopamine agonists>other
loose stool/diarrhea	entacapone
urine discoloration (orange)	entacapone
leg edema	amantadine, dopamine agonists
livedo reticularis	amantadine
sleep disruption	
impulse control disorders	dopamine agonists>other

Non-Pharmacologic Treatment of Parkinson's Disease

Surgical Treatment of PD: Where, when, how?

Surgical treatment of movement disorders has a rich history, and approaches have included lesions, infusions (e.g. glial-derived neurotrophic factor, deep brain stimulation, cell-based (i.e. transplant) therapies, and gene therapy. Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is now the most commonly performed procedure for PD in the USA, and stimulators are usually inserted bilaterally. The role of DBS in PD has been well reviewed (for recent discussion and recommendations refer to the following reviews[114]). Briefly, DBS is considered in patients with PD with intractable motor fluctuations or tremor despite best medical therapy (or who do not tolerate adequate pharmacologic treatment due to side effects). Good candidates for these procedures do not have significant cognitive or psychiatric problems. DBS in carefully chosen patients improves levodopa-

responsive features of PD including bradykinesia, rigidity and tremor, and can also ameliorate dyskinesias. In these domains the benefit is sustained. However, gait and balance typically continue to decline. The surgery should only be undertaken after careful assessment and counseling to insure expectations are realistic.

Although STN is the most commonly used target, globus pallidus pars interna (GPi) is also an effective site for DBS (for example it results in similar medication reduction,[115] The NSTPS study of 128 subjects randomized to STN versus GPi as a target found no difference in primary outcomes (Academic Medical Center Disability Scale and occurrence of cognitive/mood/behavioral adverse events). However, which site will be best in individual subjects remains to be determined, and in the NSTPS study STN appeared superior in certain secondary outcomes (including motor dysfunction during "off' periods, and in medication reduction).[116] The potential role of the PPN (pedunculopontine nucleus) is under active investigation, and there is evidence it may aid balance.[117] It also seems to aid in restoring normal sleep patterns, which is interesting given the role of the PPN in sleep.[118] There are reasons to predict that DBS in "early" PD (i.e. earlier than traditionally referred for DBS) may be beneficial. Therefore the EARLYSTIM-study is evaluating patients with <3 years of motor complications (dyskineesias and wearing off) with good social and occupational function over a 2 year period following DBS of the bilateral STN.[119]

Although still at the investigational stage, there are intensive efforts in testing the potential for gene therapy in PD. A landmark 6 month study of glutamic acid decarboxylase (GAD) gene delivery to the STN in individuals with advanced PD, with careful sham-surgery control, demonstrated greater improvement in UPDRS scores from baseline to end of the study in the group receiving gene therapy intervention compared with the sham surgery control group.[120] A double-blind, phase II trial of AAV2-neurturin (a trophic factor) failed to demonstrate that intraputaminal delivery was superior to sham surgery.[121] However, autopsy studies indicated that intra-nigral delivery might be advisable as an additional site. A phase I/II trial to assess safety and possible benefit of AAV2-neurturin into the putamen and SN bilaterally is therefore ongoing.

The role for cell-based therapies remains under investigation and, in a new research initiative as part of the European TRANSEURO study, 5 patients with PD will undergo transplant surgery in Lund, Sweden, in 2013 (http://www.transeuro.org.uk/index.html).

Exercise-Based Therapies
Despite widely perceived benefits of exercise in PD, this area has been notoriously difficult to study in a rigorous manner, and interpreting the literature can be challenging.[122] The "best" type of exercise is unclear, although there is a broad consensus that vigorous exercise should be encouraged. There is, moreover, considerable support for possible neuroprotective effects of exercise.[123] However, exercise modalities that have been investigated are widely varying, including weight training, forced aerobic exercise, gentle exercise, dance, yoga, tai chi and others. A recent study of Tai Chi, in which 195 subjects with PD were assigned to Tai Chi, resistance training, or stretching exercise for 24 weeks, demonstrated improved balance and reduced falls.[124]

ComplementaryTherapies
Complementary therapies are widely used by patients with PD, including diet, dietary and herbal supplements, vitamins, massage therapy, acupuncture, traditional Chinese medicine, and many other therapies.[125] Some of these have been formally studied. Clinical trials of vitamins and anti-oxidants have yet to show benefit. However, certain therapies are supported by the literature. For example, mucuna is an Ayurvedic preparation (prepared from seeds of Mucuna pruriens, a leguminous plant) that appears to provide benefit in PD.[126]

Optimizing Quality of Care in PD

While the majority of the discussion above is concerned with motor symptoms, the impact upon patients of non-motor symptoms cannot be overemphasized. As the disease progresses, symptoms that are poorly- or non-responsive to dopamine replacement predominate.[127] Patients frequently suffer dementia and psychosis in advanced PD,[128] and there may be increasing autonomic dysfunction, sleep disorders, and other symptoms impacting on both patient and caregivers. AAN guidelines for treating dementia, depression and psychosis were published in 2006 (see below). Options for treating cognitive dysfunction are all derived from drugs developed for Alzheimer's disease (AD) (e.g. rivastigmine,donepezil, memantine), and indeed AD pathology is clearly present in a subset of patients.[129] . Rivastigmine is the only one of these currently FDA-approved for use in PD dementia, and is available in both oral and transdermal formulations, with the latter more easily tolerated.[130] However, it remains to be established whether use of the newly approved higher dose (13.5mg per

patch) is advantageous in PDD. Treatment of MCI also remains an area of critical need. A recent evidence-based review has been published by Seppi and colleagues for the Movement Disorders Society,[131] and AAN guidelines are available for treating non-motor symptoms of PD (see below). Patients also need to be counseled on the increased risk of melanoma associated with PD, and should be advised to obtain appropriate regular screening.[132] This association was recently confirmed, with the additional finding of an association of PD and prostate cancer (including relatives)[133] Recent studies have also highlighted potential systemic nutritional disturbances associated with PD, for example low Vitamin D[134] and low Vitamin B12.[135] At present, these associations are still being explored, and practices are changing to accommodate emerging information.

Finally, with increasing recognition of motor and non-motor signs and symptoms, and their impact upon patients' quality of life, it is important that adequate screening is performed during office visits. A set of quality measures recently published by the AAN will aid in this regard.[136]

Selected AAN Treatment Guidelines

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