Innovations in the Treatment of Parkinson’s Disease and Demystifying Deep Brain Stimulation (DBS)

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UC Davis Department of Neurology
Best Practice Update: Parkinson’s Disease Treatment Options

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Objectives

1. To review the history and epidemiology of PD
2. To learn the cardinal motor symptoms of PD
3. To review the UK Brain Bank criteria for diagnosing PD
4. To appreciate the Pre-Motor phase of PD, and its involvement of diverse systems
5. To provide an update on medical management of PD
6. To appreciate the multitude of non-motor symptoms and learn strategies for clinical management to improve QOL
7. To learn the most common forms of genetic parkinsonism
8. To review the 10 Quality Measures for PD put forth by the American Academy of Neurology
Parkinson’s Disease
Dr. James Parkinson
1755 - 1824

Essay on the Shaking Palsy, 1817

AN ESSAY ON THE SHAKING Palsy.

CHAPTER I.
DEFINITION—HISTORY—ILLUSTRATIVE CASES.

SHAKING Palsy. (Paralysis Agitans.)
Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace: the senses and intellects being uninjured.

The term Shaking Palsy has been vaguely employed by medical writers in general. By some it has been used to designate or-
Epidemiology

- Affects 1-2 million people in the United States
- Likelihood of developing PD increases with age
- Average age of onset is 62.4 years
- Age is the strongest risk factor
- Men > Women, but only for age >60
- Cultural Disparity: Higher incidence in whites than African Americans or Hispanics
  - Due to true biological differences or barriers to healthcare (education, cultural beliefs about health and aging)?

Parkinson’s Motor Symptoms

- Rest tremor
- Bradykinesia and slowness of ADL’s
- Rigidity and freezing in place
- Stopped, shuffling gait
- Decreased arm swing while walking
- Difficulty arising from a chair
- Micrographia
- Hypomimia (lack of facial expression)
- Difficulty turning in bed
- Postural instability
UK PD Society Brain Bank Clinical Diagnostic Criteria

• **Inclusion Criteria** (need 2 of these 4)
  – **Bradykinesia** (and at least one of the following):
    – Muscular rigidity
    – 4 Hz to 6 Hz tremor
    – Postural instability (not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction)
UK PD Society Brain Bank Clinical Diagnostic Criteria

• **Exclusion Criteria**
  – Hx of repeated strokes with stepwise progression of parkinsonian features
  – Hx of repeated head injury
  – Hx of definite encephalitis
  – Oculogyric crisis
  – Neuroleptic treatment at onset of symptoms
  – More than one affected relative
  – Sustained remission
  – Strictly unilateral features after 3 years
UK PD Society Brain Bank
Clinical Diagnostic Criteria

• **Exclusion Criteria** (continued)
  – Supranuclear gaze palsy
  – Cerebellar signs
  – Early, severe autonomic involvement
  – Early, severe dementia or apraxia
  – Babinski sign
  – Presence of cerebral tumor or communicating hydrocephalus on CT scan
  – Negative response to large doses of levodopa
  – MPTP exposure
UK PD Society Brain Bank
Clinical Diagnostic Criteria

• Supportive Criteria (need 3 or more for diagnosis of “Definite” PD)
  – Unilateral onset
  – Rest tremor present
  – Progressive disorder
  – Persistent asymmetry
  – Excellent response (70% to 100%) to levodopa
  – Severe levodopa-induced dyskinesias
  – Levodopa response for 5 years or more
  – Clinical course for 10 years or more
Parkinson’s Disease
Parkinson’s Non-Motor Symptoms

• Anosmia (decreased sense of smell)
• Depression / anxiety
• Drooling (dysphagia)
• Blepharitis
• Hypophonia (low vocal volume)
• Postural lightheadedness (orthostatic hypotension)
• Sudomotor dysregulation (abnormal sweating)
• Sleep disturbance (RBD, OSA, RLS, PLMS, fragmentation)
• Constipation
• Urinary frequency / urgency
• Male erectile dysfunction
• Painful foot cramps (dystonia)
• Bursitis, “frozen shoulder”
Braak and Braak Pathologic Staging

- Clinicopathologic staging system for Lewy body disease-associated changes.
- Predictable topography of progression of Lewy body disease in the CNS
- Begins in olfactory structures and medulla, progresses rostrally from the medulla to the pons, then to midbrain and substantia nigra, limbic structures, and neocortex.
- Symptoms resulting from degeneration of olfactory and pontomedullary structures begin many years before prominent nigral degeneration and the typical Parkinsonian features.

### Pre-Motor Phase of PD

<table>
<thead>
<tr>
<th>Pre-Motor Symptoms</th>
<th>Brain Structures Involved</th>
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<tbody>
<tr>
<td><strong>Olfactory Loss</strong></td>
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<tr>
<td>- Hyposmia in 90%, impairment in odor detection, identification, discrimination</td>
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<td><strong>Dysautonomia</strong></td>
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<tr>
<td>- GI: gastroparesis, <strong>constipation</strong> (yrs prior)</td>
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<tr>
<td>- Urinary: frequency and urgency</td>
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<td>- Sexual: erectile dysfunction</td>
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<tr>
<td><strong>Mood</strong></td>
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<tr>
<td>- Depression</td>
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<tr>
<td>- Anxiety</td>
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<td><strong>Sleep</strong></td>
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<td>- REM behavior disorder (most common)</td>
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<td>- Excessive daytime sleepiness</td>
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<td>- Insomnia / sleep maintenance</td>
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Update on the Medical Management of PD

- Levodopa (various formulations)
- Catechol-o-methyltransferase Inhibitors
- Monoamine Oxidase Type B Inhibitors
- Dopamine Agonists
- Other agents
Formulations of Levodopa

- Mainstay of antiparkinsonian therapy since the late 1960’s
- Combined with a peripheral aromatic amino acid decarboxylase inhibitor to block conversion of dopamine outside the CNS
  - In the US: Carbidopa (Lodosyn when sold separately)
  - Overseas: Benserazide
Levodopa Effects

• **Positive effects**: dramatic reduction in PD symptoms within a few days

• **Negative effects:**
  – Early stage
    • Nausea, vomiting
    • Drowsiness
    • Dizziness, hypotension
  – Later stages
    • Hallucinations
    • Dyskinesias
Long-Term Variability with Levodopa

• Levodopa must be converted by neurons to dopamine
• These neurons degenerate over time
• Disease progression results in decreased predictability of dopamine levels
Levodopa Complications

• Motor Fluctuations
  – Dyskinesias
  – Wearing off (shortened duration of effect)

• Strategies to combat these:
  – Shorten dosing interval
  – Add an inhibitor of levodopa/dopamine catabolism

• Non-motor complications
  – Treat each directly
Dopamine Degradation

DOPAMINE

MAO → DOPAC

COMT → 3-Methoxy tyramine

COMT → Homovanillic Acid (HVA)

MAO → DOPAC
Catechol-o-methyltransferase (COMT) Inhibitors

- COMT converts levodopa to the inactive 3-O-methyldopa
- Blocking COMT increases brain levels of levodopa and dopamine, and provides longer duration of action
- TOLCAPONE (Tasmar)
  - Risk of fatal hepatic failure
- ENTACAPONE (Comtan)
Entacapone (Comtan)

• Shown to reduce OFF time (Parkinson’s Study Group, 1997)
• 200mg, given with each dose of carbidopa/levodopa
• Maximum daily dose of entacapone: 1600mg
• Combination formulation of entacapone + levodopa + carbidopa = Stalevo
• Side effects: orange discoloration of urine and bodily fluids, diarrhea, levodopa potentiation
Monoamine Oxidase Type B Inhibitors

- Increase the half-life of dopamine by blocking catabolic pathways
- Type B enzyme is in the brain, so preferentially affects PD
- SELEGILINE (Eldepryl, Deprenyl) 5mg BID
- SELEGILINE orally disintegrating tab (Zelapar)
  - Less first pass hepatic metabolism
  - Dosed 1.25 to 2.5mg per day
Monoamine Oxidase Type B Inhibitors

• RASAGILINE (Azilect) 1 mg per day
  – Studied extensively to show a reduction in disease progression, but unclear how much of any putative disease-modifying effect is related to improvement in symptoms

• Side effects of MAO-B inhibitors
  – Potentiating dopamine side effects
  – Tyramine effects (potentially fatal tachycardia and hypertensive crisis)
    • Limit tyramine in diet (fermented foods)
    • Do not combine with decongestants (pseudoephedrine, phenylephrine) and certain narcotics
Dopamine Agonists

- **Ergot Derived** (vascular toxicities)
  - Bromocriptine (Parlodel)
  - Pergolide (Permax), linked to valvular heart disease

- **Non-Ergot Derived**
  - Pramipexole (Mirapex)
  - Ropinirole (Requip)
  - Rotigotine transdermal (Neupro)

Two large multiyear studies showed a reduced incidence of dyskinesias with initial agonist therapy compared with initial levodopa TID therapy (Parkinson’s Study Group, 2000; Rascol et al, 2000)
Benefits of Dopamine Agonists

• Longer half-lives than levodopa
  – More convenient dosing in some situations
  – Fewer motor complications
• FDA approved for restless legs syndrome (RLS)
  – Often co-existent in PD
• Once-a-day formulations are available
  – Requip XL
  – Mirapex ER
  – Neupro patch
Side Effects of Dopamine Agonists

• Somnolence, Sleep Attacks
• Compulsive behaviors
  – Impulse Control Disorder
• Peripheral edema
• Nasal congestion
• Potentiating levodopa effects
  – Hypotension
  – Dyskinesias
A Unique Dopamine Agonist

- Apomorphine (Apokyn)
  - For use in advanced Parkinson’s disease
  - Injected subcutaneously by the patient
  - For treatment of acute off periods despite treatment with existing antiparkinsonian therapy
  - Benefit lasts 1 hour
Other Agents

• Amantadine (Symmetrel)
  – Partial dopamine agonist and partial NMDA receptor antagonist
  – Dosed as 100 mg 1-4 times per day
  – Usefulness has been replaced by levodopa
  – Good anti-dyskinetic effect in advanced PD

• Side Effects
  • Livedo reticularis
  • Confusion, hallucinations, depression, anxiety
Other Agents

- **Anticholinergics**
  1. Trihexyphenidyl (Artane)
  2. Benztropine (Cogentin)

  - Used to treat PD since the 1940’s
  - Preferentially treat tremor
  - Side effects: USE WITH CAUTION in the elderly!
    - Cognitive dysfunction
    - Constipation, urinary retention
    - Blurry vision
    - Dry mouth
Duodopa

• Not yet available in the US
• New gel formulation of carbidopa/levodopa
• Delivery via novel intra-intestinal pump
• Surgically inserted and programmed to deliver doses at specific times (like insulin pump)
• External controller makes dose adjustments non-invasively
• More constant blood levels minimize levodopa motor complications
Exercise in PD

• Critical component: non-negotiable

• Components of daily regimen:
  1. Stretching

• Physical Therapy, LSVT BIG

• Symptom management
  – Improvement in gait, balance, flexibility, coordination
  – Decrease in falls

• Neuroprotection: slowing disease progression

Non-Motor Symptoms
Improving Quality of Life

Depression
Anosmia, Weight Loss
Blepharitis
Shoulder Pain
Dystonia
Sleep Disturbance
Sexual Dysfunction
Constipation, Bladder dysfunction
Hypophonia, Dysphagia
Dementia, Psychosis
Orthostatic Hypotension

Many of the drugs we will discuss are off-label for these symptoms.
Mood Disorders in PD

- Depression affects 50-75% of PD patients
- Secondary to underlying neuroanatomical degeneration, rather than a reaction to psychosocial stress and disability.
- Based on changes in central serotonergic function and specific cortical and subcortical pathways.
- Depression, anxiety precede motor symptoms of PD by ~6 years (correlates with PET studies).


Depression in PD

• Challenges to diagnosis include similarities in clinical signs to PD itself.
• Look for:
  – pervasive low mood with diurnal variation for at least two weeks
  – Early morning awakening
  – Pessimistic thoughts about the world, themselves, the future
  – Suicidal ideation

Management of Depression in PD

• Rating scales have reduced validity due to emphasis on somatic / vegetative symptoms.

• Medication Management:

1. Tricyclic Antidepressants
   – Amitriptyline and Nortriptyline
   – Review of the literature by Miyasaki et al, 2006
   – Use with caution due to anticholinergic effects, which are problematic in elderly
Management of Depression in PD

2. SSRI’s
   - Fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram
   - Side effects: nausea, GI disturbance, sexual dysfunction, exacerbation of RBD, withdrawal syndrome in elderly.

3. SNRI

4. NDRI
Potential for Serotonin Syndrome

- There is a potential for Serotonin Syndrome when combining MAO inhibitors with any antidepressant.
- Risk is lower with MAO-B than MAO-A, but must discuss with patients.
- Symptoms: acute mental status changes, autonomic dysfunction, myoclonus, hyperreflexia.
- Requires proper clinical judgment, patient education, and close monitoring.
Anosmia and Depression

Loss of sense of smell $\rightarrow$ Loss of taste

 Decreased appetite

 Decreased PO intake

 Weight loss
Blepharitis

- “Dry Eye,” chronic eyelid inflammation and conjunctival injection
- Increased bacteria on surface of dry eyes
- Blepharitis in PD is a function of decreased blink rate (facial bradykinesia)
- Blepharitis often predates PD diagnosis by many years
- Management: High viscosity lubricant eye drops at bedtime (ex: Systane Gel Drops)
Shoulder Pain

- Often the presents prior to the diagnosis of PD
- Typically unilateral, on the side with more prominent Parkinsonism
- Rigidity and bradykinesia (including decreased arm swing) leads to immobility and subsequent shoulder dysfunction and discomfort.
- Bursitis, tendonitis, frozen shoulder, rotator cuff injury
- Physical Therapy
- BIG arms gait training

Dystonia

1. **Unrelated to treatment**
   - Kinesiogenic foot dystonia is a hallmark of early onset PD. Typically involves tibialis posterior and toe flexors. Painful and impairs gait/balance.
   - Blepharospasm, Torticollis
   - Management: targeted botulinum toxin injection

2. **Related to therapy**
   - Peak-dose, diphasic, and off-dystonia

Sleep Disturbance

• REM Behavior Disorder
  – Rapid eye movement (REM) sleep behavior disorder
  – Parasomnia with vivid dreams and dream enactment behavior during REM sleep.
  – Findings from animal and human studies suggest that dysfunction in REM sleep and motor control circuitry in pontomedullary structures cause RBD symptoms
  – Degeneration of these structures might explain the RBD years or decades before the onset of motor symptoms in people who develop PD

REM Behavior Disorder

• Sequela of untreated RBD
  – Excessive daytime sleepiness
  – Physical injury to patient or bed partner
  – Chronic sleep deprivation leads to exacerbation of daytime motor symptoms

• Management of RBD
  – Clonazepam (Klonopin) 0.25-1.0 mg QHS: off label
  – Melatonin 3-5mg tabs, up to 10mg QHS
Sleep Disturbance

• Sleep Fragmentation
  – Clonazepam (Klonopin) 0.25-1.0 mg QHS: off label
  – Melatonin 3mg (1-3 tabs) QHS

• Insomnia
  – Mild sedatives are well-tolerated in the non-demented patient
  – Zolpidem (Ambien), Zaleplon (Sonata), Eszopiclone (Lunesta), Ramelteon (Rozerem)
  – None are FDA-approved for use in PD
Sleep Disturbance

• Obstructive Sleep Apnea
  – CPAP, BiPAP

• Restless Legs Syndrome (RLS) & Periodic Limb Movements in Sleep (PLMS)
  – Dopamine agonists

• Diagnosis: Formal Nocturnal Polysomnography
  – Must specify application of EMG leads on the extremities in PD (RBD, RLS, PLMS)
Excessive Daytime Sleepiness

• Identify underlying sleep disorder and treat directly
• Daytime Sleep Restriction: minimize naps
• Sleep hygiene
  – Fixed bedtime and awakening time
  – Avoid alcohol, caffeine, or heavy/spicy/sugary foods 4-6 hours before bedtime
  – Bed is for sleeping (not eating, reading, office work)
• Modafinil (Provigil)
  – FDA-approved “to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, and shift-work sleep disorder;” NOT PD.
Sexual Dysfunction

- Not correlated with disease severity
- Decreased libido
- Erectile dysfunction
  - Sildenafil (Viagra)
    - Watch for hypotension
  - Dopamine Agonists
- Hypersexuality
  - Associated with dopaminergic treatment
  - Linked to inhibition of prolactin secretion
Constipation

• One of the earliest signs of autonomic dysfunction
• Affects majority of PD pts (even described in the original 1817 essay)
• Stools become less frequent and difficult to pass due to delayed gastric emptying and slowed intestinal transit time
• Lewy bodies are found in intestines post-mortem
Management of PD Constipation

- Optimize hydration
- Well-balanced, high fiber diet (fruits, vegetables, prunes, bran cereal)
- Regular exercise
- Fiber supplements, bulk formers
- Stool softeners: Daily Colace
- Laxatives: Miralax 17g packet daily or QOD
Bladder Dysfunction

• Overactive bladder
  – Abnormal central control of urinary sphincter
  – Urgency, frequency, incontinence, nighttime urination
  – Depends
  – Comodes or urinals at bedside to prevent falls
  – Sphincter relaxants: Ditropan, Detrol, Vesicare

• Urinary Retention: Incomplete bladder emptying
  – Bladder sphincter dyssinergia or contractile weakness
  – Weak urinary stream, dribbling, leaking
  – Recurrent UTI’s
Speech Disturbances

• **Hypophonia**
  – Limited vocal / pitch range
  – Low voice and volumes
  – Diminished respiratory support and coordination

• **Speech deficits**
  – Imprecise articulation
  – Accelerated rate
  – Decreased intelligibility
Speech Therapy

- **Lee Silverman Voice Treatment (LSVT LOUD)**
  - Best to initiate early
  - Goal is to think loud and “Speak LOUD!”
  - Systematic hierarchy of exercises stimulates laryngeal muscles and speech mechanism
  - Improves respiratory, laryngeal, and articulatory function to maximize speech intelligibility
  - Intensive: 16 sessions per month
Dysphagia

• Drooling
  – Not due to excessive salivary production (salivary output in PD is normal or decreased)
  – A result of difficulty transporting saliva to posterior pharynx + decreased frequency of swallowing
  – Often exacerbated by forward-flexed posture
  – Socially embarrassing but not dangerous
  – Gum and hard candy trigger swallow reflex
  – Risks of anticholinergics are not worth the benefit
  – Atropine eye drops on the tongue minimizes systemic effects
  – Targeted botulinum toxin injection of the parotids
Dysphagia

- Difficulty swallowing in 50-80% of pts
- 90-100% show impaired swallowing on MBS or FEES
- Impaired pharyngeal peristalsis
- Restricted opening of the upper esophageal sphincter
- Lingual tremor
- Increased risk of aspiration and pneumonia
- Primary cause of mortality in PD
- Throat clearing, sensation of food “sticking” in the chest
- Often not improved by dopaminergic meds

Dysphagia

• Speech and Swallow Therapy
  – Swallow techniques
    • Second swallow
    • Chin tuck
    • Straws
  – Food consistency
    • Thickened liquids
    • Softer food texture
Nausea and Bloating

• Levodopa effect
  – Peripheral dopaminergic stimulation
  – Treat with supplemental dopa-decarboxylase inhibitor
  – Lodosyn (carbidopa) 25mg with each Sinemet dose to achieve higher carbidopa:levodopa ratio

• Gastroparesis
  – Management of constipation
  – Small, more frequent meals
PD Dementia

- Acetylcholinesterase Inhibitors
  - Rivastigmine (Exelon)
    - FDA approved for PD dementia
    - Tablet, liquid, transdermal patch
  - Donepezil (Aricept)
    - FDA approved for Alzheimer’s disease only
  - Galantamine (Razadyne)
    - FDA approved for Alzheimer’s disease only
- Memantine (Namenda)
  - Chemically similar to Amantadine
  - FDA approved for Alzheimer’s, under study for PD dementia
Psychosis in PD

• Hallucinations are typically visual, not auditory
• Paranoia
• Avoid CNS dopamine receptor antagonists
• No antipsychotics are FDA approved for hallucinations in PD
• FDA warns against use of antipsychotics in pts with dementia due to increased risk of death
Psychosis in PD (con’t)

• Clozapine (Clozaril)
  – 12.5 mg to 25 mg BID
  – Risk of agranulocytosis requires frequent monitoring of WBC count
  – Somnolence

• Quetiapine (Seroquel)
  – Atypical neuroleptic with some antipsychotic efficacy data in PD clinical trials
  – 25 mg to 75 mg QD-BID; higher doses may worsen parkinsonism
  – Somnolence
Orthostatic Hypotension (OH)

• Feature of advanced PD, and some atypical parkinsonian syndromes (Multiple System Atrophy)
• Use CAUTION when using dopaminergic agents which can worsen OH
• Compression stockings
• Increase water and salt intake
• Rise slowly
• Raise head of bed
• Watch for SUPINE HYPERTENSION
• Monitor orthostatic vitals at every visit
Orthostatic Hypotension (OH)

• Midodrine (ProAmantine)
  – Agonist at peripheral alpha-1 adrenergic receptors
  – Increases systemic vascular resistance
  – 2.5 mg to 5 mg TID

• Fludrocortisone (Florinef)
  – 0.1 mg to 0.3 mg daily
  – Watch for excessive hypertension, edema
Prodromal Dysautonomia in PD

- Patients with RBD were followed annually in a prospective cohort established in 2004.
- Urinary, orthostatic, erectile, and constipation symptoms, and SBP drop from lying to standing were assessed annually.
- Estimated onset of autonomic dysfunction is ~11-20 years before diagnosis of PD. (SBP drop: 20.4 yrs, constipation: 15.3 yrs)
- SBP drop + ED + constipation = correct identification of PD 5 yrs prior to motor symptom diagnosis with sensitivity of 50-90%.

Young-Onset Parkinson’s Disease

• Onset before age 30 is rare
• Up to 10% of cases begin by age 40
• 10-15% have a strong family history
• Dystonia may be a presenting symptom
Familial Parkinsonism

- **Autosomal Dominant PD**
  - PARK 1 and PARK 4 account for 2% of AD PD
    - Mutations of the alpha-synuclein gene
  - PARK 8 (10% of familial cases)
    - Mutations in leucine-rich repeat kinase 2 gene (LRRK2)

- **Autosomal Recessive PD**
  - PARK 2 (50% of familial, 20% of “sporadic” YOPD)
    - Mutations in parkin gene, encoding ubiquitin E3 ligase
    - High incidence of dystonia
10 Quality Measures for PD Care

The 10 Measures (and frequency of inquiry) are:

1. Annual PD diagnosis review (annually)
2. Psychiatric assessment (annually)
3. Cognition assessment (annually)
4. Query autonomic dysfunction (annually)
5. Query sleep disturbances (annually)
6. Query about falls (every visit)
7. PD rehab therapy options (annually)
The 10 Quality Measures (con’t)

8. PD related safety issues counseling (annually)
9. Query about PD medication-related motor complications (every visit)
10. Review of PD medical and surgical treatment options (annually)
Questions?

• Thank You!