Mood Disorders in Parkinson’s Disease: What’s New?

Laura Marsh, MD
Executive Director, Mental Health Care Line
Michael E. DeBakey Veterans Affairs Medical Center
Professor, The Menninger Department of Psychiatry
and The Department of Neurology
Baylor College of Medicine
Disclosures

Research Support
National Institutes of Health: R01-MH 069666, Dystonia Foundation American Psychiatric Association
> 2 years: NIH: P50 NS 58377, Boehringer Ingelheim GmbH, Forest Research Institute, Eli Lilly, Michael J. Fox Foundation

Consultancies (> 2 years)
Acadia Pharmaceutical, Boehringer Ingelheim GmbH, Merck Serono, Ovation

Royalties
Taylor & Francis/Informa

Approved/Unapproved Uses
This presentation may discuss use of medications that do not have FDA approval for treatment of psychiatric aspects of PD
Parkinson’s Disease and Depression

“THIS IS MY DEPRESSED STANCE.”

“WHEN YOU'RE DEPRESSED, IT MAKES A LOT OF DIFFERENCE HOW YOU STAND…”

“THE WORST THING YOU CAN DO IS STRAIGHTEN UP AND HOLD YOUR HEAD HIGH BECAUSE THEN YOU'LL START TO FEEL BETTER…”

“IF YOU'RE GOING TO GET ANY JOY OUT OF BEING DEPRESSED, YOU'VE GOT TO STAND LIKE THIS.”
Learning Objectives

1. Describe the occurrence of depressive phenomena at different stages of PD

2. Recognize the features of depression in PD patients (and PD in depression)

3. Discuss treatment strategies for patients with PD and depression
Case History

- 86 yo WWF, deceased sec NSC met. Lung ca-2009
- Prior National Table Tennis Champ-Senior Division
- Onset Major Depressive Episode age 69
  - Recurrent episodes of depression
- Diagnosed with PD age 72 with dragging foot x 3 years, left hand tremor x 6 months
- Onset Generalized Anxiety Disorder age 80
- Cognitive changes age 80, decline age 82
- Intermittent Visual Hallucinations age 81
- Imbalance age 83
Case History
I. PD Overview

II. Impact of depression on PD Phenotype

III. Recognition of depression in PD

III. Treatment
PD Overview
Parkinson's Disease

- Affects ~ 1 million Americans, ~ 0.3% general population
  ~ 1% of the population over age 50
  ~ 2.5% > 70 years; ~ 4% > 80 years

- All races, ethnicities
- Affects Men > Women
- Estimated Direct Costs (2004) $34 Billion/Year

Motor Features of PD

Classic Motor Triad
- Tremor
- Rigidity
- Bradykinesia/Akinesia

- Gait and Postural Disturbances
  - Dragging, Shuffling, Start Hesitation, Festination
  - Later loss of righting reflexes, Unsteadiness, Imbalance

- Absence of Parkinson-Plus Features

- Motor signs $\neq$ Disability $\neq$ Psychological distress

Schrag et al., 2001
Traditional View of Course of PD

Nigral Dopamine cell death begins

Symptom Onset
Diagnosis
Treatment
Death

Disease Free state
Presymptomatic phase
No treatment needed
Controlled Symptoms
Motor Complications

“Cognitive Decline”

DA Neurons
Disease
Undiagnosed symptoms
Symptomatic threshold
Pre-PD Psychopathology
Risk factor or early symptom of PD?

- **Gonera et al., 1997**
  - 4-8 year prodrome before PD diagnosis - Increased mood and anxiety symptoms

- **Shiba et al., 2000**
  - Up to 20 years before motor signs - anxiety dos (OR=2.2)
  - Up to 5 years before motor signs - depressive dos (OR=1.9)

- **Weisskopf et al., 2002**
  - 12-year follow-up of 35,000 men
  - Relative risk of developing PD (1.5-1.6) - High anxiety and anxiolytic use
On average, affective diagnoses precede PD by 4 to 6 years

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

Onset of depression is not related to disease stage or disability

- Ishihara and Brayne 2006 (review)
  - On average, affective diagnoses precede PD by 4 to 6 years
  - 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
# Initial Symptoms of PD (n=183)

<table>
<thead>
<tr>
<th>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
Increased rates of Depression in Early PD [DATATOP Study (Uc et al., 2009)]

Annual incidence rate = 1.4% (1.0-1.8)
Time to Depression, based on HAM-D Score = 4.9 2.7 years
Depressive Symptoms Associated With Initiation of Motor Treatment

NET-PD Study/Neuroprotective Treatment Trials

n=413 early untreated PD
- Depressive symptoms - GDS-15 ≥ 5
- 27.6% + Depression screen over ~ 15 months
- 40% Depression cases left untreated

- Depressive symptoms predicted
  - Increased ADLS (p<0.0002)
  - Increased need for symptomatic PD therapy (HR=1.86; 95% CI 1.29-2.68)

Ravina et al., 2007
Course of Depression
NET-PD Study/Neuroprotective Treatment Trials

- Depressive Symptoms remained mild
- 47% remission within 6 months
- Mild depressive symptoms predicted
  - Development of more severe symptoms (RR=6.16 [95%CI 2.14-17.73])
- Sx severity, older age, longer PD duration predicted failure to remit (HR=0.83-0.92)

Ravina et al., 2009
Neuropsychiatric features have greatest impact on quality of life.

Clinical features associated with significantly impaired PDQL (quality of life) scores

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression (BDI&gt;17); n=18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MMSE&lt;25; n=13</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>History of hallucinations; n=15</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>History of falls; n=58</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Postural instability; n=43</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Gait impairment; n=61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Akinetic-rigid subtype; n=68</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Schrag et al, JNNP, 2000
Neuropsychiatric Features – Most disabling over Disease Course

Sydney Multi-center Study – 15-year Follow-up
- n=149, 52 surviving (71 ± 8; 55-86 years)

- Most disabling long term symptoms
  - Cognitive decline - 84%
  - Dementia - 48%, MCI - 36%
  - Hallucinations – 50%
  - Depression – 39%

Hely et al, 2005
Treatment Options in PD

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

- Neuropsychiatric
  - Mood Changes
  - Psychosis
  - Confusion/delirium
  - Disinhibition, gambling, hypersexuality
Antiparkinsonian Medications: Fluctuating Effects

• Motor
  - Loss of efficacy
  - End of dose deterioration/On-off phenomena
  - Dose-limiting side effects
    - Hyperkinesia/Dyskinesias
    - Dystonias
  - Concomitant fluctuating psychiatric & cognitive symptoms
Nonmotor Fluctuations

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

Levodopa-related Fluctuations

Motor state

Motor

Dyskinetic

On

Off

Mood

Happy

Neutral

Dysphoric

levodopa

Motor state

Mood state

Richard et al, 2004
Neuropathology of Parkinson’s Disease

A Dopamine Deficiency Disease

- Substantia Nigra pars compacta Neuronal Loss
- Substantia Nigra Lewy bodies
Neuropathology of PD
Affects multiple dopaminergic systems

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

Mesostriatal, Mesolimbic, Mesocortical Dopaminergic Systems
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

Sleep Disorders
Restless Legs
Periodic Limb Movements
REM Sleep Behavior Disorder
Non-REM Sleep Mvt Disorders
Insomnia, EDS, Vivid Dreams
Sleep-disordered breathing

Autonomic Symptoms
Bladder DOs-Urgency, Nocturia, Frequency
Sweating
Orthostasis
Sexual Dysfunction
Dry eyes
GI-drooling, ageusia, dysphagia, reflux, Constipation, Incontinence

Other symptoms
Sensory – Pain, paresthesias, Olfactory changes
Fatigue
Seborrhea
Blurred Vision, Diplopia

Early Non-motor features correspond to earliest signs of pathology, e.g., Braak’s 6-stages

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Lesions in the dorsal IX/X motor nucleus and/or intermediate reticular zone</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=21; medulla oblongata</td>
<td>Lesions in the dorsal IX/X motor nucleus and/or intermediate reticular zone</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 2</th>
<th>Pathology of stage 1 plus lesions in caudal raphe nuclei, gigantocellular reticular nucleus, and coeruleus-subcoeruleus complex</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=13; medulla oblongata and pontine tegmentum</td>
<td>Pathology of stage 1 plus lesions in caudal raphe nuclei, gigantocellular reticular nucleus, and coeruleus-subcoeruleus complex</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 3</th>
<th>Pathology of stage 2 plus midbrain lesions, in particular in the pars compacta of the substantia nigra</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=24; midbrain</td>
<td>Pathology of stage 2 plus midbrain lesions, in particular in the pars compacta of the substantia nigra</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 4</th>
<th>Pathology of stage 3 plus prosencephalic lesions. Cortical involvement is confined to the temporal mesocortex (transentorhinal region) and allocortex (CA2-plexus). The neocortex is unaffected</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=24; basal prosencephalon and mesocortex</td>
<td>Pathology of stage 3 plus prosencephalic lesions. Cortical involvement is confined to the temporal mesocortex (transentorhinal region) and allocortex (CA2-plexus). The neocortex is unaffected</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 5</th>
<th>Pathology of stage 4 plus lesions in high order sensory association areas of the neocortex and prefrontal neocortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=17; neocortex</td>
<td>Pathology of stage 4 plus lesions in high order sensory association areas of the neocortex and prefrontal neocortex</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stage 6</th>
<th>Pathology of stage 5 plus lesions in first order sensory association areas of the neocortex and premotor areas, occasionally mild changes in primary sensory areas and the primary motor field</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=11; neocortex</td>
<td>Pathology of stage 5 plus lesions in first order sensory association areas of the neocortex and premotor areas, occasionally mild changes in primary sensory areas and the primary motor field</td>
</tr>
</tbody>
</table>

Braak H et al, Neurobiology of Aging 24: 197-211, 2003
Prevalence of depressive disturbances in PD
Wide Range of Psychiatric Symptoms

Neuropsychiatric Inventory Scores, n=139

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percent with symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euphoria</td>
<td>1%</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>7%</td>
</tr>
<tr>
<td>Irritability</td>
<td>10%</td>
</tr>
<tr>
<td>Aberrant Motor Behavior</td>
<td>11%</td>
</tr>
<tr>
<td>Delusions</td>
<td>16%</td>
</tr>
<tr>
<td>Agitation</td>
<td>17%</td>
</tr>
<tr>
<td>Apathy</td>
<td>27%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>38%</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>61%</td>
</tr>
<tr>
<td>Depression</td>
<td>61%</td>
</tr>
<tr>
<td>Any one symptom</td>
<td>61%</td>
</tr>
</tbody>
</table>

Aarsland et al., 1999, Rogaland, Norway Epidemiological Sample
Range of Psychiatric Diagnoses in PD
(MOOD-PD Study, n=250)
Depressive Disorders in PD

- Epidemiology
  - ~40% prevalence (range 3% - 90%)
  - Clinically significant depressive symptoms 35%
  - Anxiety disorders are a common co-morbidity
  - Rates of recurrence or treatment resistance unclear

Reijnders 2008; Mayeux, 1981; Starkstein, 1992; Meara, 1999; Global PD Survey, 2002; Weintraub 2004
There is a range of depressive diagnoses

MOOD-PD Study (n=250)
Mean (SD, range) PD Duration= 7.8 (6.4, 0-35 years)

- No Mood Disorder
- Major Depressive Disorder
- Dysthymia or Minor Depressive Disorder
- Bipolar Affective Disorder or Mania
- Other Mood Disorder NOS Only

Palanci 2009
But even worse ...
Symptomatic Depression Worsens Physical ADLs in PD (n=136)

At any assessment point, subjects with a symptomatic depressive disorder have greater disability, averaging 3.8 points lower on the NWDS score. (GEE Regression: SD vs ND, $B=-3.8$, $p<.001$)

**PD Subjects (Baseline)**
Age=67.1 (10.5) yrs; PD Duration=9.4 (6.9) yrs
Symptomatic Depression (SD), n=36
Remitted Depression (RD), n=12
Not Depressed (ND), n=88

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

Marsh et al, 2007

![Graph showing group differences in Physical ADLs (NWDS) at baseline and 2-year intervals.](image)
PD Phenotype is Influenced by Depression

- Associated with increased
  - Motor deficits
  - Cognitive impairment
  - Disability
  - Caregiver burden
  - Economic Strain
  - Concurrent psychiatric conditions

- Depression is not related to disease stage or disability
  - Before motor signs
  - Early or late in PD Course

Reijnders 2008; Mayeux, 1981; Starkstein, 1992; Meara, 1999; Global PD Survey, 2002; Weintraub 2004
Yet, despite that ...
Under-recognition of Depressive Symptoms

Physician Identification of Psychiatric Symptoms in PD

- Depression
- Anxiety
- Fatigue
- Sleep

Depressive disorders are unrecognized or undertreated

Major Depression, n=97 (MOOD-PD Study)

- Asymptomatic, Treated
- Symptomatic, Partially Treated
- Symptomatic, No Treatment

Duration major depressive episode (n=86) = 182.4 (218.8) weeks
Range 2-1612 weeks. Median 104 weeks.

Palanci et al. 2009
Depressive Disorders

- Under-recognized …
  - ~ 75% missed diagnoses (Shulman, 2002)
  - ~ 65% missed diagnoses (Weintraub 2004)

- Under-treated …
  - 94% untreated (Meara 1999)
  - 45% under-treated (Weintraub 2004)

- Mis-treated?
  - Medicare Claims for PD patients (n=10,445)
  - 45.2 % Treated with antidepressant medication (Orsini, 2004)
Recognition of Depression in PD
PD-Depression: Barriers to Recognition

- Motor symptoms
  - Define the disease
  - Primary focus of care/interest
  - Mask psychiatric changes

- Depressive symptoms
  - Regarded as ‘understandable’ reactions
  - Need to be monitored
  - Occur with other mood disorders
  - Stigma
  - Don’t ask, don’t tell
How to Detect Depression in PD
Problem of Overlapping Features
Major Depression | Parkinson’s Disease

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

≠

Depressive Disorder
Depression

• An emotion characterized by sad and unhappy feelings

• A normal psychological reaction, especially to loss

• A loosely used term
  – Frustration, anger, disgust, anxiety, overwhelmed, apathetic, tired
Depressive Disorder

- A psychiatric (medical) condition
- An abnormal and persistent mental state
- Accompanied by physical and mental changes
- Affects function and causes significant distress
DSM Criteria helpful, but Depressive Disorders have Distinct Emotional Features

- A pervasive change in **Mood**
  - Persistent sadness
  - Decreased interest and enjoyment, anhedonia
  - Pessimism, hopelessness
  - Negative ruminations
  - Inappropriate guilt
  - Negative view of sense of self
  - Morbid and/or suicidal thoughts
  - Feeling overwhelmed, anxious, unable to cope
  - Irritability
Symptoms of Depressive Disorder Vary

- n=52 PD, Baseline symptoms before treatment for Major Depression (Dobkin 2010)
  - >75% depressed mood, guilt, middle insomnia, early awakening, lack of interest, psychic anxiety, fatigue, low sexual interest
  - <50% suicidal thinking, early insomnia, poor appetite, loss of weight

- n=58 PD, not depressed

Subjective performance of cognition related to mood and not objective performance (Marino 2009)
Depressive Symptom Rating Scales

- **Clinician-rated**
  - Hamilton Depression Rating Scale
  - Montgomery-Asberg Depression Rating Scale
  - Cornell scale for Depression in Dementia

- **Self-rated**
  - Beck Depression Inventory
  - Hospital Anxiety and Depression Scale
  - Geriatric Depression Scale
  - CES-D
  - Zung Depression Rating Scale

*Inclusive Rating Approach Recommended

Schrag et al. 2008; Williams 2010
# Methods of Optimal Depression Detection-PD (MOOD-PD) Sample

<table>
<thead>
<tr>
<th>Overall Depressive Disorder Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depression - Symptomatic</strong></td>
</tr>
<tr>
<td>Major Depression</td>
</tr>
<tr>
<td>Non-Major Depression</td>
</tr>
<tr>
<td>Depression - Remitted</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>No Active Depressive Disorder (n=136)</th>
<th>Active Depressive Disorder (n=93)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>66.1 (10.0)</td>
<td>66.0 (10.8)</td>
<td>&lt;0.951</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>93 M (68%)</td>
<td>60 M 65%</td>
<td>&lt;0.542</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td>16.5 (3.1)</td>
<td>15.6 (2.6)</td>
<td>&lt;0.025</td>
</tr>
<tr>
<td><strong>PD Symptom Duration</strong></td>
<td>8.4 (6.7)</td>
<td>8.7 (6.2)</td>
<td>&lt;0.721</td>
</tr>
<tr>
<td><strong>H&amp;Y Stage</strong></td>
<td>I-21; I½-7; II-61; II½-27</td>
<td>I-10; I½-0; II-43; II½-18</td>
<td>&lt;0.137</td>
</tr>
<tr>
<td></td>
<td>III-13; IV-5; V-2</td>
<td>III-18; IV-3; V-1</td>
<td></td>
</tr>
<tr>
<td><strong>UPDRS-Motor</strong></td>
<td>15.9 (9.9) (n=133)</td>
<td>21.6 (12.0) (n=89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>MMSE</strong></td>
<td>28.7 (1.3)</td>
<td>27.9 (1.8)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
## MOOD-PD Depression Rating Scale Scores

<table>
<thead>
<tr>
<th>Scale</th>
<th>No Active Depressive Disorder (n=136)</th>
<th>Active Depressive Disorder (n=93)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI-II</td>
<td>6.5 (5.2)</td>
<td>14.7 (7.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CESD-R</td>
<td>9.3 (10.1)</td>
<td>22.1 (15.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GDS-30</td>
<td>5.8 (5.2)</td>
<td>13.7 (6.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IDS-SR</td>
<td>13.3 (8.0)</td>
<td>24.8 (10.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>3.8 (3.8)</td>
<td>8.9 (5.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>UPDRS-Depression</td>
<td>0.2 (0.5)</td>
<td>1.0 (0.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HAM-D-17</td>
<td>4.5 (3.2)</td>
<td>11.1 (5.2)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Mean (SD)

Williams et al., Neurology n press
Most Depression Scales have Adequate Psychometric Properties in PD Samples

MOOD-PD and Comparison Studies

<table>
<thead>
<tr>
<th>Measure</th>
<th>AUC</th>
<th>α</th>
<th>Cut-off Score†</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI-II</td>
<td>0.85</td>
<td>0.90</td>
<td>≥7</td>
<td>0.95</td>
<td>0.60</td>
<td>0.62</td>
<td>0.94</td>
</tr>
<tr>
<td>CESD-R</td>
<td>0.79</td>
<td>0.92</td>
<td>≥12</td>
<td>0.72</td>
<td>0.70</td>
<td>0.62</td>
<td>0.79</td>
</tr>
<tr>
<td>GDS-30</td>
<td>0.83</td>
<td>0.92</td>
<td>≥10</td>
<td>0.72</td>
<td>0.82</td>
<td>0.73</td>
<td>0.81</td>
</tr>
<tr>
<td>Ertan 2005</td>
<td></td>
<td></td>
<td>≥14</td>
<td>0.78</td>
<td>0.85</td>
<td>0.84</td>
<td>0.79</td>
</tr>
<tr>
<td>McDonald 2006</td>
<td>0.86</td>
<td></td>
<td>≥10</td>
<td>0.81</td>
<td>0.84</td>
<td>0.58</td>
<td>0.94</td>
</tr>
<tr>
<td>IDS-SR</td>
<td>0.83</td>
<td>0.88</td>
<td>≥14</td>
<td>0.90</td>
<td>0.60</td>
<td>0.61</td>
<td>0.90</td>
</tr>
<tr>
<td>PHQ-9</td>
<td>0.81</td>
<td>0.85</td>
<td>≥6</td>
<td>0.66</td>
<td>0.80</td>
<td>0.69</td>
<td>0.77</td>
</tr>
<tr>
<td>UPDRS-Depression</td>
<td>0.75</td>
<td>N/A</td>
<td>≥1</td>
<td>0.70</td>
<td>0.77</td>
<td>0.68</td>
<td>0.79</td>
</tr>
<tr>
<td>Starkstein 2007</td>
<td>0.79</td>
<td>N/A</td>
<td>≥2</td>
<td>0.66</td>
<td>0.81</td>
<td>0.81</td>
<td>0.66</td>
</tr>
<tr>
<td>HAM-D-17</td>
<td>0.86</td>
<td>0.77</td>
<td>≥7</td>
<td>0.77</td>
<td>0.76</td>
<td>0.69</td>
<td>0.83</td>
</tr>
<tr>
<td>‡ Leentjens 2000</td>
<td>0.95</td>
<td></td>
<td>≥14</td>
<td>0.88</td>
<td>0.89</td>
<td>0.74</td>
<td>0.96</td>
</tr>
<tr>
<td>McDonald 2006</td>
<td>N/A</td>
<td></td>
<td>≥13</td>
<td>0.81</td>
<td>0.82</td>
<td>0.58</td>
<td>0.93</td>
</tr>
<tr>
<td>IDS-C</td>
<td>0.88</td>
<td>0.86</td>
<td>≥12</td>
<td>0.81</td>
<td>0.79</td>
<td>0.73</td>
<td>0.86</td>
</tr>
<tr>
<td>MADRS</td>
<td>0.88</td>
<td>0.83</td>
<td>≥8</td>
<td>0.74</td>
<td>0.88</td>
<td>0.81</td>
<td>0.83</td>
</tr>
<tr>
<td>‡ Leentjens 2000</td>
<td>0.90</td>
<td></td>
<td>≥15</td>
<td>0.88</td>
<td>0.89</td>
<td>0.74</td>
<td>0.96</td>
</tr>
<tr>
<td>Silberman 2006</td>
<td>0.84</td>
<td></td>
<td>≥8</td>
<td>0.72</td>
<td>0.82</td>
<td>0.72</td>
<td>0.82</td>
</tr>
</tbody>
</table>

†The cut-off point that maximized the sum of sensitivity and specificity are presented for comparison to other studies, not as a recommendation for a cut-off score to be used in clinical practice.

Williams in press
# Symptoms Assessed in Different Rating Scales

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Ham-D</th>
<th>BDI-I</th>
<th>CESDR</th>
<th>PHQ9</th>
<th>GDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphoria</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Anhedonia</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Weight/Appetite Changes</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Sleep Disturbance</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Psychomotor Retardation</td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Worthlessness/Guilt</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Bradyphrenia</td>
<td></td>
<td></td>
<td>?</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Suicide/Death</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td># DSM Criteria</td>
<td>7</td>
<td>7</td>
<td>9</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td># Somatic Sx</td>
<td>3</td>
<td>3</td>
<td>4</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

DSM Depressive Criteria: Sad mood, Anhedonia/Interest, Appetite, Sleep, Agitation/Retardation, Energy, Self-attitude/guilt, Cognitive, Suicidality
Fluctuating Mood States
Motor and “Non-motor” Fluctuations

Motor
Dyskinetic
On
Off

Mood
Happy
Neutral
Anxious
Sad

levodopa
Motor state
Mood/Cognitive state

Fluctuating Mood States
Motor and “Non-motor” Fluctuations

Motor
Dyskinetic
On
Off

Mood
Happy
Neutral
Anxious
Sad

levodopa
Motor state
Mood/Cognitive state
Anxiety Disorders

- **Clinical Features**
  - 25-40% prevalence
  - Onset may precede PD
  - Often accompany depressive disorders
  - Not an understandable reaction to motor symptoms

- **Types**
  - Panic Disorder, Generalized Anxiety, Phobias, Wearing-off anxiety/panic
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
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
Co-morbidities drive complexity in the Assessment and Management of Psychopathology in PD

- Mood Disorder: 59.2% (n=148)
- Anxiety Disorder: 41.6% (n=104)
- Psychotic Disorder: 25.2% (n=63)
- 22% (n=55)
- 8.4% (n=21)
- 4.4% (n=11)
- 7.6% (n=19)
- 4.8% (n=12)

% of total sample (n=250) with diagnosis

Marsh et al. Unpublished
Treatment of Depression
Psychiatric Treatment

- Targeted and individualized approach
- Adjust/Optimize anti-parkinsonian regimen
- Treat medical conditions/delirium
- Use specific psychiatric medications
  - Anti-depressants
  - Sleep medicines
  - Anti-anxiety medicines
  - Anti-psychotics
• **Use Non-pharmacologic Treatments**

- **Education**
  - Psychiatric aspects of PD
  - Coping strategies
  - Caregiver issues

- **Psychotherapy**
  - Counseling/problem-solving
  - Supportive, directive, insight-oriented, grief counseling, Cognitive-behavioral therapy
  - Caregiver support

- **Rehabilitative therapies**
  - Occupational, Physical, Speech Therapies
  - Exercise/Exercise classes/Personal trainers
  - Relaxation training

- **Social Supports**
  - Socialization, Support groups, Home care
<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Dx</th>
<th>Sessions</th>
<th>Outcome</th>
<th>RCT?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dobkin 2006</td>
<td>3</td>
<td>MDD</td>
<td>12-14</td>
<td>Min Δ Anxiety</td>
<td>Case Series</td>
</tr>
<tr>
<td>Dobkin 2007</td>
<td>15</td>
<td>MDD</td>
<td>10-14</td>
<td>Trend ↓ anxiety</td>
<td>Pilot study</td>
</tr>
<tr>
<td>Dobkin in press</td>
<td></td>
<td>MDD</td>
<td>10-14</td>
<td>↓ Depression</td>
<td>Yes</td>
</tr>
<tr>
<td>Dreisig 1999</td>
<td>79</td>
<td>Depression</td>
<td>6</td>
<td>Impr Anx</td>
<td>1 month</td>
</tr>
<tr>
<td>Feeney 2005</td>
<td>4</td>
<td>Depr/Anxiety</td>
<td>8 group</td>
<td>No Δ Anxiety</td>
<td>Pilot</td>
</tr>
<tr>
<td>Macht 2007</td>
<td>3</td>
<td>Depr, Social anxiety, freezina</td>
<td>12-18 months</td>
<td>↓ anxiety</td>
<td>Case series</td>
</tr>
<tr>
<td>Veazey 2009</td>
<td>14</td>
<td>Anxiety/Depression</td>
<td>9 (8 on phone)</td>
<td>↓ anxiety (BAI)</td>
<td>Yes-CBT vs Support grp</td>
</tr>
</tbody>
</table>
Components of Various CBT Trials in PD Patients

Basic CBT components: Automatic thoughts, Triggers, PD specific adaptations
Problem Solving
Breathing strategies
Exposure
Activity Scheduling
Stress management
Behavior Modification
Sleep Hygiene
Relaxation
Cognitive Restructuring
Caregiver Strategies to reinforce therapy for patient
Self Monitoring
Health Promotion
Symptom (depression/anxiety) management
Social Skills Training
Written strategies

Armento M, In review
Coping Strategies

- Best if
  - Flexible
  - Vary Active versus Passive Approaches
  - Dynamic
  - Individualized

Frazier and Marsh, 2005
Pharmacological Treatments
The Motion–Emotion Conundrum

Maintain motion

Control emotion

# Antidepressants

<table>
<thead>
<tr>
<th>Class</th>
<th>Reuptake Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>SNRIs</td>
<td>Serotonin-Norepinephrine</td>
</tr>
<tr>
<td></td>
<td>Tricyclic Antidepressants, Venlafaxine, Duloxetine</td>
</tr>
<tr>
<td>NDRIs</td>
<td>Norepinephrine-Dopamine</td>
</tr>
<tr>
<td></td>
<td>Bupropion</td>
</tr>
<tr>
<td>SSRIs</td>
<td>Serotonin</td>
</tr>
<tr>
<td></td>
<td>Fluoxetine, sertraline, paroxetine, fluvoxamine, es/citalopram</td>
</tr>
<tr>
<td>SARIs</td>
<td>Serotonin Antagonist</td>
</tr>
<tr>
<td></td>
<td>Trazodone, nefazodone</td>
</tr>
<tr>
<td>NASAs</td>
<td>Norepinephrine/ Serotonin Antagonists</td>
</tr>
<tr>
<td></td>
<td>Mirtazapine</td>
</tr>
<tr>
<td>ECT</td>
<td></td>
</tr>
</tbody>
</table>
Antidepressant studies

- **Paroxetine (Paxil)**
  - Chung et al., 2005, n=12
    - No effects on PD symptoms
    - May affect balance

- **Nefazodone (Serzone) vs Fluoxetine (Prozac)**
  - Avila et al. 2003, n=16
    - Both reduced depressive symptoms
    - Motor symptoms improved on Nefazodone

- **Citalopram (Celexa)**
  - Menza et al., 2004, n=10, open-label
    - Celexa improved depressive and anxiety symptoms
  - Wermuth et al., 1998: No difference between placebo and Cit

- **Amitryptiline vs fluoxetine**
  - Serrano-Duenas, 2002: Ami>Fluoxetine, but +++Side-effects

- **Sertraline vs placebo**
  - Leentjens et al., 2003, n=12: No group difference
Antidepressant studies

- **Atomoxetine** (Weintraub et al., 2010)
  - Norepinephrine Reuptake inhibitor
  - n=55 PD patients, 8week RCT
  - Depression unchanged
  - Improvement global cognition (MMSE score)/enhanced attention

- **Citalopram** (Menza et al., 2004)
  - SSRI
  - n=10, 8week Open-label Trial
  - Improved depression and anxiety
  - Improvement global cognition (MMSE score)/enhanced attention

- **Citalopram** (Culang et al. 2009)
  - N=174 unipolar depression, >75 years, no PD
  - 8-week trial RCT
  - Non-responders: Decline in verbal fluency, psychomotor speed
  - Responders: improved visuospatial functioning (not c/t placebo)
  - Seek additional treatment for non-response
Antidepressant studies

• **Dopamine agonists**
  – Moller et al., 2005; Reichman et al. 2004
    • Open-label pramipexole ↓ PD Depressive symptoms
  – Barone et al. 2006, n=67
    • 12 wk RCT pramipexole (1.5-4.5 mg/d) vs sertraline (50 mg/day)
    • More pts in remission on pramipexole (61% vs 27%)
  – Barone et al. 2010, n=287
    • 12 wk RCT pramipexole (0.125-1 mg tid) vs Placebo
    • Decreased Depressive and Motor Symptoms on pramipexole
    • Improved depression independent of motor function
Antidepressant studies

- **Recent placebo-controlled trials**
  - Devos et al 2008, n=48
    - 14 days: Desipramine 75 mg > Citalopram 20 mg, Placebo
    - 30 days: Desipramine = Citalopram > Placebo
  - Menza et al 2009, n=52
    - 8 weeks: Nortriptyline (64 mg) > paroxetine 32 mg, placebo
  - Richard et al (in press) (SAD-PD Study), n=115, 17 sites
    - 12 weeks: Paroxetine (24 mg), venlafaxine XR (121mg) > Placebo
    - Remitters (Ham-D ≤ 7 at week 12): PAR=44%, VEN=37%, PLB=32%
    - Responders (Ham-D ≥ 50% ↓ baseline to Week 12)
      - PAR=68%, VEN 53%, PLB 44%
Antidepressants are Effective for PD-Depression, but Response often Incomplete

- **N=52, Major Depression/Dysthymia + PD**
  - 8 week trial: Nortriptyline vs paroxetine vs placebo
  - Clinical response: 50% reduction in Ham-D score
    - Nortriptyline superior to placebo and paroxetine
    - 16 responders (3 paroxetine, 4 Placebo, 9 NTP)
    - 36 nonresponders (15 paroxetine, 13 placebo, 8 NTP)

- Responders
  - Sig improved Mood, middle insomnia, interest, somatic anxiety

- Residual symptoms in Responders
  - >50% depressed mood, lack of interest, psychic anxiety, low energy

Menza et al., Neurology 2009; Dobkin et al., AGJP 2010
Important Side Effects/Interactions

- Potential for hypertensive Crisis or Serotonin Syndrome
  - Selegeline, Rasageline plus MAO’s

- Orthostasis
- GI Upset
- Sedation
- Anticholinergic side effects
- Benzodiazepine side effects

- Increased parkinsonism
  - Antidepressants (+)
  - Lithium
  - Sodium Valproate
  - Amoxapine
  - Neuroleptics
Conclusions

- **Depressive Disorders**
  - Common in PD over its course
  - Have a negative impact
  - Are under-recognized
  - Have features that overlap with motor symptoms of PD as well as other psychiatric conditions
  - Are treatable

- Treating depressive disorders effectively, and to remission, reduces excess disability