Objectives

- Delineate non-motor aspects of Parkinson’s disease (PD)
- Differentiate the pharmacology, safety, and efficacy of available pharmacologic treatment options
- Construct a therapeutic plan to manage non-motor symptoms of PD
- Identify operational strategies to navigate new LTCF requirements and the revised survey process when considering the use of psychotropic medications
- Discuss the role of consultant pharmacists and the LTCF care team in managing the neuropsychiatric symptoms of psychosis

Disclosures

Dana Saffel, PharmD, BCGP, CPh, FASCP
President, CEO
PharmaCare Strategies

- Acadia Pharmaceuticals – Consultant, Speaker
- Mylan Pharmaceuticals – Consultant
- Sunovion Pharmaceuticals – Consultant, Speaker
- Sun Pharmaceutical Industries - Consultant
Case Study

- JG is a 78 yo male residing in a nursing home with a history of PD, hypertension, diabetes, Afib, and osteoarthritis. His medications include:
  - Losartan 50mg po daily
  - Dulaglutide 0.75mg sq weekly
  - Metformin 750mg po BID
  - Levodopa/carbidopa 100mg po QID
  - Selegiline 5mg po BID
  - Pramipexole 1mg po TID

- Nursing staff are reporting that JG is increasingly withdrawn, is unwilling to participate in social activities and has lost 5lbs in the past few weeks.

- The DON asks your opinion on how to best manage JG.

- What non-motor symptoms should JG be assessed for?
- How/what would you suggest to improve JG’s symptoms?

Parkinson’s Disease (PD) is Commonly Thought of as a Movement Disorder

<table>
<thead>
<tr>
<th>Cardinal symptoms</th>
<th>Other common motor symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor at rest</td>
<td>Mask-like expression</td>
</tr>
<tr>
<td>Rigidity</td>
<td>Soft voice</td>
</tr>
<tr>
<td>Akinesia / Bradykinesia</td>
<td>Drooling</td>
</tr>
<tr>
<td>Postural instability</td>
<td>Reduced stepping</td>
</tr>
<tr>
<td></td>
<td>Freezing/limp</td>
</tr>
<tr>
<td></td>
<td>Small handwriting</td>
</tr>
</tbody>
</table>

Parkinson’s Disease (PD) is More Than Motor Symptoms

<table>
<thead>
<tr>
<th>Motor Symptoms</th>
<th>Common Nonmotor Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradykinesia</td>
<td>Cardiovascular (including falls)</td>
</tr>
<tr>
<td>Resting tremor</td>
<td>Sleep/disorder</td>
</tr>
<tr>
<td>Rigidity</td>
<td>Mood/impairment</td>
</tr>
<tr>
<td>Gait disturbance/instability</td>
<td>Perceptual problems/hallucinations</td>
</tr>
<tr>
<td>Small writing</td>
<td>Attention/memory</td>
</tr>
<tr>
<td>Masked face</td>
<td>Gastrointestinal tract</td>
</tr>
<tr>
<td>Reduced eye blink</td>
<td>Urinary</td>
</tr>
<tr>
<td>Soft voice</td>
<td>Sexual dysfunction</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Miscellaneous (i.e., pain, changes to taste/smell)</td>
</tr>
<tr>
<td>Dyskinesia</td>
<td></td>
</tr>
<tr>
<td>Freezing</td>
<td></td>
</tr>
</tbody>
</table>

“Parkinson’s disease is a very complex, neuropsychiatric, neurodegenerative disease that involves far more than just the motor symptoms ... that may even emerge before a patient develops motor symptoms.” Dan Kernion, MD - Neurologist
Clinical Symptoms and Time Course of Parkinson’s Disease

Pre-motor/prodromal period

Parkinson’s disease diagnosis

- Early
- Advanced/late

Complications
- Fluctuations
- Dyskinesia
- Psychosis
- Complications
- Motor

Constipation
- RBD
- EDS
- Hyposmia
- Depression
- Pain
- Fatigue
- MCI
- Bradykinesia
- Rigidity
- Tremor
- Urinary symptoms
- Orthostatic hypotension
- Falls
- Dementia
- Dysphagia
- Postural instability
- Freezing of gait
- Falls

Fluctuations
- Dyskinesia
- Psychosis

Image adapted from Kalia LV, Lang AE. Lancet. 2015;386:896-812.

Hallmark Neuropathology of Parkinson’s Disease (PD)

PD is characterized by a loss of dopaminergic neurons in the substantia nigra and presence of Lewy bodies

Lewy bodies within melanized dopamine neurons in PD

Reduction of pigment in substantia nigra in PD

Reduced number of cells in substantia nigra in PD


Lewy body deposition in cerebral cortex contributes to:
- Cognitive impairment
- Depression
- Visual hallucinations
- Downstream effects that increase dopamine release in mesolimbic system - Delusions


Serotonin Theory of Dementia, Depression & Psychosis

- Lewy body deposition in cerebral cortex contributes to:
  - Cognitive impairment
  - Depression
  - Visual hallucinations
  - Downstream effects that increase dopamine release in mesolimbic system - Delusions
Question 1

• The pathogenesis of Parkinson’s disease includes imbalance of which of the following neurotransmitters?
  a) Dopamine
  b) Serotonin
  c) Glutamate
  d) a & b
  e) All of the above

- Serotonin Dysfunction is Linked to Motor and Nonmotor Symptoms


Levodopa-induced dyskinesia

Tremor

Psychosis

Depression

Anxiety

Constipation

Tremor

Depression

Anxiety

Constipation

- Depression
- Anxiety
- Psychosis
- Constipation
- All of the above

- Depression
- Anxiety
- Psychosis
- Constipation
- All of the above

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- Constipation
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- Psychosis
- Constipation
- All of the above

- Depression
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RECOGNITION AND TREATMENT OF NON-MOTOR SYMPTOMS OF PD

Non-Motor Symptoms of Parkinson’s Disease

Non-Motor Symptoms of Parkinson’s Disease

Non-Motor Symptoms of Parkinson’s Disease
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<table>
<thead>
<tr>
<th>Neuropsychiatric Symptoms</th>
<th>Autonomic Dysfunction</th>
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</thead>
<tbody>
<tr>
<td>• Depression and depressive symptoms</td>
<td>• Drooling</td>
</tr>
<tr>
<td>• Anxiety and anxiety symptoms</td>
<td>• Orthostatic hypotension</td>
</tr>
<tr>
<td>• Apathy</td>
<td>• Urinary dysfunction</td>
</tr>
<tr>
<td>• Psychosis</td>
<td>• Erectile dysfunction</td>
</tr>
<tr>
<td>• Impulse control and related disorders</td>
<td>• Gastrointestinal dysfunction</td>
</tr>
<tr>
<td>• Dementia</td>
<td>• Excessive sweating</td>
</tr>
<tr>
<td>• Cognitive impairment (other than dementia; mainly mild cognitive impairment)</td>
<td>• Disorders of sleep and wakefulness</td>
</tr>
<tr>
<td>• Pain</td>
<td>• Sleep fragmentation and insomnia</td>
</tr>
<tr>
<td>• Fatigue</td>
<td>• Rapid eye movement sleep behavior disorder</td>
</tr>
<tr>
<td>• Olfactory dysfunction</td>
<td>• Excessive daytime sleepiness</td>
</tr>
<tr>
<td>• Ophthalmologic dysfunction</td>
<td></td>
</tr>
</tbody>
</table>

| Other                                                                                   |                                                             |
| • Pain                                                                                   |                                                             |
| • Fatigue                                                                                |                                                             |
| • Olfactory dysfunction                                                                   |                                                             |
| • Ophthalmologic dysfunction                                                             |                                                             |

### Question 2

Non-motor symptoms of Parkinson’s disease can cause the patient more distress than the typical motor symptoms? True or False

**True**

### Movement Disorder Specialist Guidelines

**Update on Treatments for Nonmotor Symptoms of Parkinson’s Disease—An Evidence-Based Medicine Review**

Depression

- Between 20% and 50% of PD patients experience major depression during the course of the disease.
  - Depression precedes motor symptoms in approximately 30% of cases
- PD depression typically differs from depression in the general population:
  - Less expressed feelings of sadness
  - Little tearfulness or guilt
  - Low suicide rate
  - Prominent anxiety, anhedonia, and apathy.
- Cause: complex dysfunction of numerous structures including noradrenergic, serotoninergic, and dopaminergic regions of the brainstem.
  - Mood swings and depression can occur with wearing off or during off periods.

Depression Treatments

<table>
<thead>
<tr>
<th>Drug Class / Intervention</th>
<th>Drug / Intervention</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Practice Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine Agents</td>
<td>Pramipexole</td>
<td>Efficacious</td>
<td>Acceptable risk</td>
<td>Clinically useful</td>
</tr>
<tr>
<td></td>
<td>Pergolide</td>
<td>Insufficient Evidence</td>
<td>Acceptable risk</td>
<td>Not useful</td>
</tr>
<tr>
<td></td>
<td>Rotigotine</td>
<td>Unlikely efficacious</td>
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<td>Investigational</td>
</tr>
<tr>
<td>MAO-B Inhibitors</td>
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<td>Acceptable risk</td>
<td>Investigational</td>
</tr>
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<td></td>
<td>Selegeline</td>
<td>Insufficient Evidence</td>
<td>Acceptable risk</td>
<td>Investigational</td>
</tr>
<tr>
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<td>Moclobemide</td>
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<td>Investigational</td>
</tr>
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<td>Tricyclic Antidepressants</td>
<td>Nortriptyline</td>
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<td>Possibly useful</td>
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<td>Desipramine</td>
<td>Likely Efficacious</td>
<td>Acceptable risk</td>
<td>Possibly useful</td>
</tr>
<tr>
<td></td>
<td>Amitriptyline</td>
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<td>Acceptable risk</td>
<td>Possibly useful</td>
</tr>
<tr>
<td>SSRI / SNRI</td>
<td>Citalopram</td>
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<td>Possibly useful</td>
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<td></td>
<td>Sertraline</td>
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<td>Possibly useful</td>
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<td>Paroxetine</td>
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<td>Possibly useful</td>
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<tr>
<td></td>
<td>Fluoxetine</td>
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<td>Acceptable risk</td>
<td>Possibly useful</td>
</tr>
<tr>
<td></td>
<td>Venlafaxine</td>
<td>Efficacious</td>
<td>Acceptable risk</td>
<td>Clinically useful</td>
</tr>
<tr>
<td>Other antidepressants</td>
<td>Atomoxetine</td>
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<td>Acceptable risk</td>
<td>Investigational</td>
</tr>
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<td></td>
<td>Nefazodone</td>
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<td>Unacceptable risk</td>
<td>Not useful</td>
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<td>Alternative Therapies</td>
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</tr>
<tr>
<td></td>
<td>Antidepressants</td>
<td>Insufficient Evidence</td>
<td>Acceptable risk</td>
<td>Investigational</td>
</tr>
<tr>
<td>Alternative Therapies</td>
<td>rTMS</td>
<td>Insufficient Evidence</td>
<td>Acceptable risk</td>
<td>Possibly useful</td>
</tr>
<tr>
<td></td>
<td>CBT</td>
<td>Likely Efficacious</td>
<td>Insufficient evidence</td>
<td>Possibly useful</td>
</tr>
</tbody>
</table>

Anxiety

- Between 30 and 40% of PD patients experience a significant anxiety disorder during the course of the illness.
  - These anxiety disorders can be expressed as panic, phobic (particular situations trigger the anxiety), or generalized anxiety.
  - Frequently occur with depression
- Anxiety can be present with or without depression and is often worse when the motor symptoms of PD are worse.

There are no RCTs that met inclusion criteria for the treatment of anxiety disorders and therefore no recommended treatment guidelines in PD. Anxiolytic agents may be contraindicated in PD and may worsen symptoms of the illness. Benzodiazepines are associated with falls, ataxia, and cognitive dysfunction.
Apathy

• Reported in 12% to 16% of PD patients.
• Apathy is a reduced emotion, interest in activity or motivation.
• It is important to distinguish if the apathy is a symptom of depression or an independent symptom.
• Apathy is most noticeable when PD patients quit participating in activities they normally enjoyed such as:
  - Exercising
  - Cooking
  - Watching TV
  - Hobbies
• Cause: Degeneration of 'goal-directed' areas (frontal subcortical areas) or reward centers (dopamine projections between the ventral tegmental area and nucleus accumbens) may cause apathy.

<table>
<thead>
<tr>
<th>Drug Class / Intervention</th>
<th>Drug / Intervention</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Practice Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine Agonists</td>
<td>Amantadine</td>
<td>Insufficient Evidence</td>
<td>Acceptable Risk</td>
<td>Investigational</td>
</tr>
<tr>
<td>Acetylcholinesterase Inhibitors</td>
<td>Rivastigmine</td>
<td>Efficacious</td>
<td>Acceptable Risk</td>
<td>Possibly Useful</td>
</tr>
</tbody>
</table>

Impulse Control and Related Disorders

• Impulse Control Disorder (ICD) is characterized by an excessive drive or interest in certain activities.
  - Examples of these activities include:
    - Compulsive shopping
    - Hypersexuality
    - Pathologic gambling
    - Binge eating
    - Compulsive cleaning
• Between 10% and 15% of PD patient experience ICD
• ICD arises as a side effect from some PD medications, specifically dopamine agonists.
  - Reducing or discontinuing dopamine agonists may improve ICD

<table>
<thead>
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</thead>
<tbody>
<tr>
<td>NMDA Antagonists</td>
<td>Amantadine</td>
<td>Insufficient Evidence</td>
<td>Acceptable Risk</td>
<td>Investigational</td>
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<td>Anti-opioids</td>
<td>Naltrexone</td>
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<td>Insufficient Evidence</td>
<td>Investigational</td>
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<tr>
<td>Nonpharmacological Interventions</td>
<td>CBT</td>
<td>Likely Efficacious</td>
<td>Insufficient Evidence</td>
<td>Possibly Useful</td>
</tr>
</tbody>
</table>

Cognitive Impairment (Parkinson's Disease Dementia – PDD)

• Up to 70% of patients with PD will eventually develop cognitive impairment (mild cognitive impairment or dementia)
• Major cause: Lewy Body degeneration of cortical structures
• Secondary changes: Alzheimer-like changes and vascular lesions.
• Probable risk factors for PDD include:
  - Age (>65)
  - Hallucinations and delusions
  - Family history of dementia
  - Depression, advanced disease
  - REM sleep behavior disorder.
• If the dementia occurs at the same time or within a year of motor symptoms, the diagnosis is formally defined as Dementia with Lewy Bodies.
Cognitive Impairment & Dementia

- Acetylcholinesterase Inhibitors are useful in treating dementia.
  - Rivastigmine has been proven efficacious and is considered clinically useful for PD dementia.
- There were no clinically useful interventions identified to treat non-dementia-level cognitive impairment.

<table>
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<th>Safety</th>
<th>Practice Implications</th>
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</thead>
<tbody>
<tr>
<td>DEMENTIA</td>
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<td></td>
<td></td>
<td>Rivastigmine</td>
<td>Efficacious</td>
<td>Acceptable risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Galantamine</td>
<td>Insufficient Evidence</td>
<td>Acceptable risk</td>
</tr>
<tr>
<td>NONDEMENTA-COGNITIVE IMPAIRMENT</td>
<td>Acetylcholinesterase Inhibitors</td>
<td>Rivastigmine</td>
<td>Insufficient Evidence</td>
<td>Acceptable risk</td>
</tr>
<tr>
<td></td>
<td>MAO-B Inhibitors</td>
<td>Rasagiline</td>
<td>Insufficient Evidence</td>
<td>Acceptable risk</td>
</tr>
<tr>
<td></td>
<td>Nonpharmacological Interventions</td>
<td>Transcranial direct current stimulation (T-DCS)</td>
<td>Insufficient Evidence</td>
<td>Insufficient Evidence</td>
</tr>
<tr>
<td></td>
<td>Cognitive rehabilitation</td>
<td>Insufficient Evidence</td>
<td>Insufficient Evidence</td>
<td>Investigational</td>
</tr>
</tbody>
</table>


Sleep and Insomnia

- Up to 90% of PD patients experience sleep problems at some point in their illness.
- 40 - 90% of PD patients experience sleep maintenance insomnia or difficulty falling and staying asleep.
  - Most of these individuals do not feel refreshed after awakening from sleep.
- Insomnia in PD is related to:
  - Immobility
  - Muscle cramps
  - Side effects of medication
  - Frequent need to get up and urinate
  - Anxiety

Excessive Daytime Sleepiness & Sleep Apnea

- Excessive Daytime Sleepiness
  - Up to 50% of PD patients experience intense daytime fatigue and sleepiness.
  - Excessive daytime sleepiness in PD may be due to a variety of factors including:
    - Insomnia
    - Sleep apnea
    - Depression
    - Medication
  - Cause: Degeneration of regulators of the sleep-wake cycle, particularly the reticular activating system and circadian rhythm generators.

- Sleep Apnea
  - As many as 20% of PD patients may have sleep apnea.
  - Sleep apnea is a major cause of both nighttime insomnia and daytime sleepiness in PD.
  - Sleep apnea contributes to insomnia and daytime sleepiness by:
    - Oxygen flow to the brain impaired, daytime concentration and thinking impaired.
REM Behavioral Disorder

- RBD is predictive of developing PD
  - Up to 70% of patients with REM Behavior Disorder (RBD) will develop PD within 10 years.
  - Between 15 and 48% of PD patients also have RBD.
- REM sleep, or Rapid Eye Movement sleep, is a form of deep sleep in which dreams occur.
  - Physical movement is temporarily paralyzed during REM sleep due to muscle suppression that occurs to prevent acting out the dream.
- Cause: Degeneration of lower brainstem nuclei - particularly in the periolive nucleus area.
- Patients with RBD often act out violent or frightening dreams and may:
  - Kick
  - Punch
  - Talk or Scream

There are no RCTs that met inclusion criteria for the treatment of anxiety disorders and therefore no recommended treatment guideline.

Psychosis

- >50% of patients with Parkinson’s disease will develop PD psychosis during the course of their disease
- 81% of patients with hallucinations with insight progressed to hallucinations without insight or delusions within 3 years

=pd=""nlications Without Insight or Delusions"">3 PD Patients Progressed to Hallucinations Without Insight or Delusions
</td>
</tr>
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Treatment for Disorders of Sleep and Wakefulness

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<tbody>
<tr>
<td>Neurotransmitters</td>
<td>Continuous release formulation of levodopa</td>
<td>Insufficient Evidence</td>
<td>Acceptable risk</td>
<td>Investigational</td>
</tr>
<tr>
<td>Dopaminergic Agonists</td>
<td>Rotigotine</td>
<td>Likely Efficacious</td>
<td>Acceptable risk</td>
<td>Possibly useful</td>
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<td></td>
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<td>Perbidil</td>
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</tr>
<tr>
<td>Medications</td>
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<td>Possibly useful</td>
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<td>Nonpharmacological Interventions</td>
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<td></td>
<td>Modafinil</td>
<td>Insufficient Evidence</td>
<td>Insufficient Evidence</td>
<td>Possibly useful</td>
</tr>
<tr>
<td></td>
<td>Caffeine</td>
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<td>Acceptable risk</td>
<td>Investigational</td>
</tr>
</tbody>
</table>

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REM Behavioral Disorder

- RBD is predictive of developing PD
  - Up to 70% of patients with REM Behavior Disorder (RBD) will develop PD within 10 years.
  - Between 15 and 48% of PD patients also have RBD.
- REM sleep, or Rapid Eye Movement sleep, is a form of deep sleep in which dreams occur.
  - Physical movement is temporarily paralyzed during REM sleep due to muscle suppression that occurs to prevent acting out the dream.
- Cause: Degeneration of lower brainstem nuclei - particularly in the periolive nucleus area.
- Patients with RBD often act out violent or frightening dreams and may:
  - Kick
  - Punch
  - Talk or Scream

There are no RCTs that met inclusion criteria for the treatment of anxiety disorders and therefore no recommended treatment guideline.

Psychosis

- >50% of patients with Parkinson’s disease will develop PD psychosis during the course of their disease
- 81% of patients with hallucinations with insight progressed to hallucinations without insight or delusions within 3 years


1. For this purpose, the term PD refers to patients who meet the diagnostic criteria for PD. If only the term PD is used, it is assumed to refer to PD.
2. For this purpose, the term PD refers to patients who meet the diagnostic criteria for PD. If only the term PD is used, it is assumed to refer to PD.
Psychosis is a Non-Motor Symptom of Parkinson's Disease

Hallucinations
Perceptual experiences in the absence of real external sensory stimuli

Delusions
Fixed false beliefs that run contrary to reality

Visual Hallucinations are the Most Common Symptom of PDP

Auditory hallucinations
0% to 22%
- Hearing voices
- Hearing music

Olfactory hallucinations
<1%

Tactile hallucinations
~12%

Gustatory hallucinations
~3%

Symptoms of PDP

Visual hallucinations
16% to 72%
- Seeing people or animals

Auditory hallucinations
0% to 22%
- Hearing people or animals
- Voices

Tactile hallucinations
<12%

Olfactory hallucinations
<1%

Gustatory hallucinations
<3%

Delusions
1% to 14%
- Jealousy
- Persecutory
- Reference

Antipsychotic Receptor Binding Properties

Muscarinic Acetylcholine Receptors
M1 M2 M3 M4

H1 Histamine Receptors

Adrenergic Alpha Receptors
a1 a2A a2B a2C

Transporters
SERT NET

Dopamine Receptors
D1 D2 D3 D4

5HT1A Serotonin Receptors
2A 1B 1D 2B 2C 1E 3 5 6 7
Muscarinic Acetylcholine Receptors: M1, M2, M3, M4
Histamine Receptors: H1
Adrenergic Alpha Receptors: α1, α2A, α2B, α2C
Dopamine Receptors: D1, D2, D3, D4
Serotonin Receptors: 5HT1A, 5HT2A, 5HT1B, 5HT1D, 5HT2B, 5HT2C, 5HT1E

Common Effects of Antipsychotic Receptor Blockade

- Cognitive impairment
- Disinhibition
- Mania
- Antisocial
- Euphoria
- Tachycardia
- Constipation
- Sedation
- Orthostatic hypotension (falls)
- Depression
- Low energy
- Movement disorders (falls)
- Parkinson’s Disease
- Endocrine changes
- Antipsychotic
- Anxiolytic

Receptor Selectivity of Antipsychotic Drugs

- Shown are potencies (in nM) at the indicated receptor targets
- Off-target side effects of other antipsychotic drugs are due to poor selectivity

Binding Profile of Quetiapine at Different Doses

- 800 mg antipsychotic
- 300 mg antidepressant
- 50 mg hypnotic
Psychosis Treatment

- Clozapine and Pimavanserin are both efficacious and considered clinically useful
- Quetiapine was equal to placebo in 5 trials and equal to clozapine in 2 trials (w/o placebo arm) earning it a possibly useful designation
- All antipsychotics have a boxed warning warning of an increased mortality risk in elderly dementia patients and may be associated with QT interval prolongation

<table>
<thead>
<tr>
<th>Drug Class / Intervention</th>
<th>Drug / Intervention</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Practice Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotic</td>
<td>Clozapine</td>
<td>Efficacious</td>
<td>Acceptable risk with specialized monitoring</td>
<td>Clinically useful</td>
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<tr>
<td>Antipsychotic</td>
<td>Olanzapine</td>
<td>Not Efficacious</td>
<td>Unacceptable risk</td>
<td>Not useful</td>
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<tr>
<td>Antipsychotic</td>
<td>Quetiapine</td>
<td>Insufficient Evidence</td>
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<td>Possibly useful</td>
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<tr>
<td>Antipsychotic</td>
<td>Pimavanserin</td>
<td>Efficacious</td>
<td>Acceptable risk</td>
<td>Clinically useful</td>
</tr>
</tbody>
</table>

Question 3

Which medications have demonstrated efficacy in treating Parkinson’s Disease psychosis?

a) Clozapine
b) Pimavanserin
c) Quetiapine
d) a & b
e) All of the above
Autonomic Dysfunction

- Up to 60% of PD patients experience autonomic dysfunction
- Downstream neurotransmitter deficits in PD affecting dopamine, serotonin, acetylcholine, and norepinephrine contribute to:
  - Orthostatic Hypotension (drop in systolic blood pressure by > 20 mmHg or diastolic pressure > 10 mmHg from supine to standing)
  - Sexual Dysfunction
  - Constipation
  - Anorexia, Nausea, Vomiting associated with Levodopa or Dopamine Agonist
  - Drooling
  - Urinary Frequency, Urgency, and/or Urge Incontinence

Autonomic Dysfunction Treatments

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Drug / Intervention</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Practice Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthostatic Hypotension</td>
<td>Fludrocortisone</td>
<td>Insufficient Efficacy</td>
<td>Insufficient evidence</td>
<td>Possibly useful</td>
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<tr>
<td></td>
<td>Midodrine</td>
<td>Insufficient Efficacy</td>
<td>Insufficient evidence</td>
<td>Possibly useful</td>
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<tr>
<td></td>
<td>Domperidone</td>
<td>Insufficient Efficacy</td>
<td>Acceptable risk with specialized monitoring</td>
<td>Possibility useful</td>
</tr>
<tr>
<td></td>
<td>Yohimbine</td>
<td>Non Efficacious</td>
<td>Insufficient evidence</td>
<td>Investigational</td>
</tr>
<tr>
<td></td>
<td>Droxidopa</td>
<td>Efficacious (short term)</td>
<td>Acceptable risk</td>
<td>Possibly useful</td>
</tr>
<tr>
<td>Sexual Dysfunction</td>
<td>Sildenafil</td>
<td>Efficacious</td>
<td>Acceptable risk</td>
<td>Clinically useful</td>
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<tr>
<td>Constipation</td>
<td>Macrogol</td>
<td>Likely efficacious</td>
<td>Acceptable risk</td>
<td>Possibly useful</td>
</tr>
<tr>
<td></td>
<td>Lubiprostone</td>
<td>Likely efficacious</td>
<td>Acceptable risk</td>
<td>Possibly useful</td>
</tr>
<tr>
<td></td>
<td>Probiotics &amp; prebiotic fiber</td>
<td>Efficacious</td>
<td>Acceptable risk</td>
<td>Clinically useful</td>
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<tr>
<td></td>
<td>Abdominal massage</td>
<td>Insufficient Evidence</td>
<td>Insufficient Evidence</td>
<td>Investigational</td>
</tr>
<tr>
<td>Anorexia, Nausea, Vomiting associated with Levodopa or Dopamine Agonist</td>
<td>Domperidone</td>
<td>Likely efficacious</td>
<td>Acceptable risk with specialized monitoring</td>
<td>Possibly useful</td>
</tr>
<tr>
<td>Drooling</td>
<td>Solifenacin</td>
<td>Insufficient Evidence</td>
<td>Acceptable risk</td>
<td>Possibly useful</td>
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<tr>
<td></td>
<td>Botulinum Toxin A or B</td>
<td>Efficacious</td>
<td>Insufficient evidence</td>
<td>Clinically useful</td>
</tr>
</tbody>
</table>

Fatigue

- Up to 33% of PD patients report fatigue
  - Often considered fatigue the single most bothersome symptom
- May occur alone or in combination with depression, apathy or sleep disorders

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>MAO-B Inhibitors</td>
<td>Rasagiline</td>
<td>Efficacious</td>
<td>Acceptable risk</td>
<td>Possibly useful</td>
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<tr>
<td></td>
<td>Modafinil</td>
<td>Insufficient Evidence</td>
<td>Insufficient evidence</td>
<td>Investigational</td>
</tr>
<tr>
<td></td>
<td>Selegiline</td>
<td>Insufficient Evidence</td>
<td>Insufficient evidence</td>
<td>Investigational</td>
</tr>
<tr>
<td></td>
<td>Ipratropium</td>
<td>Insufficient Evidence</td>
<td>Insufficient evidence</td>
<td>Investigational</td>
</tr>
<tr>
<td></td>
<td>Botulinum Toxin A or B</td>
<td>Efficacious</td>
<td>Acceptable risk with specialized monitoring</td>
<td>Clinically useful</td>
</tr>
<tr>
<td></td>
<td>Acupuncture</td>
<td>Insufficient Evidence</td>
<td>Acceptable risk</td>
<td>Investigational</td>
</tr>
<tr>
<td></td>
<td>Acupuncture</td>
<td>Insufficient Evidence</td>
<td>Acceptable risk</td>
<td>Investigational</td>
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</tbody>
</table>
Pain

- Between 33% - 66% of PD patients experience pain directly related to PD
  - Presents as stiffness, spasms or muscle pain in calves, neck or back
- Decreased pain thresholds in PD can be due to:
  - Degeneration of dopamine-dependent centers that regulate pain inhibition.
  - Norepinephrine degeneration in the locus coeruleus
- Adjust PD medication: Increasing dopaminergic therapy may help both primary and secondary pain in PD.
  - If the pain is occurring during off periods, reducing fluctuations may be helpful.

Pain may be a signal that dopaminergic medications should be adjusted.

<table>
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<th>Safety</th>
<th>Practical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine Agonist</td>
<td>Rotigotine</td>
<td>Insufficient Evidence</td>
<td>Acceptable risk</td>
<td>Investigational</td>
</tr>
<tr>
<td>Opioid</td>
<td>Oxycodone</td>
<td>Insufficient Evidence</td>
<td>Acceptable risk</td>
<td>Possibly useful</td>
</tr>
</tbody>
</table>

Case Study

- JG is a 78 yo male residing in a nursing home with a history of PD, hypertension, diabetes, AFib, and osteoarthritis. His medications include:
  - Losartan 50mg po daily
  - Dulaglutide 75mg sq weekly
  - Metformin 750mg po BID
  - Levodopa/carbidopa 100mg po QID
  - Salsalate 5mg po BID
  - Pramipexole 1mg po TID
- Nursing staff are reporting that JG is increasingly withdrawn, is unwilling to participate in social activities and has lost 5lbs in the past few weeks.
- The DON asks your opinion in how to best manage JG.

- What non-motor symptoms should JG be assessed for?
- How/what would you suggest to improve JG's symptoms?