Recognizing and Treating the Cognitive and Behavioral Symptoms of Parkinson’s Disease

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Topics Covered

• Cognitive changes (Mild cognitive impairment & Dementia)
• Psychosis (Hallucinations & Delusions)
• Affective Disorders (Depression & Anxiety)
• Impulse Control Disorders
Parkinson’s Disease
Psychiatric & Behavioral Features

• Cognitive decline
• Depression
• Anxiety & Panic disorder
  • Generalized anxiety disorder, social phobias
• Psychosis
  • Visual hallucinations
  • Paranoid delusions
  • Hypersexuality
• Apathy
• Impulse Control Disorders
PD patients’ well-being, general health perceptions, health satisfaction and overall health related quality of life are strongly influenced by mental health symptoms and more weakly influenced by physical symptoms.”

Chrischilles EA et al Parkinsonism & Related Disorders 2002
Psychiatric Conditions (95 patients)

- Depression: 56.8%
- Anxiety: 17.9%
- Psychosis: 9.5%
- Impulse Control Disorder: 6.3%
- Other psychiatric: 16.8%
- None of these: 21.1%
Braak Hypothesis: Evolving Concept of Disease Progression and Timing

- Hyposmia
- Constipation
- Bladder disorder
- Sleep disorder
- Depression
- Rigidity
- Akinesia
- Bilateral disease
- Poor balance
- Dependency
- Cognitive decline
- Psychosis

Definitions: MCI & Dementia

• Diagnosis of MCI (mild neurocognitive disorder) requires
  • Evidence of modest cognitive decline from a previous level of performance in one or more of the cognitive domains.
  • Must be insufficient to interfere with independence in daily activities, although greater effort and compensatory strategies may be required to maintain the level of independence.

• Diagnosis of Dementia (major neurocognitive disorder) requires
  • Evidence of significant cognitive decline from a previous level of performance in one or more of the cognitive domains.
  • Must be sufficient to interfere with independence in activities of daily living.
Types of Dementia

- Dementia with Lewy Bodies - 10%
- Vascular Dementia - 20%
- Alzheimer’s Disease - 60% - 80%
- Other Types:
  - Frontotemporal dementia
  - Normal pressure hydrocephalus
  - Creutzfeldt-Jackob disease
Dementia with Parkinsonism

• **Neurochemistry**: decreased cortical and subcortical cholinergic transmission - Basal nucleus of Meynert decreased dopamine in nigrostriatal tract

• **Cause**: McKeith et al Neurol 1996
  - **Parkinson’s disease dementia (PDD)** consequence of PD subcortical pathology
    - If dementia occurs > 12 mos after motor symptoms
  - **Alzheimer’s disease**
    - If dementia is the defining feature (AD & PD may occur together, or just AD)
  - **Lewy Body Dementia (LBD)**
    - If dementia and motor symptoms occur within 1 Yr

Dickson 2007
Frequency of Mild Cognitive Impairment in Parkinson’s Disease

- 20%-50% of patients have mild cognitive impairment (PD-MCI)
- PD-MCI is present early in the disease, with estimates of 25% of patients having cognitive impairments
- PD-MCI is a risk factor for the development of Parkinson’s disease with dementia (PDD):
  - 40-60% of patients with MCI progress to PDD within 5 years
  - 20% revert to normal

Pedersen et al. Neurology Feb 2017:88
Frequency of Dementia in PD

- PD carries an approximately 5-6-fold increased risk for dementia compared to the general population.
- PDD occurs on average 10 years after PD diagnosis.
- Incidence is age related:
  - 2.7%/yr ages 55-64
  - 13.7%/yr ages 70-79
- Prevalence ~40% cross-sectional studies,
- Higher with long longitudinal studies (78% in 17 yrs)

Emre. Mov Disord 18 (Suppl. 6) (2003 Sep), pp. S63–S71
Aarsland 2006
Mean age at onset of dementia 72 yrs (10 years after PD onset)
After a diagnosis of dementia mean survival was 54 months.
PDD vs. LBD

DLB: diagnosed when onset of dementia precedes or occurs within a year of development of the motor symptoms.

Central Feature: Progressive cognitive decline that interferes with social and occupational function

Core Features: (any 2=probable DLB; any 1=possible DLB)
- Fluctuating cognition
- Recurrent visual hallucinations
- Spontaneous motor parkinsonism

Suggestive Features: (1 or more+a core feature=Probable DLB, any 1 alone=Possible DLB)
- REM sleep behavior disorder
- Severe neuroleptic sensitivity
- Decreased tracer uptake in striatum on SPECT dopamine transporter imaging or on MIBG myocardial scintigraphy
Neuropsychological Domains

- Memory - Amnestic
- Language
- Frontal/Executive Functions
- Visuomotor Abilities
- Attention
Cognitive Profile of Parkinson’s Disease “Frontal-Subcortical”

Areas Most Commonly Affected

• Word Finding difficulties
• Attention (Complex)
• Executive Functioning (Reasoning, Problem Solving, multi-tasking)
• Memory (Learning and Recall)
• Information Processing Speed (“Bradyphrenia” or slow thinking)
• Visuomotor Processing Speed
Executive Functioning

• Set Shifting
• Conceptualization
Trails B

Begin

End

4

D

A

B

2

3

C
“I want you to imagine that this circle is a clock. Put the numbers on the clock and set the time at 10 after 11.”
LBD
Neuropsychological Patterns in PD ("frontal-subcortical dementia") vs. Early AD ("cortical dementia")

MEMORY

**PD**
Memory impaired; recognition relatively preserved (benefit from retrieval support)

**Early AD**
Pronounced problems in recent memory; Little benefit from cues
Hopkins Verbal Learning Test

- Patient reads 12 words over 3 trial presentations
- Immediate recall and delayed recall are assessed
- Recognition memory is assessed
Immediate and Delayed Recall

![Bar chart showing Immediate and Delayed Recall for AD and PD subjects. The chart compares Trial 3 and Delayed recall.](chart.png)
Recognition Memory

![Graph showing Recognition Memory]
Judgement of Lines
Fig. 1 Overview of the diagnosis and management of PDD

**Diagnosis of PDD**
- Dementia syndrome, insidious onset, slow progression in context of PD
- Impairment in > 1 cognitive domain
- Decline from pre-morbid level
- Deficits severe enough to impair daily life (independent of motor symptoms)

**If acute changes, exclude other causes:**
- Laboratory, imaging, and other investigations
- Review medication list for PD and non-PD drugs

**Care planning topics:**
- Driving
- Work
- Home safety
- Medication safety
- Changes in activities of daily living, instrumental activities of daily living
- Advance directives
- Caregiver support

**Management considerations:**
- Treat underlying cause if acute medical condition
- Stop or reduce medications that could contribute to cognitive problems
- Prescribe cognitive medications for PDD
- Utilize non-pharmacological interventions (e.g., physical exercise, cognitive exercises, social activities, optimal nutrition)

Goldman 2019
LBD & PDD

Treatment

• Lower doses or discontinue anticholinergics, dopaminergics and other drugs.
• Treat depression and sleep disturbances
• Treat low blood pressure
• Cognitive training
• Physical Exercise
• Acetylcholinesterase inhibitors
• Atypical antipsychotics - for psychosis and agitation
## Cholinesterase Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Approximate maximum daily dose</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Rivastigmine oral</td>
<td>12 mg</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Rivastigmine patch</td>
<td>13.3 mg/24 hours</td>
<td>Daily</td>
</tr>
<tr>
<td>Donepezil</td>
<td>10 mg</td>
<td>Daily</td>
</tr>
<tr>
<td>Galantamine</td>
<td>24 mg</td>
<td>Twice daily</td>
</tr>
<tr>
<td>Memantine</td>
<td>20 mg</td>
<td>Twice daily</td>
</tr>
</tbody>
</table>
Psychosis in PD
Definitions

• **Psychosis**: a major psychiatric illness in which reality testing is impaired, typically by the presence of hallucinations and delusions

• **Hallucinations**: perception without stimulus

• **Illusions**: misperception of a stimulus

• **Delusions**: false belief (often unacceptable) based on incorrect inference, held despite evidence to the contrary

• **Hallucinosis**: Hallucinations with preserved insight
Psychosis in PD

Hallucinations

• **Minor:** May occur in early untreated patients
  • Presence (extracampine hallucinations - 64% of hallucinators
    Fenelon et al Brain 2000)
  • Passage
  • Illusions

• **Major:**
  • Visual (10 to 60% of PD patients – most common)
  • Auditory (6 to 50%; can occur in isolation)
  • Tactile (usually in demented patients)
From: JH Friedman, MD
Psychosis in PD

Delusions (7-16%)

• Paranoid: persecutory in content
  • Fear of being injured, poisoned, influenced, filmed recorded
  • Elaborate conspiracies
• Spousal infidelity is a common delusion (Othello Syndrome)
• Delusional Misidentification syndrome (Roane et al J Neuropsych Clin Neurosci 1998)
• Generally more serious requiring immediate attention
<table>
<thead>
<tr>
<th>Delusions (any)</th>
<th>23/144 (16%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Types of Delusions</td>
<td></td>
</tr>
<tr>
<td>SAPS (N=23)</td>
<td></td>
</tr>
<tr>
<td>Persecutory</td>
<td>5 (22%)</td>
</tr>
<tr>
<td>Jealousy</td>
<td>3 (13%)</td>
</tr>
<tr>
<td>Sin or Guilt</td>
<td>8 (35%)</td>
</tr>
<tr>
<td>Grandiose</td>
<td>8 (35%)</td>
</tr>
<tr>
<td>Religious</td>
<td>6 (39%)</td>
</tr>
<tr>
<td>Somatic</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Reference</td>
<td>7 (30%)</td>
</tr>
<tr>
<td>Thought Broadcasting</td>
<td>1 (4%)</td>
</tr>
</tbody>
</table>
Symptomatic

- Dopamine
  - Psychosis secondary to dopaminergic medications; isolated delusional disorder
  - Psychosis in treated PD; minor and formed hallucinations

- Serotonin
  - Mood-congruent psychosis secondary to a mood or anxiety disorder; includes minor hallucinations

- Acetylcholine
  - Psychosis secondary to dementia (e.g. misidentification syndrome); advanced motor symptoms: FOG and falls
  - Progressive cascade

- Psychosis due to anticholinergic/dopaminergic medications in those with cognitive decline
  - Psychosis in PD with dementia, depression and advanced motor symptoms: FOG and falls
## ATYPICAL ANTIPSYCHOTICS & PD

<table>
<thead>
<tr>
<th>Agent</th>
<th>Worsens PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>No*</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Yes*</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Yes*</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>No**+</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>Yes</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Yes</td>
</tr>
<tr>
<td>Pimavanserin</td>
<td>No*</td>
</tr>
</tbody>
</table>

*Double blind data available
+ one open trial yes in demented patients
TREATMENT OF PSYCHOSIS IN PD & LBD

- Simplify and reduce adjunctive anti-PD medications: remove anticholinergics, MAOI, DA agonists, amantadine, COMT inhibitors
- Reduce levodopa sparing motor function
- 1st Choice antipsychotic – Pimavanserin 34 mg per day
- 2nd Choice antipsychotic - Quetiapine 12.5 - 25 QHS and increase as needed to ~ 50mg BID.
- 3rd choice antipsychotic - Clozapine 6.25mg QHS and increase Q4-7 days to ~50mg. Will improve >90%.
- Acetylcholinesterase inhibitors
Depressive Disorders in PD

• Symptom of PD just like tremor and slowness
• Prevalence: ~ 40-50% of PD patients have clinically significant depressive symptoms
• SCID 8% met criteria for major depression, BDI II 25% had scores of >14
• Annual incidence 1.9% (0.2% Healthy elderly)
• Early disease – 27.6%
• Ranges from subsyndromal depressive symptoms to major depressive syndrome
• More common in PD than DM, osteoarthritis
• Progressive and occurs at any time in the course of PD

Depressive Disorders in PD

• Palanci et al 2009: Major depression under-recognized

• 250 pts (223 informants) interviewed with SCID
Symptoms of Depression

- Mood change (sad, blue, down, feelings of hopelessness, helplessness)
- Anhedonia (an inability to experience pleasure)
- Apathy (decreased motivation)
- Insomnia
- Fatigue
- Decreased concentration (cognitive impairment)
- Decreased facial expression
- Poverty of movement
- Speech with low volume and reduced inflection
Diagnosis of Depression

- Often missed - 35% accuracy by neurologist (Shulman et al, 1997, Weintraub 2003)
- Patients (50%) with clinically significant depression may not consider themselves depressed (Weintraub 2003). Need other informants (Caregivers)
- Features of PD itself (e.g. bradykinesia, loss of facial expression) confused with signs/symptoms of depression
- Syndromic criteria as outlined by DSM may not apply in PD
Figure 2. Antidepressant Treatment and Remission Status (n=97)

Palanci et al. 2009

Those with co-morbid anxiety are more likely to be treated
Anxiety

• Core features: Unpleasant sense of apprehension, fear, worry
• Heterogeneous clinically
• Categories of anxiety DSM5
  Generalized Anxiety Disorder.
  Social Phobia (or Social Anxiety Disorder)
  Panic Disorder.
  Post-Traumatic Stress Disorder (PTSD)
  Obsessive-Compulsive Disorder (OCD)
Generalized Anxiety Disorder

• Excessive anxiety and worry relating to various activities.
• The symptoms must last 6 or more months and be present for the majority of that time period.
• Difficult to control
• Associated with three or more of the following symptoms:
  • restlessness or feeling keyed up
  • becoming easily fatigued
  • concentration difficulties
  • irritability, muscle tension
  • sleep disturbances
• The symptoms cause clinically significant distress, impairing functioning, and are not attributable to the physiological effects of a substance or another medical disorder.
Social phobia

- Marked fear of one or more social situations where the individual can be exposed to scrutiny.
- A frequent fear in patients with PD is about being observed while eating or drinking in public, where their symptoms may become exposed.
- These social situations provoke fear or anxiety, often resulting in avoidance and intense fear.
- To meet the DSM 5 criteria for social phobia, the fear, anxiety, or avoidance must cause clinically significant distress or impairment in social, occupational, or other areas of functioning.
Anxiety in PD

- Under-diagnosed: 40% do not meet DSM criteria
- Some may predate motor features
- Not closely correlated with motor features
- No Relation to anti-PD meds

- Lifetime risk 49%; current prevalence 43% SCID pt/informant (Pontone et al, 2009)
- 24% with panic attacks in “complicated” PD (Vazquez et al, 1993)

- SCID 10% for anxiety disorder (32% GAD, 32% Panic disorder)
- BAI 21% had scores of > 1 (Factor et al MDCP 2016)
Panic Attacks

• Discrete, sudden onset periods of intense fear and discomfort
• 24% of PD patients
• Associated with depression
• Symptoms: SOB, feeling faint, palpitations, tachycardia, trembling, abdominal distress, urinary frequency, depersonalizations, paresthesias, flushing, chills, chest pain, motor freezing, fear of dying and being out of control
• Most commonly occurs with off periods
Anxiety & Depression in PD

- Gen Population
  - 60% with depression have anxiety
  - 30% major depression have panic attacks
- Overlaps with PD & depression (Menza 1993); Greater association of depression & panic attacks in PD
  - Depressed PD has more anxiety (agitated depression (Cummings 1992)
  - 65-92% of PD with anxiety also had depression (Pontone 2009)
  - 67% of PD with depression had anxiety
Treatment of Depression

• Treat fluctuations in response to levodopa
• Cognitive behavioral therapy for the treatment of depression
• Counseling and/or insight-oriented psychotherapy
• Medications: SSRI and an SRNI
• Transcranial magnetic stimulation (TMS)
• ECT
Anxiety in PD Treatment

• Generalized anxiety and social phobia
  • Maximize treatment of PD and depression
  • Utility of psychotherapy (mindfulness-based cognitive therapy (MBCT)) and cognitive behavioral therapy (CBT), behavior modification, biofeedback
  • Utility of benzodiazepines, antidepressants, ECT - not established

• Panic attacks
  • Treat motor fluctuations aggressively including Apomorphine
  • Benzodiazepines - clonazepam may be particularly helpful
  • SSRI, SNRI
  • No trials
<table>
<thead>
<tr>
<th>Medications</th>
<th>Approximate target daily dose</th>
<th>Clinical pearls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citalopram</td>
<td>Max 40mg in younger pts. Max 20mg in patients &gt;60 y/o. Once per day</td>
<td>Black box warning for possible QTc prolongation</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>20 mg per day (typically in AM)</td>
<td>Start 10mg per day. Some patients need up to 30 mg.</td>
</tr>
<tr>
<td>Sertraline</td>
<td>200 mg per day (typically in AM)</td>
<td>Could cause diarrhea. Titrate from 25 mg in elderly pts. Increase weekly</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>15 to 45 mg at bedtime</td>
<td>Lower doses are generally more sedating</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Max 300 mg per day. (Typically in AM)</td>
<td>It requires a titration Monitor BP</td>
</tr>
<tr>
<td>Desvenlaxine</td>
<td>50 to 100 mg per day. (Typically in AM)</td>
<td>Titration not needed It has relatively higher Norepinephrine reuptake inhibition than Venlafaxine Monitor BP</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>60 mg per day. (Typically in AM)</td>
<td>Approved also for Diabetic Peripheral Neuropathic Pain, Fibromyalgia, Chronic Musculoskeletal Pain</td>
</tr>
<tr>
<td>Vilazodone</td>
<td>20- 40 mg per day</td>
<td>Give with food Increase dose no more frequently than q 7 days</td>
</tr>
<tr>
<td>Buspirone</td>
<td>5 to 10 mg BID to QID</td>
<td>Max 60 mg per day. Watch for serotoninergic syndrome when augmenting an SSRI</td>
</tr>
</tbody>
</table>
Impulse Control Disorders

• ICD Definition: failure to resist an impulse, drive or temptation, with or without urges, associated with negative consequences
Impulse Control Disorders

• Pathological behaviors up to 17%
  • Pathological Gambling 2.5%
  • Pathological shopping up to 6%
  • Hypersexuality 2.5%
• Punding
  • intense fascination with complex, excessive, repetitive, non-goal oriented behaviors
• Compulsive medication use: Dopamine dysregulation syndrome 4%
  • Pathological use of dopaminergic medications by levodopa-responsive PD patients in excess of that required for motor response
• Compulsive eating 4%
Impulse Control Disorders
co-morbidities

• Depression
• Irritability
• Disinhibition
• Appetite changes
• Mania or hypomania

• Motor – fluctuations in response

Similar to non-PD gamblers

Pontone et al 2006, Voon et al 2006
Pathological Gambling/Compulsive shopping & dopamine agonists

• Dose related? Or idiosyncratic
  Seen with low doses in RLS treated with DA Tippmann-Peikert 2007)

• Occurs with dopamine agonist therapy, alone or as adjunct
  (Lifetime prevalence 17% - adjunct use predictive) (Evans 2009)

• Frequency similar with all agonists

• Occurs with levodopa monotherapy 0.7%

• IC symptoms in 30% untreated PD patients (Siri 2008)

• Reversible Withdrawal of dopamine agonists?
  • Reduced or worsened by DBS (Witjas 2005)
Treatment*

• Optimal therapy is unknown
• Decrease dosage of Dopamine agonists
• Decrease dosage of other dopaminergic drugs

• Pharmacotherapy
  • Atypical antipsychotics
  • SSRI’s & SNRI’s
  • Cholinesterase inhibitors
  • Topiramate?
  • Opioid antagonists

• STN DBS: Variable results (Lim et al 2009)
  • 71% with Pre-op DDS worsen or are unchanged (Higginbotham et al 2018)

• Counseling & Caregiver intervention

*There are no controlled trials