Mental Health and PD

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None

**Honoraria**
None

**Royalties**
Taylor & Francis/Informa

**Approved/Unapproved Uses**
Dr. Marsh **does** intend to discuss the use of off-label /unapproved use of drugs or devices for treatment of psychiatric disturbances in Parkinson’s disease.
Learning Objectives

• Describe relationships between motor, cognitive, and psychiatric dysfunction in Parkinson’s disease (PD) over the course of the disease.

• List the common psychiatric diagnoses seen in patients with PD.

• Describe appropriate treatments for neuropsychiatric disturbances in PD.
“Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace; …
“Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace; the senses and intellects being uninjured.”

James Parkinson 1755 - 1828
The Complex Face of Parkinson’s Disease

• **Affects**  
  ~ 0.3% general population  
  ~ 1.5 million Americans, 7-10 Million globally  
  ~ 1% population over age 50; ~ 2.5% > 70 years; ~ 4% > 80 years  
  ~ All races, ethnicities: Men > Women; C,H > As, AA

• **Dynamic, varied longitudinal course**  
  ~ Pre-motor, Motor, and Non-motor phenomena

• **Systemic disease that impacts disability and quality of life**  
  ~ Psychiatric and Cognitive Disturbances > Motor

Noyes 2006; Whetten-Goldstein 1997; Wright Willis 2010, Schrag 2000; Schrag 2001; McDonald 2003; Starkstein 1992; Kuopio 2000; Marsh 2004, 2007; Pontone 2011; Postuma 2015 (MDS Criteria); Okun 2017
Initial Symptoms of PD Involve Depressive Phenomena (n=183)

<table>
<thead>
<tr>
<th>Initial Symptom</th>
<th>#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>129 (70%)</td>
</tr>
<tr>
<td>Gait disturbance</td>
<td>21</td>
</tr>
<tr>
<td>Stiffness</td>
<td>18</td>
</tr>
<tr>
<td>Slowness</td>
<td>18</td>
</tr>
<tr>
<td>Muscle pain, cramps, aching</td>
<td>15</td>
</tr>
<tr>
<td>Loss of dexterity</td>
<td>14</td>
</tr>
<tr>
<td>Handwriting disturbance</td>
<td>9</td>
</tr>
<tr>
<td>Depression, nervousness</td>
<td>8</td>
</tr>
<tr>
<td>Speech disturbance</td>
<td>7</td>
</tr>
<tr>
<td>General fatigue, muscle weakness</td>
<td>5</td>
</tr>
<tr>
<td>Drooling</td>
<td>3</td>
</tr>
<tr>
<td>Loss of arm swing</td>
<td>3</td>
</tr>
<tr>
<td>Facial masking</td>
<td>3</td>
</tr>
</tbody>
</table>

Yahr, 1967
Pre-PD Anxiety Disturbances
Risk factor or Early Symptom of PD?

Gonera et al., 1997
– Anxiety symptoms often coincide with onset of PD

Shiba et al., 2000
– Anxiety disorders, present up to 20 years before onset of motor signs, associated with development of PD

Weisskopf et al., 2002
– 12-year follow-up of 35,000 men
– High anxiety and anxiolytic use associated with increased relative risk of developing PD (1.5-1.6)
Are Depressive Disorders in PD an Early (pre-motor) Symptom of PD?

– On average, depression precedes PD by 4 to 6 years

Ishihara and Brayne 2006 (review)

RR 3.13 (1.95-5.01) Schuurman et al 2002
RR 2.4 (1.72-2.93) Nilsson et al 2001
RR 2.40 (2.10-2.70) Leentjens et al 2003

(MOOD-PD Study, Unpublished Data)

| Major Depression Before PD Dx | 51 | 46 |
| Major Depression at or after PD Dx | 60 | 54 |

Frequency

Duration between Earliest Major Depression Episode Onset and PD Diagnosis (years)
PD Treatments

- Levodopa/carbidopa
- Dopamine agonists
  - Bromocriptine
  - Pergolide
  - Pramipexole
  - Ropinirole
  - Rotigotine
  - Apomorphine
- MAO-B inhibitors
  - Rasagiline
  - Selegiline
- Other
  - Anticholinergics
    - Benztropine
    - Trihexyphenidyl
  - Amantadine
- Nonpharmacologic
  - Exercise/PT
  - Acupuncture
  - Deep Brain Stimulation
  - Pallidotomy
  - Other
Antiparkinsonian Medications: Fluctuating Motor Effects

- Loss of efficacy

- End of dose deterioration
  - On-off phenomena

- Dose-limiting side effects
  - Hyperkinesia/Dyskinesias
  - Dystonias

- Concomitant fluctuating psychiatric & cognitive symptoms
Antiparkinsonian Medications: Neuropsychiatric Effects

• Mood Changes
• Psychosis
• Confusion/delirium
• Disinhibition
• Impulse control disorders
  • e.g., gambling, hypersexuality
• Fluctuating neuropsychiatric/non-motor symptoms
Nonmotor Fluctuations

**Dysautonomic**
- Drenching sweats, hot sensations, flushing, dry mouth, dyspnea, dysphagia, constipation, distal cold sensations, excessive salivation, urinary urgency, visual complaints, palpitations, bloating, chest pain

**Cognitive/Psychiatric**
- Slowed thinking, mental hyperactivity, impaired memory, mental emptiness
- Off-Anxiety (81%), Off-depression (63%), On-hypomania (24%), irritability, psychosis

**Sensory/Vegetative**
- Fatigue, akathisia, tightening sensations, tingling, pain

Witjas 2002; Racette 2002.
Levodopa-related Fluctuations

Motor state

Mood

Dyskinetic

Happy

On

Neutral

Off

Anxious

Levodopa dose

Richard et al, 2004
Neuropathology Influences Psychopathology

Primary Dopamine Deficiency Affects Mesostriatal, Mesolimbic & Mesocortical DA Systems

Cortico-striatal-Thalamic Circuits: Motor, Reinforcement, Higher Order Processing
Non-dopaminergic Neuropathology

Neuronal loss
- Locus Coeruleus – NE
- Midbrain raphe – 5HT
- Nucleus basalis – Ach

Alzheimer-type Changes

Lewy Body Pathology
PD Non-Motor Symptom Complex

**Neuropsychiatric Symptoms**
- Mood disturbances
  - Depression, anxiety, apathy
- Psychosis
  - Hallucinations, delusions
- Behavioral changes
  - Impulsive, repetitive
- Cognitive Changes
  - Selective deficits, Dementia

**Autonomic Symptoms**
- Bladder dysfunction
  - Urgency, Nocturia, Frequency
- Sweating
- Orthostasis
- Sexual Dysfunction
- Dry eyes
- Gastrointestinal changes
  - Drooling, ageusia, dysphagia, reflux, Constipation, Incontinence

**Sleep Disorders**
- Restless legs
- Periodic limb movements
- REM sleep behavior disorder
- Non-REM Sleep movement disorders
- Insomnia, EDS, Vivid Dreams
- Sleep-disordered breathing

**Other Symptoms**
- Sensory – Pain, paresthesias
- Olfactory changes
- Fatigue
- Seborrhea
- Blurred Vision, Diplopia

PD Progression Involves Treatment of Motor and Non-motor Symptoms

<table>
<thead>
<tr>
<th>Sequence of symptoms in progression of Parkinson disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early symptoms</td>
</tr>
<tr>
<td>Pharmacologic treatment</td>
</tr>
<tr>
<td><strong>Treatment of motor symptoms</strong></td>
</tr>
<tr>
<td>MAO-B inhibitor</td>
</tr>
<tr>
<td>Levodopa</td>
</tr>
<tr>
<td>Dopamine agonist</td>
</tr>
<tr>
<td>COMT inhibitors</td>
</tr>
<tr>
<td>Amantadine</td>
</tr>
<tr>
<td>Pump-delivered therapy</td>
</tr>
<tr>
<td>Levodopa intestinal gel</td>
</tr>
<tr>
<td>Subcutaneous apomorphine</td>
</tr>
<tr>
<td>Treatment of nonmotor symptoms</td>
</tr>
<tr>
<td>Antidepressants</td>
</tr>
<tr>
<td>Antipsychotics</td>
</tr>
<tr>
<td>Cholinesterase inhibitors</td>
</tr>
<tr>
<td>Nonpharmacologic treatment</td>
</tr>
<tr>
<td>Deep brain stimulation</td>
</tr>
<tr>
<td>Exercise</td>
</tr>
<tr>
<td>Physical and occupational therapy</td>
</tr>
<tr>
<td>Speech and swallow therapy</td>
</tr>
<tr>
<td>Psychosocial care</td>
</tr>
</tbody>
</table>

Bars indicate approximate periods of initiation and duration of each treatment except where noted. COMT indicates catechol-O-methyl transferase.

For the treatment of motor symptoms, drugs are usually added sequentially. Monoamine oxidase type B (MAO-B) inhibitor monotherapy may be started in the early symptom period followed by the addition of levodopa or a dopamine agonist. As symptoms progress, other drugs may be added and then discontinued as medication-resistant symptoms and adverse effects emerge. Levodopa may be continued through late stages of the disease as monotherapy.

Medication-resistant symptoms refer to symptoms resistant to medications for the treatment of motor symptoms.

<sup>a</sup> Gait dysfunction, soft speech (hypophonia), and memory and cognitive problems.

<sup>b</sup> Dysphagia, falls, and memory and cognitive problems.

<sup>c</sup> Beyond this point, pump-delivered therapy and deep brain stimulation should not be initiated but may be continued if already prescribed.

Okun, JAMA 2017
II. Impact of Psychiatric Disturbances in PD
Neuropsychiatric Disturbances Broad Negative Impact

↑ Motor deficits, dysfunction, progression
↑ Influence on perceived need for motor therapy
↑ Cognitive deficits and dysfunction
↑ Co-morbid medical and other psychiatric conditions
↑ Carer burden
↑ Healthcare and other costs to family and society
↑ Disability over longitudinal course of PD (~20 yr)

↓ Quality of life

Schrag 2000; McDonald 2003; Starkstein 1992; Kuopio 2000; Marsh 2004, 2007; Pontone 2011; Hely et al, 2005
Neuropsychiatric Features – Most Disabling over Disease Course

<table>
<thead>
<tr>
<th>Most disabling long-term symptoms</th>
<th>15 years</th>
<th>20 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=149</td>
<td>52 surviving</td>
<td>36 surviving</td>
</tr>
<tr>
<td>Age (SD) yrs</td>
<td>71 (8)</td>
<td>74(8)</td>
</tr>
<tr>
<td>Cognitive Decline</td>
<td>84%</td>
<td>100%</td>
</tr>
<tr>
<td>Dementia</td>
<td>48% (MCI-36%)</td>
<td>83%</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>50%</td>
<td>74%</td>
</tr>
<tr>
<td>Depression</td>
<td>39%</td>
<td>50%</td>
</tr>
</tbody>
</table>

Depressive Symptoms Influence when Antiparkinsonian Treatment is Started

NET-PD Study/Neuroprotective Treatment Trials

n=413, early untreated for PD with dopaminergic or other PD meds

- Depression Screen: Geriatric Depression Scale (GDS-15) \( \geq 5 \)
  - 27.6% positive for Depression screen over ~ 15 months
  - 40% Depression cases left untreated

- Depressive symptoms predicted
  - Increased deficits in Activities of Daily Living (ADLs) \((p<0.0002)\)
  - Increased need for symptomatic PD therapy \((HR=1.86; 95\% \text{ CI } 1.29-2.68)\)

Ravina et al., 2007
Depression Remission Improves Physical ADLs in PD (n=136)

Group differences in Physical ADLs (NWDS) at baseline and 2-year intervals

Marsh et al, 2007; Pontone et al, 2015
Up to 2/3 of PD-Depressive Disturbances Under-recognized or Under-treated

1. Shulman 2002, n=101 PD

2. Weintraub 2003, n=100 PD
   34% DSM Depressive Disorder; 2/3 were not receiving treatment

3. Hoek et al. 2011, n=256 PD
   36.3% minor depression with 8.6% treated
   12.9% Major Depression with 30.3% treated
   49.2% +Depression      61.1% not treated
III. Recognizing Psychiatric Syndromes in PD
Psychiatric Disturbances are Common in PD (Mood-PD Study, n=250, MMSE>23)

Marsh et al. in preparation
Psychiatric Co-morbidities Drive Complexity in Assessment and Management of PD Psychiatric Disturbances

% of total sample (n=250) with psychiatric dx

- Mood Disorder: 59.2% (n=148)
- Anxiety Disorder: 41.6% (n=104)
- Psychotic Disorder: 25.2% (n=63)
- Depression: 21.2% (n=53)
- Obsessive-Compulsive Disorder: 4.4% (n=11)
- Bipolar Disorder: 7.6% (n=19)
- Schizophrenia: 4.8% (n=12)

Marsh et al. Unpublished
Other Psychiatric Diagnoses
Independent or Co-morbid with Depression

Apathy
Emotionalism/Pathological Crying
Anxiety Disturbances
Psychosis
Impulse Control Disorders
Dementia and other Cognitive Impairment
Depressive Disorders in PD

• ~40% prevalence (range 3% - 90%)

• Several types of depressive disturbances
  – Clinically significant depressive symptoms 35% (Major Depression)
  – Mild states (minor depression), may remit (50%), but may also worsen

• Recurrence or treatment resistance rates unclear
  – Symptom severity, older age, PD Duration

• Onset can be before overt motor signs/PD Dx
  – i.e., onset not related to disease stage or disability

• Anxiety disorders often co-occur

Reijnders 2008; Mayeux, 1981; Starkstein, 1992; Meara, 1999; Global PD Survey, 2002; Weintraub 2004; Ravina 2009; Even 2012; Shakeri 2015; Ghaddar 2016; Reidel 2016
PD and Depression Have Overlapping Features

**Motor**

**Depression**
- Psychomotor Retardation
- ± Stooped Posture
- Restricted/sad affect
- Agitation

**PD**
- Bradykinesia
- Stooped Posture
- Masked Facies
- Tremor

**Cognitive**
- Impaired Memory
- Impaired Concentration

**Vegetative**
- Decreased Energy
- Fatigue
- Sleep/Appetite changes

**Somatic**
- Physical Complaints
- Sexual, GI, muscle tension
Major Depressive Episode DSM-IV/V Criteria

1. Depressed or sad mood
   AND/OR
2. Decreased interest or pleasure
   (Anhedonia - Without Pleasure)

3. Appetite/Weight changes
4. Sleep disturbances
5. Psychomotor agitation or retardation
6. Fatigue or loss of energy
7. Feelings of Worthlessness/Excessive Guilt
8. Decreased ability to think or concentrate or indecisiveness
9. Recurrent thoughts of death or suicidal ideation, attempt or plan
Major Depressive Disorders have Persistent Emotional Features

A pervasive change in Mood
• Persistent sadness
• Decreased interest and enjoyment
• Inability to enjoy previously enjoyable experiences
• Pessimism, hopelessness
• Negative ruminations
  • Pessimism, hopelessness
• Inappropriate guilt
• Negative view of sense of self
• Morbid and/or suicidal thoughts
• Feeling overwhelmed, anxious, unable to cope
• Irritability

“I can cope with PD, as long as I am not depressed.”
- Many Patients
PD-depressive phenomena are similar to idiopathic depressive disorders

• **Subtle statistical differences in PD & non-PD depression**
  - Absence of guilt or self-blame (n=132) (Brown 1988)
  - ↓ rates guilt, worthlessness, self-blame (n=189) (Gotham 1986)
  - ↓ sadness, anhedonia, guilt (Ehrt 2006)
  - No differences from non-PD (Merschdorf 2003)

• **Suicidality in PD is not trivial**
  - Lower or same rate c/t general population (Myslobodsky 2001)
  - ↑ completed suicides & attempts with STN DBS (Voon 2008)
  - No ↑ Suicidality in STN vs Gpi DBS (Weintraub 2013)
  - Subthalamic DBS may be complicated by increased depression, apathy, and impulsivity (Weintraub 2009)
  - 28% Death ideation, 11% Suicide ideation
  - 4% lifetime suicide attempt (Weintraub 2008)
  - 22.7% suicide/death ideation (Kostic 2010)
Anxiety Disorders in PD

- Several Types
  - Episodic (Panic Disorder)
  - Situational (Phobias)
  - Continuous (Generalized Anxiety)
  - PD-Specific (Wearing-off anxiety/panic)

- Depressive disorders are a common co-morbidity

- Not understandable reactions to motor symptoms
  - Non-motor fluctuations
  - Onset of Anxiety may precede PD

## Prevalence of Specific Anxiety Disorders

<table>
<thead>
<tr>
<th>Category / %</th>
<th>Prior studies</th>
<th>Pontone 2011</th>
<th>Dissanayaka 2010</th>
<th>Leentjens 2011</th>
<th>Population NEMESIS/ NCS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panic disorder</td>
<td>13 – 30</td>
<td>5</td>
<td>8</td>
<td>4</td>
<td>1.5/1</td>
</tr>
<tr>
<td>Specific Phobia</td>
<td></td>
<td>16</td>
<td>-</td>
<td>-</td>
<td>5.5/5.5</td>
</tr>
<tr>
<td>GAD</td>
<td>0 - 40</td>
<td>4</td>
<td>3</td>
<td>21</td>
<td>0.8/1.6</td>
</tr>
<tr>
<td>Social phobia</td>
<td>15</td>
<td>7</td>
<td>13</td>
<td>10</td>
<td>3.7/4.5</td>
</tr>
<tr>
<td>Agoraphobia</td>
<td>-</td>
<td>1.6</td>
<td>-</td>
<td>16</td>
<td>-/2.3</td>
</tr>
<tr>
<td>Post-traumatic stress disorder</td>
<td>-</td>
<td>0</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Anxiety Dis NOS (not otherwise specified)</td>
<td>-</td>
<td><strong>22%</strong></td>
<td>-</td>
<td><strong>11%</strong></td>
<td>-</td>
</tr>
</tbody>
</table>

*DSM-IV-TR; **Based on NPI anxiety subscale cut-off >3
Nonmotor Fluctuations

Dysautonomic
- Drenching sweats, hot sensation, flushing, dry mouth, dyspnea, dysphagia, constipation, distal cold sensations, excessive salivation, urinary urgency, visual complaints, palpitations, bloating, chest pain

Cognitive/Psychiatric
- Slowed thinking, mental hyperactivity, impaired memory, mental emptiness
- Off-Anxiety (81%), Off-depression (63%), On-hypomania (24%), irritability, psychosis

Sensory/Vegetative
- Fatigue, akathisia, tightening sensations, tingling, pain

Fluctuating Motor and Non-Motor Symptoms

Motor

Dyskinetic

On

Off

Levodopa dose

Motor state

Mood

Happy

Neutral

Anxious

Richard et al, 2004
Anxiety Disorders Non-Psychiatric Impact

Increased
- PD motor symptoms and signs
- Increased PD motor complications
  - Freezing
  - On-Off Fluctuations
  - Dyskinesias
- Gait difficulties

Reduced
- Quality of life
- Self-perceived health status

Siemers 1993; Dissanayaka 2010; Vazques 1993; Lauterbach 2003; Leentjens 2011; Henderson 1992; Pontone 2009; Pontone 2011
### Symptom Overlap: Depression and Anxiety in PD

<table>
<thead>
<tr>
<th>Parkinsonism</th>
<th>Depression</th>
<th>Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Decreased facial expression</td>
<td>On-off fluctuations</td>
</tr>
<tr>
<td></td>
<td>Psychomotor changes – Slowness, motor restlessness</td>
<td>Restlessness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Insomnia</td>
</tr>
<tr>
<td>Somatic</td>
<td>Pain, Muscle tension</td>
<td>Muscle tension, Fatigue</td>
</tr>
<tr>
<td></td>
<td>Fatigue, energy loss</td>
<td>Autonomic Symptoms</td>
</tr>
<tr>
<td></td>
<td>Insomnia, Decreased appetite</td>
<td>Insomnia</td>
</tr>
<tr>
<td></td>
<td>Weight Loss</td>
<td></td>
</tr>
<tr>
<td>Cognitive Impairment</td>
<td>Executive dysfunction</td>
<td>Executive dysfunction</td>
</tr>
<tr>
<td></td>
<td>Decreased memory &amp; Concentration</td>
<td>Decreased concentration</td>
</tr>
<tr>
<td>Other Psychiatric Symptoms</td>
<td>Anxiety, ICDS, Apathy, Psychosis</td>
<td>Depression, ICDs, Psychosis</td>
</tr>
</tbody>
</table>
Psychological Features of Anxiety

Excessive
- Avoidance
- Apprehension
- Worry
- Anticipation
- Overly-detailed
- Emotional Reactivity
- Fearfulness
- Somatic concerns
- Ruminative

No pervasive
- Guilt
- Sadness
- Decreased self-worth
- Lack of interest
- Morbid
Apathy

Prevalence
– ~ 30% as a feature of a depressive disorder
– ~ 10% as an independent disorder

Clinical features
– Loss of motivation
– Emotional indifference
– Reduced goal-directed activities
– Patients with primary apathy do NOT complain

Weiss and Marsh, 2009
Emotionalism/Pathological Crying

Prevalence
- 40-50%
- Associated with Depressive Disorders, Delirium, Benzodiazepines

Clinical Features
- Heightened, excessive sentimentality/tear
- Inappropriate, unmotivated, involuntary
- Precipitated by a variety of emotions
- Social embarrassment/Phobic avoidance
I. Prevalence

- Depends on definition of psychosis, PD, and cognitive impairment
- ~8%–40% reported rates
  - ~5%–17% without significant dementia
  - ~42%–81% with significant dementia
- Persistent and progressive

II. Impact

- Major Clinical Challenge
- Major source of caregiver burden
- #1 factor in nursing home placement
- Associated with increased disability and mortality
- Prognosis improved with advent of atypical antipsychotics

Hallucinations in PD

- Three categories
  - “Minor” Hallucinations
    - Presence – Vivid sensation
    - Passage – Brief visions in peripheral field
    - Illusions – sensory distortions
  - “Benign” Hallucinations/Hallucinosis
  - Hallucinations without insight
    - Formed/Complex versus Unformed
    - Visual, Auditory, Olfactory, Gustatory, Somatic/Tactile/Cenesthetic
Psychosis in PD: Never ‘Minor’ or ‘Benign’

- Community-based PD (n=250)
  - 26% any current psychotic Symptom
  - 47.7% Isolated Minor Hallucinations
  - 52.3% Hallucinations or Delusions

- Minor Hallucinations (vs. No Psychosis)
  - Greater physical disability
  - More severe depressive symptoms
  - Reduced quality of life

Mack et al 2012.
Parkinson’s Disease Psychosis (PDP)

**NINDS-NIMH Diagnostic Criteria**

Symptoms (presence of at least 1)
- Illusions, false sense of presence, hallucinations, delusions

Chronology
- Psychotic symptoms occur in a patient with diagnosed Parkinson’s disease

Duration of symptoms
- Recurrent or continuous for ≥ 1 month

Other causes excluded
- Differential diagnosis

Associated features
- With or without insight, dementia, or Parkinson’s disease treatment

Abbreviations: NINDS-NIMH, National Institute of Neurological Disorders and Stroke – National Institute of Mental Health.

Risk Factors for PDP

**Intrinsic**
- Cognitive impairment/family history of dementia
- Older age, severity, and duration of PD
- Visual Deficits
- Other Psychiatric Pathology
- Rapid eye movement (REM) sleep behavior disorder (RBD)

**Extrinsic**
- Dopaminergic medications for PD
- Anticholinergic & other central nervous system–acting agents (benzodiazepines and opiates)
- Polypharmacy with psychoactive drugs


PD-specific Medication-related Mood Syndromes

1) Early morning off (EMO) states (Rizos 2014)
   - Anxiety, Low mood
   - Urinary urgency, Drooling
   - Paresthesias, Dizziness

2) Dopamine Agonist Withdrawal Sd (DAWS) (Rabinak & Nirenberg, 2010)
   - Anxiety, Panic attacks
   - Depression, Dysphoria,
   - Suicidality, Agitation, Irritability
   - Insomnia, Fatigue, Dizziness,
   - Nausea, Diaphoresis, Pain
   - Orthostatic Hypotension
   - Drug Cravings

3) On-off Motor and Non-motor fluctuations (Racette 2002)
## Impulse Control and Behavioral Disorders

<table>
<thead>
<tr>
<th>Disturbance</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathological Gambling</td>
<td>3-8%</td>
</tr>
<tr>
<td>Hypersexuality</td>
<td>2.5%</td>
</tr>
<tr>
<td>Pathological Shopping</td>
<td>0.4-1.5%</td>
</tr>
<tr>
<td>Punding</td>
<td>1.5-14%</td>
</tr>
<tr>
<td>Compulsive Dopaminergic Med Use</td>
<td>3.4-4%</td>
</tr>
</tbody>
</table>

Factors associated with Impulse Control Disorders

I. Individual related factors
- Personal history of behaviors
- Sex
- Family history of alcohol use
- Personal history of alcohol use
- Depression
- Novelty seeking/sensation seeking traits
- Impulsivity traits

II. Medications
- Dopamine agonists
- Excessive dopaminergic dose

III. PD-related factors
- Pathological subgroups (e.g., early-onset PD)
- Medication practices (e.g., levodopa use or higher doses)
- Pathologic or compensatory mechanisms
- PD effects on cognitive function

IV. Behaviors
- Problem gambling
- Hypersexuality
- Compulsive shopping
- Compulsive eating
- Punding
- Compulsive medication use
Treatment

General Approaches

1. Treatment Works - People Recover

2. Targeted and Individualized Approach
Targeted and Individualized Treatment

Medica(l)tions, Education, Skills, Support (MESS)

M - Adjust/Optimize/Adhere anti-parkinsonian medications
» Identify and treat medical conditions, delirium
» Adjust medications causing cognitive/psychiatric problems

ESS - Non-pharmacological approaches
» Educational Programs
» Skills: Psychotherapies
  OT, PT, ST, RT
» Social Support, Support Groups
» Support + Exercise + Fun: Singing, Yoga, Dance, Boxing, etc.
» Address Caregiver Needs
  Home Care, Respite, Support
Targeted and Individualized Treatment (2)

Medications, Education, Skills, Support (MESS)

M - Add/Adjust/Optimize/Adhere specific psychiatric medications
- Anti-depressants
- Sleep medicines
- Anti-anxiety medicines
- Anti-psychotics
- Cognitive-enhancing agents

Consider other somatic treatments
- Electroconvulsive Therapy (ECT)
- Repetitive Transcranial Magnetic Stimulation (rTMS)
- transcranial Direct Current Stimulation (tDCS)
- Vagal Nerve Stimulation (VNS)
- Deep Brain Stimulation (DBS)
Depression Treatment for PD
Systematic Review & Meta-analysis

ALL INTERVENTIONS
SMD=0.30

ANTIDEPRESSANTS
SMD=0.56

Test of SMD = 0 : z = 1.93 p = 0.054

Test of SMD = 0 : z = 3.56 p = 0.000

Bomasang-Layno 2015
Residual Symptoms Can Persist Despite Antidepressant Medication Response

Menza et al 2009, N=52, MDD/Dysthymia
– 8-week trial: Nortriptyline (NTP) > paroxetine (PXT), placebo (PLC)
– Clinical response: 50% reduction in Ham-D score
  • 16 responders (3 PXT, 4 PLC, 9 NTP)
  • 36 non-responders (15 PXT 13 PLC, 8 NTP)

– Responders (n=16)
  • Improved Mood, middle insomnia, interest, somatic anxiety
  • Persistent residual symptoms
    – >50% depressed mood
    – lack of interest
    – psychic anxiety
    – low energy

Menza et al., Neurology 2009; Dobkin et al., AGJP 2010
Antidepressive Behavioral Treatments for PD
Systematic Review & Meta-analysis

SMD = .87

Test of SMD=0 : z = 3.72 p = 0.000

Bomasang-Layno 2015
Psychosis Treatment
Adjust/Eliminate Select PD Meds

Discontinue First

Anticholinergics
Selegiline/Rasagline
Amantadine
Dopamine agonists
Controlled release meds
COMT inhibitors
Levodopa dosage

Discontinue Last
Antipsychotic Medications

- May allow increase in PD meds
- But, several types of antipsychotics
  - Typical D$_2$ blockers— ↑ parkinsonism
  - Atypical agents—block D$_3$, D$_4$, D$_5$, 5-HT
  - Selective 5HT2A inverse agonist (Pimavanserin)
- Open-label and controlled trials
  - Clozapine: gold standard
  - Pimavanserin: + efficacious
  - Quetiapine: fairly well-tolerated + but – efficacy in trials
  - Ziprasidone: anecdotal only—profile limits use
  - Aripiprazole: anecdotal only—variable tolerance
  - Risperidone, olanzapine: poor tolerance

Friedman & Hernandez. 2002; Seppi 2011
# Antipsychotic Treatments for PDP*

<table>
<thead>
<tr>
<th>Treatment for Psychosis</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Practice Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>Efficacious</td>
<td>Acceptable risk with specialized monitoring</td>
<td>Clinically useful†</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Unlikely efficacious</td>
<td>Unacceptable risk</td>
<td>Not useful†</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Insufficient evidence</td>
<td>Acceptable risk without specialized monitoring</td>
<td>Investigational†</td>
</tr>
<tr>
<td>Pimavanserin</td>
<td>Efficacious³</td>
<td>No treatment-related impairment of motor function³; increase in QT interval without association to cardiac events³</td>
<td>Clinically useful</td>
</tr>
</tbody>
</table>

* Black box warning for typical and atypical antipsychotics in elderly patients who have dementia-related psychosis⁴
† Not FDA approved for the treatment of PDP

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1. MDS evidence-based medicine review designations (2011)
2. FDA-approved for PDP (2016)
3. Pimavanserin
4. Clozapine
5. Olanzapine
6. Quetiapine
7. FDA-approved for PDP (2016)
Other Strategies to Treat Psychosis

- **Cognitive Enhancing Agents**
  - Cholinesterase inhibitors
    - + PD-D and DLB
    - Variable tolerance, May benefit from lower doses
  - Memantine—DLB, PD-D

- **Electroconvulsive therapy (ECT)**
  - Especially psychotic depression

- **Ondansetron**
  - May be useful post-operatively
Mental Health and PD: Conclusions

Psychiatric Disturbances in PD
• PD motor features overlap with psychiatric conditions
• Very common, related to disease and its treatment
• Develop over the course of PD, including before diagnosis
• Negative impact across multiple domains

Treatment Works!
• Medication, Education, Skills, Support (MESS)
• Treat assiduously and to remission to reduce excess disability
• Address caregiver burden and quality of life
• Interdisciplinary coordinated teams
Register Today for ATTP Atlanta!

Allied Team Training for Parkinson’s Disease (ATTP®)

Apply today to reserve your seat at ATTP in Atlanta for a 3.5 day on-site course to help us take PD care to the next level. State of the art care can make the difference between satisfaction and despair for people affected by PD. Parkinson.org/Attp
Resources

**National Helpline**
Available at 1-800-4PD-INFO or Helpline@Parkinson.org
Mon- Fri 9 am to 8 pm ET

**Podcast: Substantial Matters**
New episodes every other Tuesday featuring Parkinson’s experts highlighting treatments, techniques and research. Parkinson.org/Podcast

**Fact Sheets and Publications**
- Mood: A Mind Guide to Parkinson's Disease
- Psychosis: A Mind Guide to Parkinson's Disease
- Combating Depression in PD

**Aware in Care Kit**
Includes tools and information for people with PD to share with hospital staff during a planned or emergency hospital stay. Parkinson.org/Awareincare