Expert Briefings

Parkinson's Foundation

Mental Health and PD

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September 18, 2018 1pm ET

Better Lives. Together.

Disclosures

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Consultancies (< 2 years)
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

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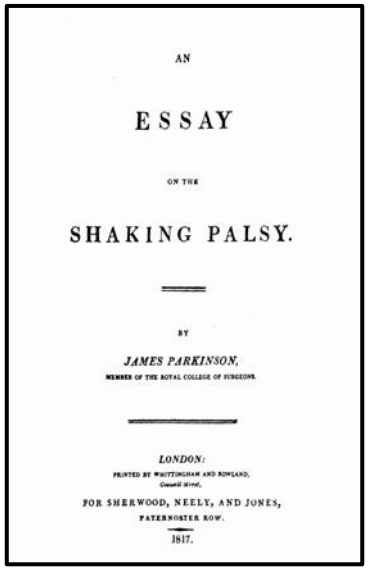
- Describe relationships between motor, cognitive, and psychiatric dysfunction in Parkinson's disease (PD) over the course of the disease.
- List the common psychiatric diagnoses seen in patients with PD.
- Describe appropriate treatments for neuropsychiatric disturbances in PD.

James Parkinson 1755 - 1828



AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,

MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:

PRINTED BY WHITTINGHAM AND ROWLAND,

Crane Court,

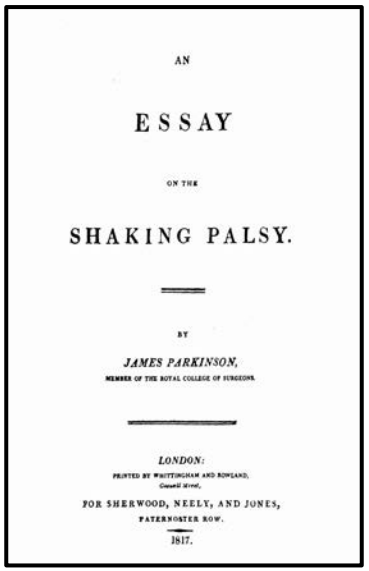
FOR SHERWOOD, NEELY, AND JONES,

PATERNOSTER ROW.

1817.

"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;
…

James Parkinson 1755 - 1828



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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."

The Complex Face of Parkinson's Disease

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- **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)

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

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?

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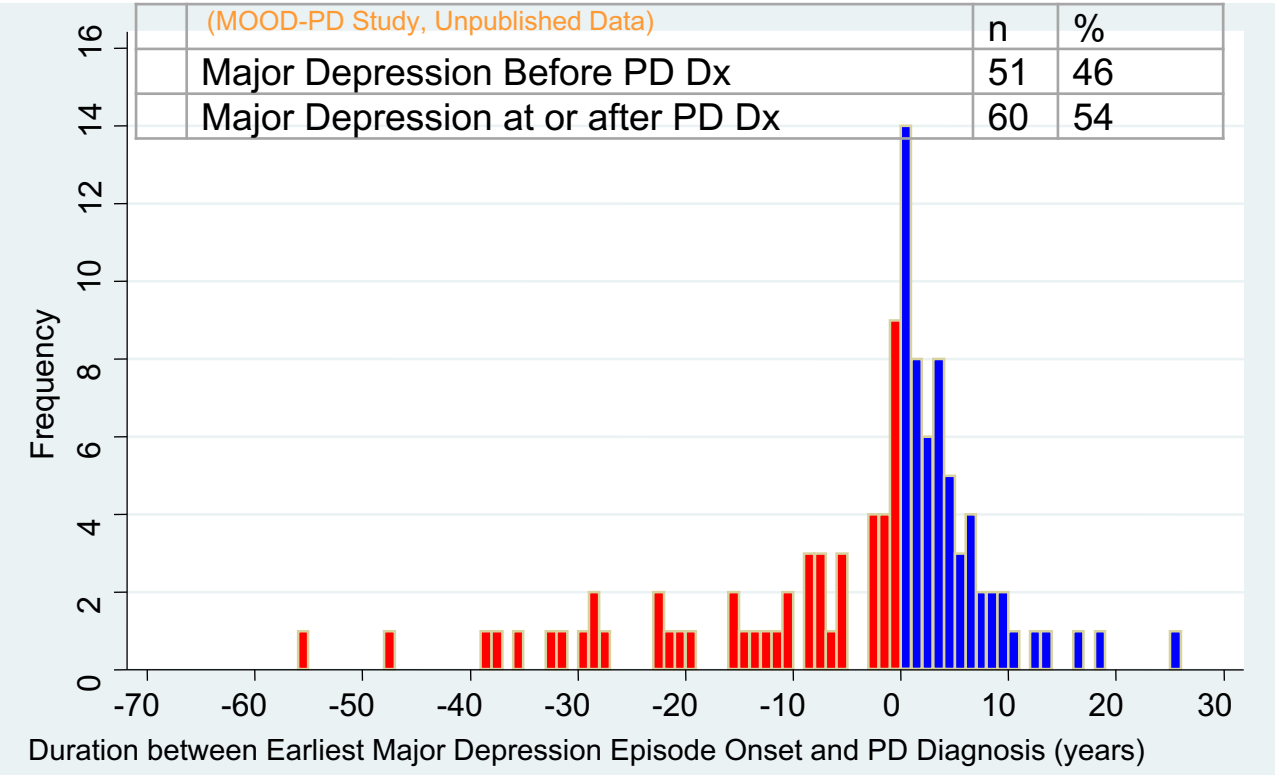

– On average, depression precedes PD by 4 to 6 years

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

PD Treatments

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- 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

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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

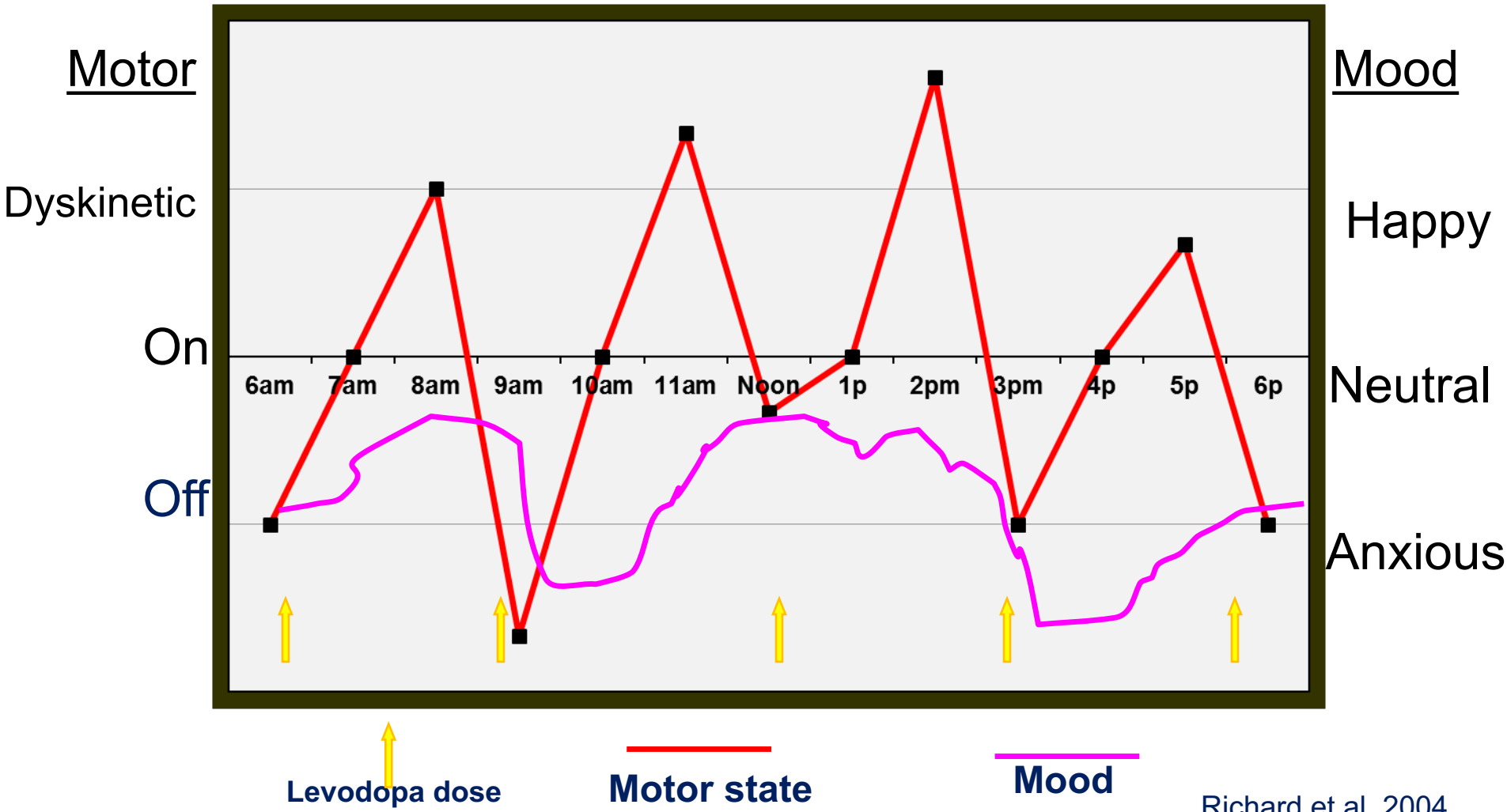
- Slowed thinking, mental hyperactivity, impaired memory, mental emptiness
- Off-Anxiety (81%), Off-depression (63%), On-hypomania (24%), irritability, psychosis

Sensory/Vegetative

- Fatigue, akathisia, tightening sensations, tingling, pain

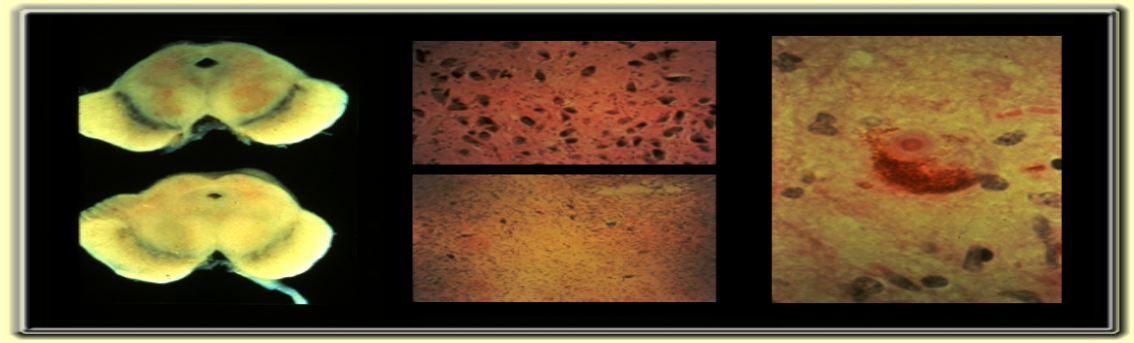
Witjas 2002; Racette 2002.

Levodopa-related Fluctuations

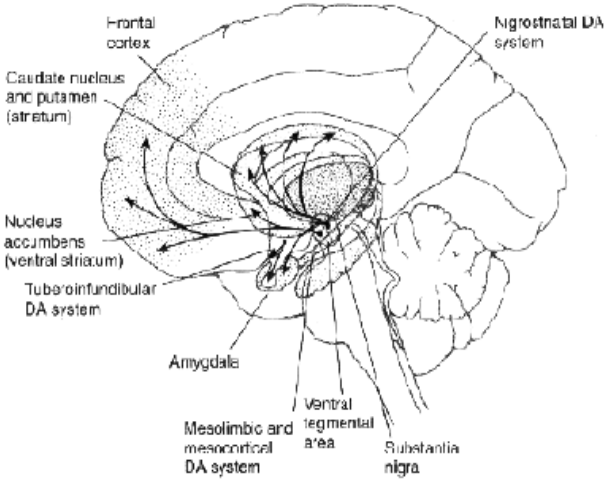


Richard et al, 2004

Neuropathology Influences Psychopathology



Primary Dopamine Deficiency
Affects Mesostriatal, Mesolimbic & Mesocortical DA Systems



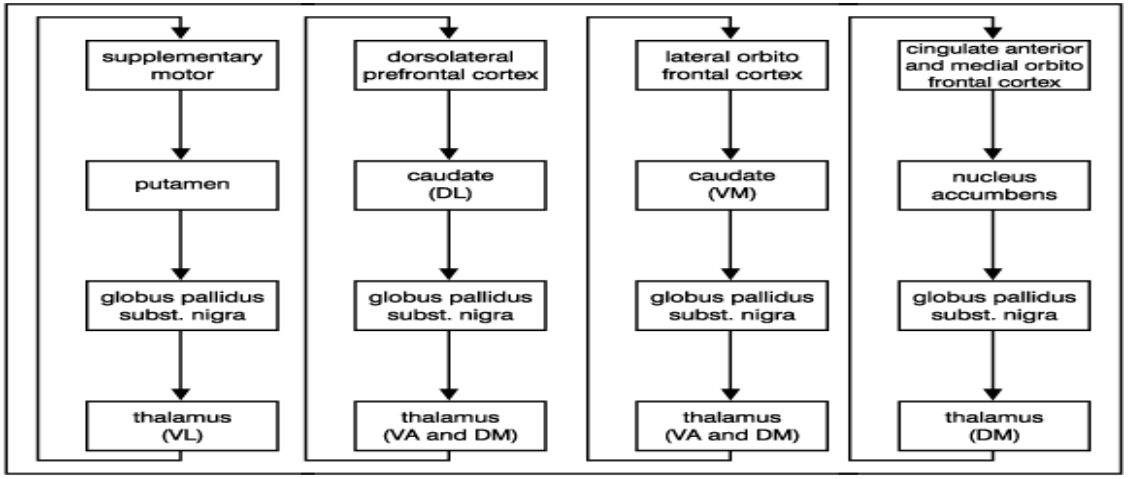
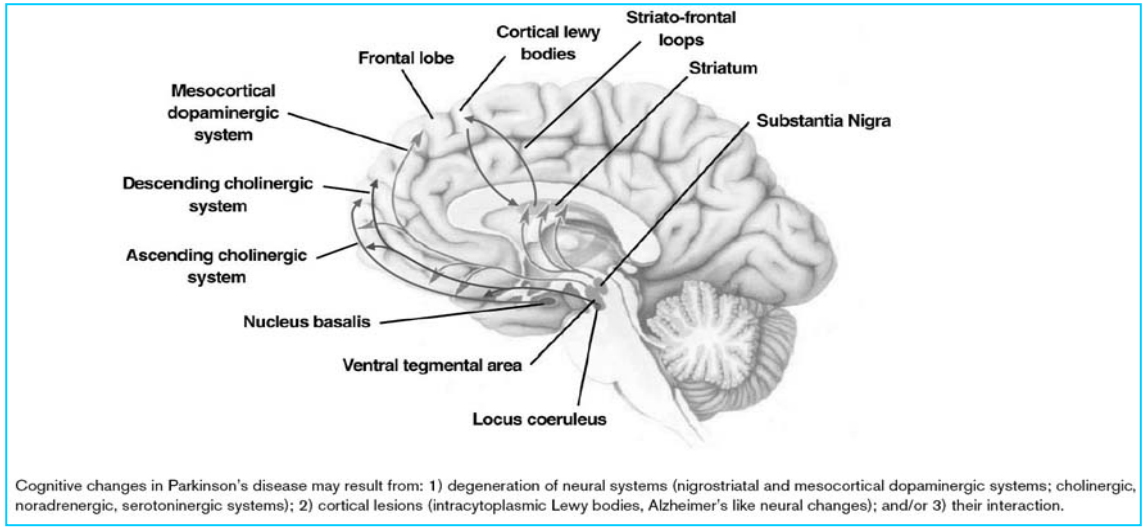


Figure 1 - Frontal-striatal connections.
DL: dorsolateral; DM: dorsomedial; VL: ventrolateral;
VA: ventroanterior; VM: ventromedial.

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

Non-dopaminergic Neuropathology

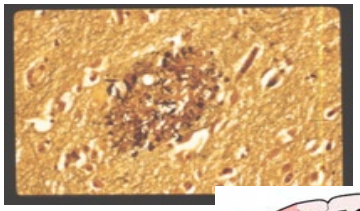


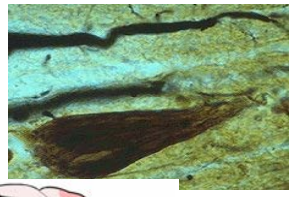
Cognitive changes in Parkinson's disease may result from: 1) degeneration of neural systems (nigrostriatal and mesocortical dopaminergic systems; cholinergic, noradrenergic, serotoninergic systems); 2) cortical lesions (intracytoplasmic Lewy bodies, Alzheimer's like neural changes); and/or 3) their interaction.

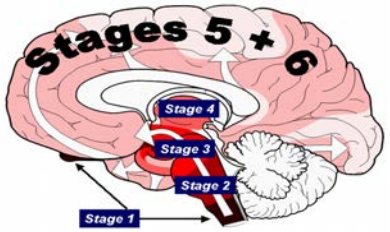
Neuronal loss

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

Alzheimer-type Changes







Lewy Body Pathology

PD Non-Motor Symptom Complex

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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

Chaudhuri KR, Lancet Neurology, 2006

PD Progression Involves Treatment of Motor and Non-motor Symptoms

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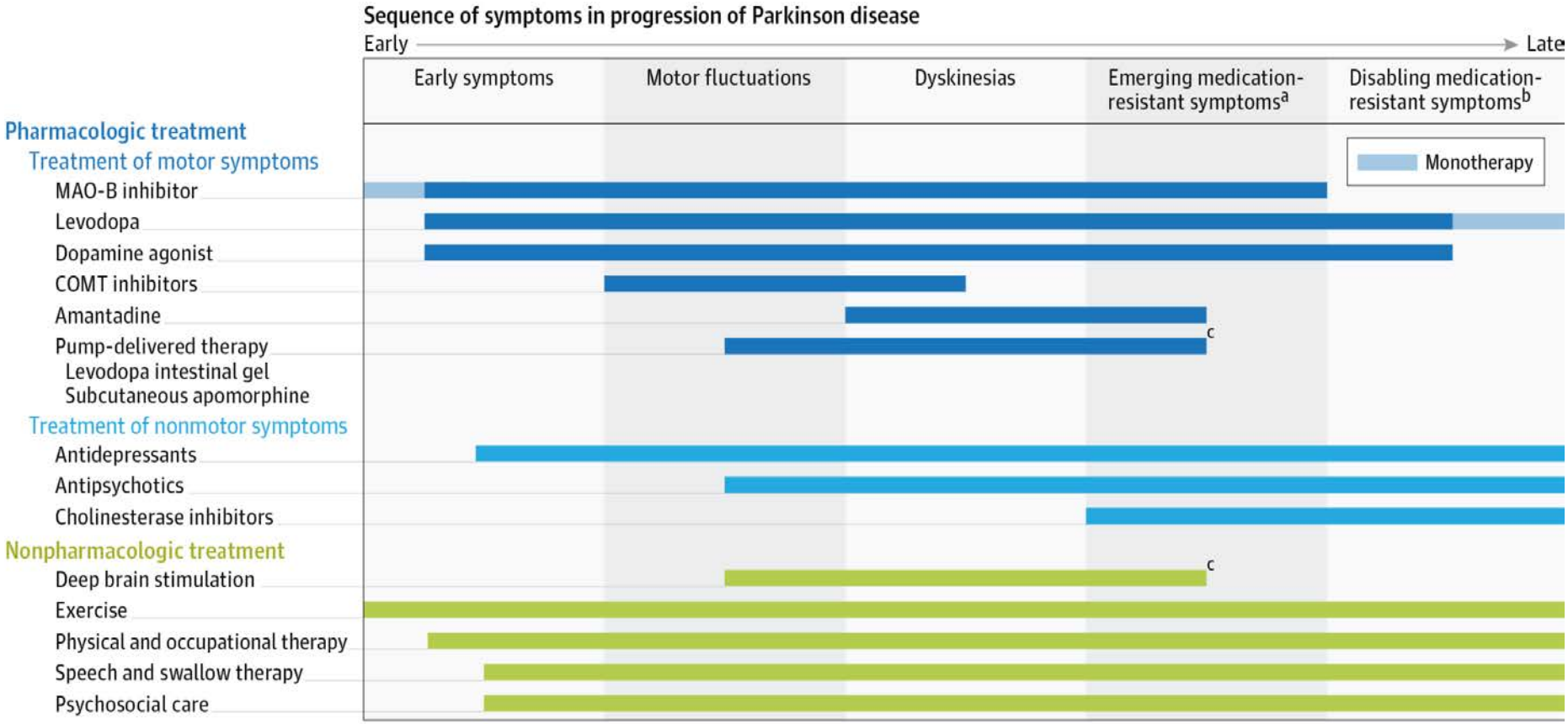


Bars indicate approximate periods of initiation and duration of each treatment except where noted. COMT indicates catechol-O-methyl transferase.

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.

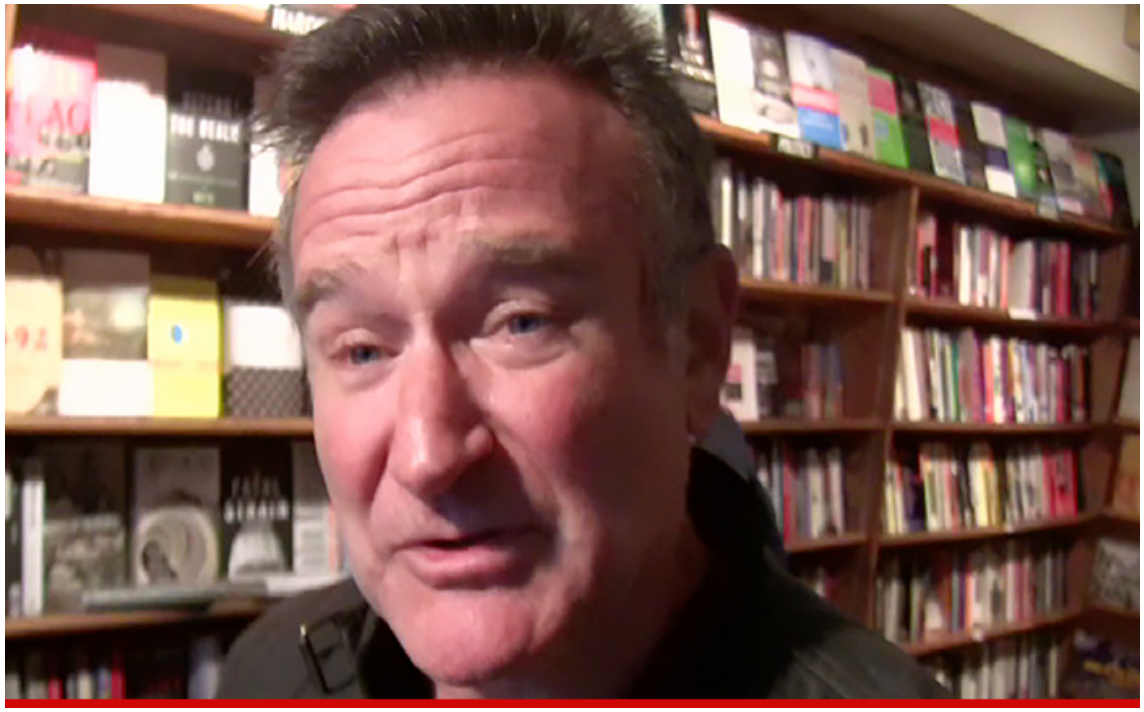
[a] Gait dysfunction, soft speech (hypophonia), and memory and cognitive problems.

[b] Dysphagia, falls, and memory and cognitive problems.

[c] 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

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↑ 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

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

Hely et al, 2005, 2008

Depressive Symptoms Influence when Antiparkinsonian Treatment is Started

NET-PD Study/Neuroprotective Treatment Trials

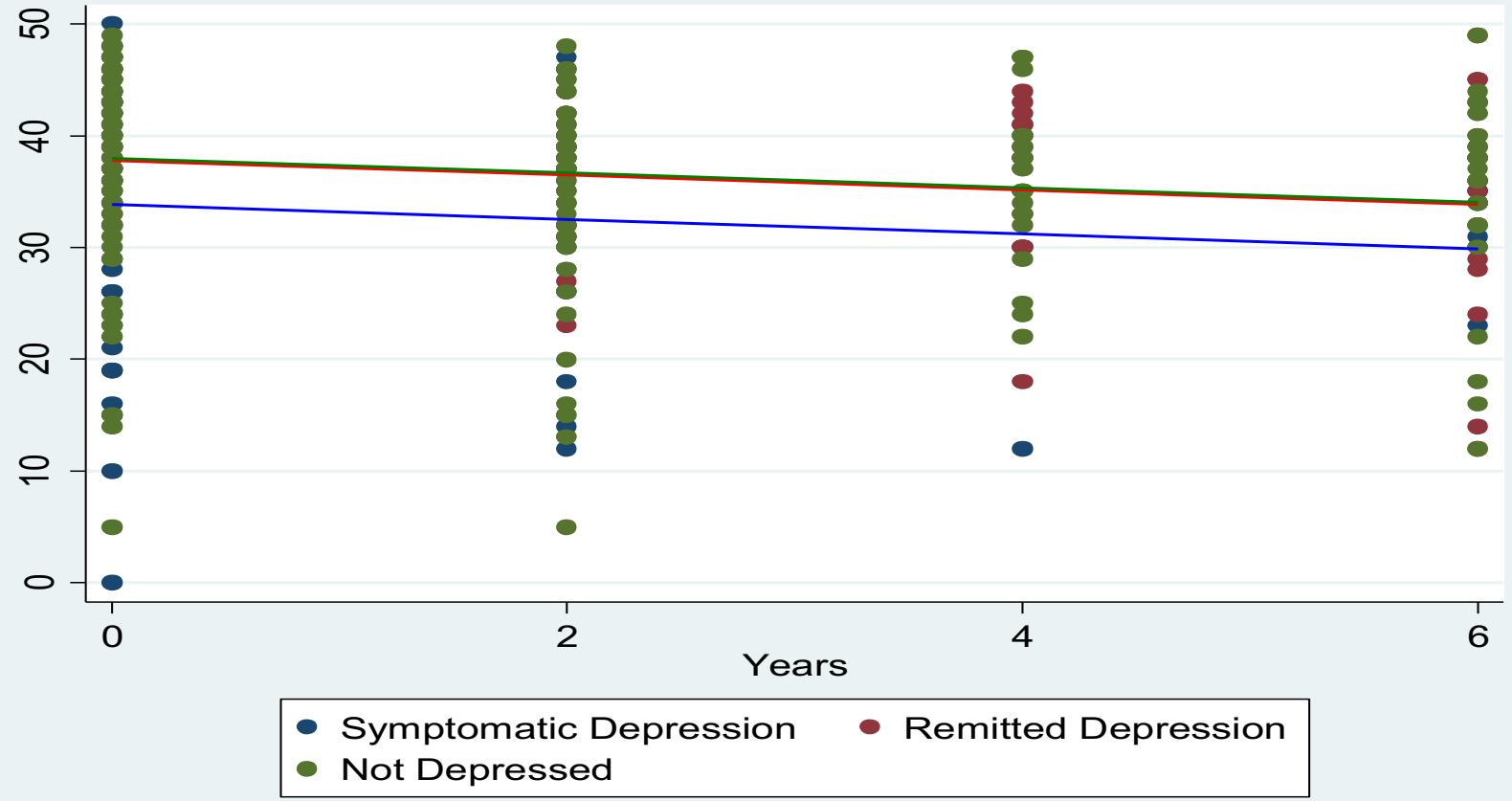
n=413, early untreated for PD with dopaminergic or other PD meds

- Depression Screen: Geriatric Depression Scale (GDS-15) ≥ 5
  - 27.6% +ve 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% CI 1.29-2.68)

Ravina et al., 2007

Depression Remission Improves Physical ADLs in PD (n=136)



Marsh et al, 2007; Pontone et al, 2015

Up to 2/3 of PD-Depressive Disturbances Under-recognized or Under-treated

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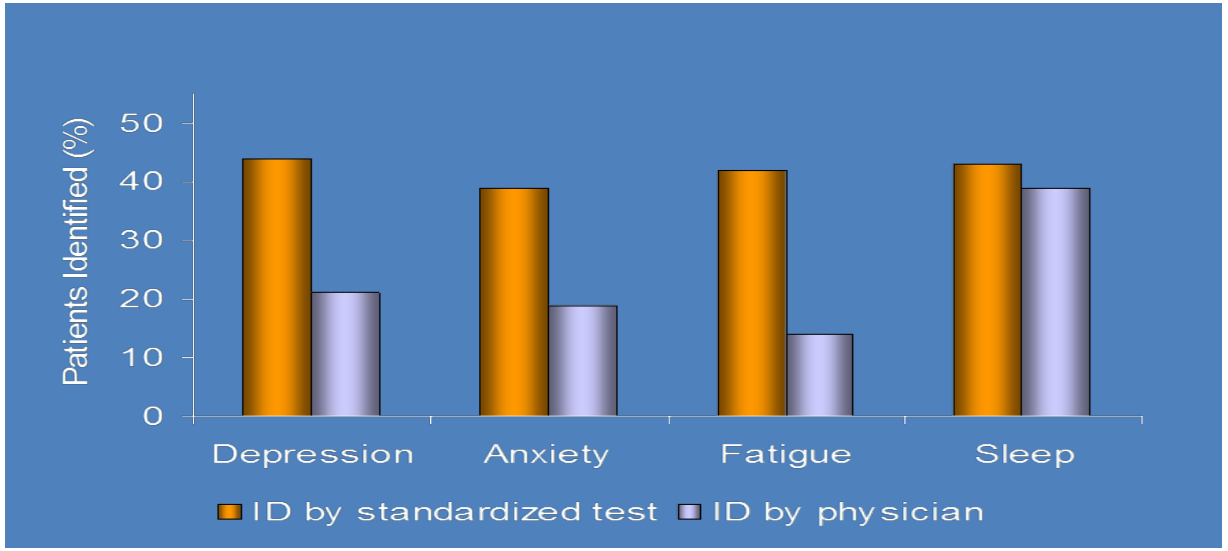
1. Shulman 2002, n=101 PD



2. Weintraub 2003, n=100 PD

34% DSM Depressive Disorder; 2/3 were not receiving treatment

3. Hoek et al. 2011, n=256 PD

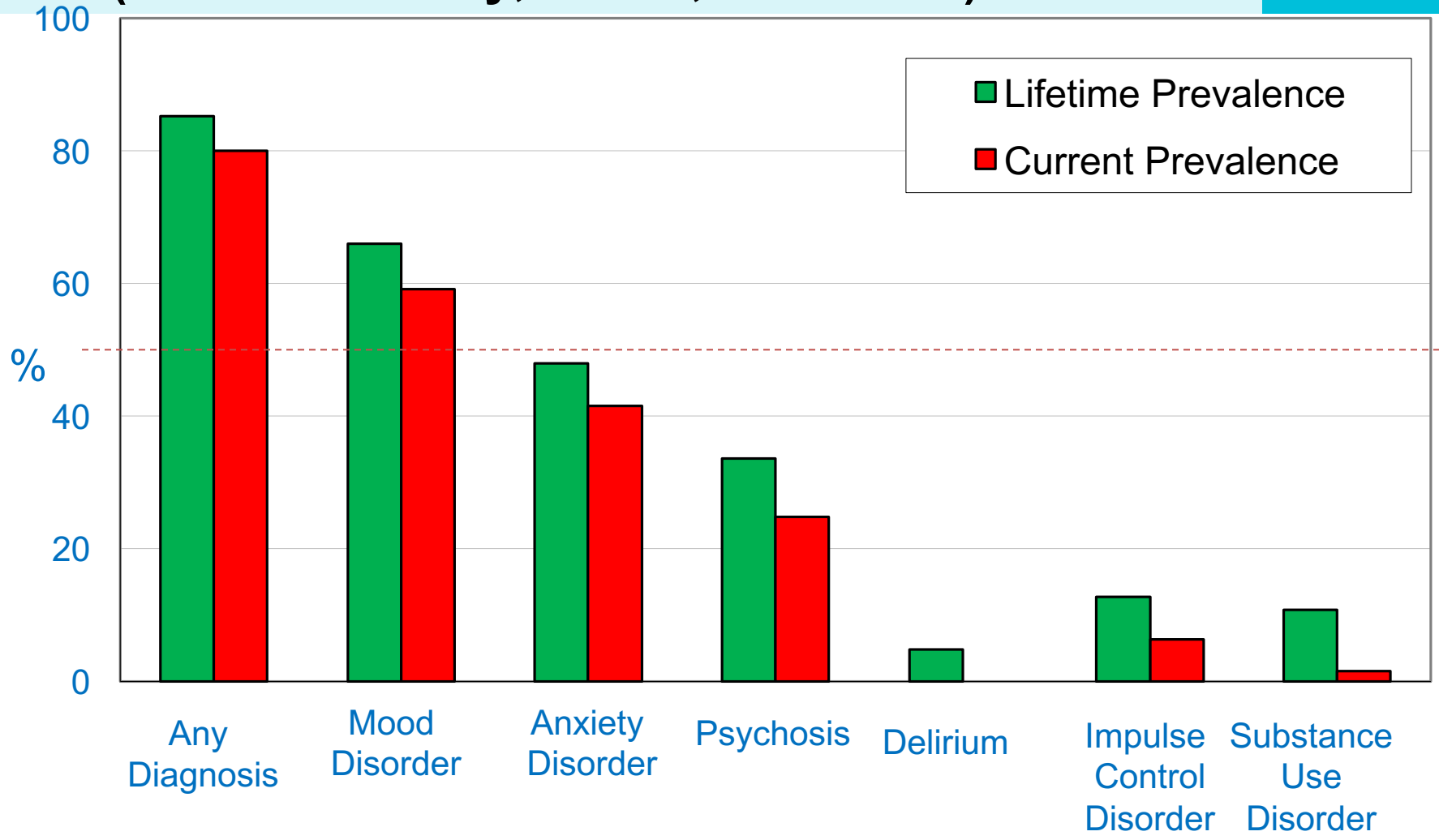
36.3% minor depression with 8.6% treated

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

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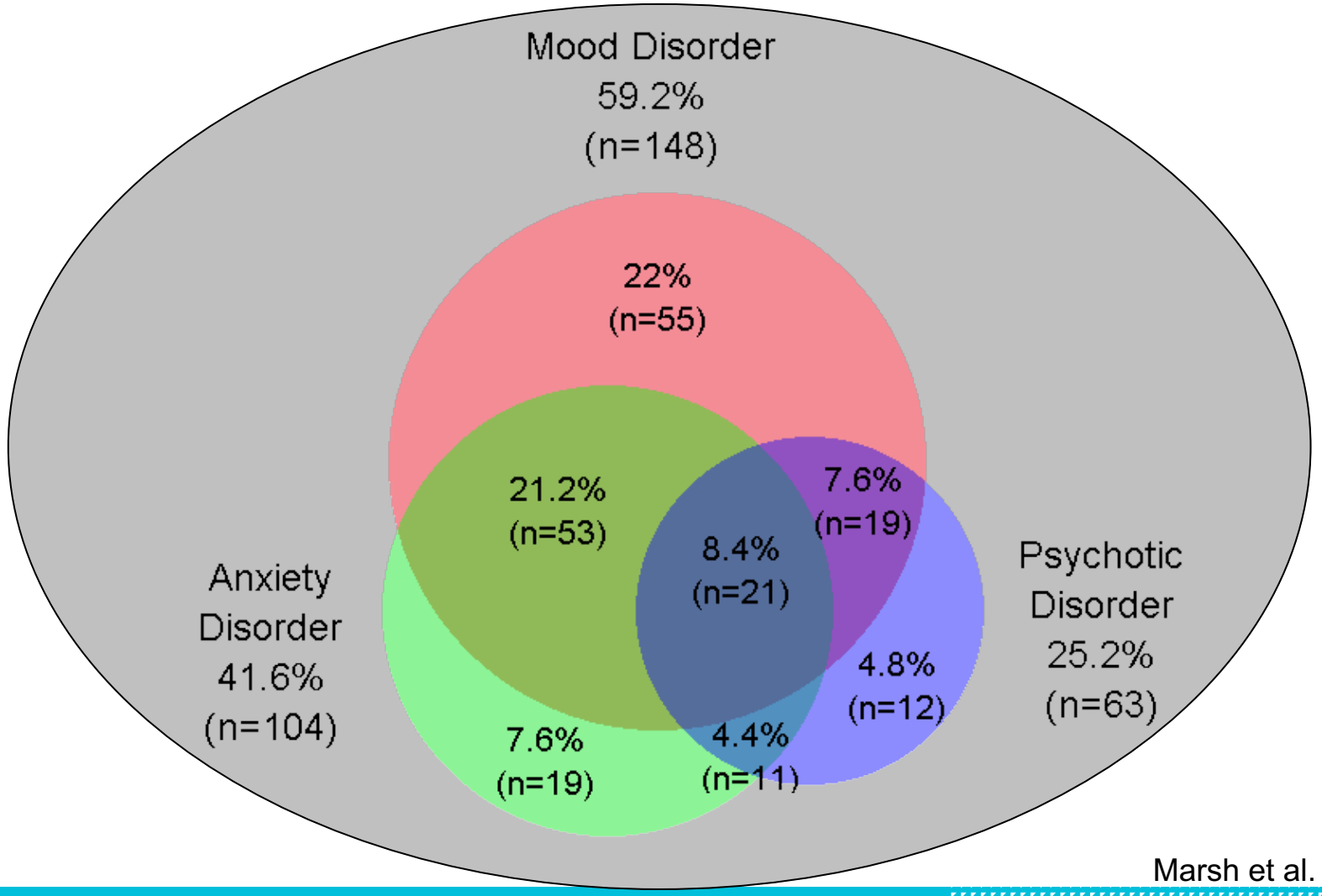
% of total sample (n=250) with psychiatric dx



Marsh et al. Unpublished

Other Psychiatric Diagnoses Independent or Co-morbid with Depression

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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

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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

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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

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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

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- **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

Kummer et al. 2008; Maricle et al. 1995, Witjas et al. 2002, Arabia 2007

Prevalence of Specific Anxiety Disorders

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

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

Nonmotor Fluctuations

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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

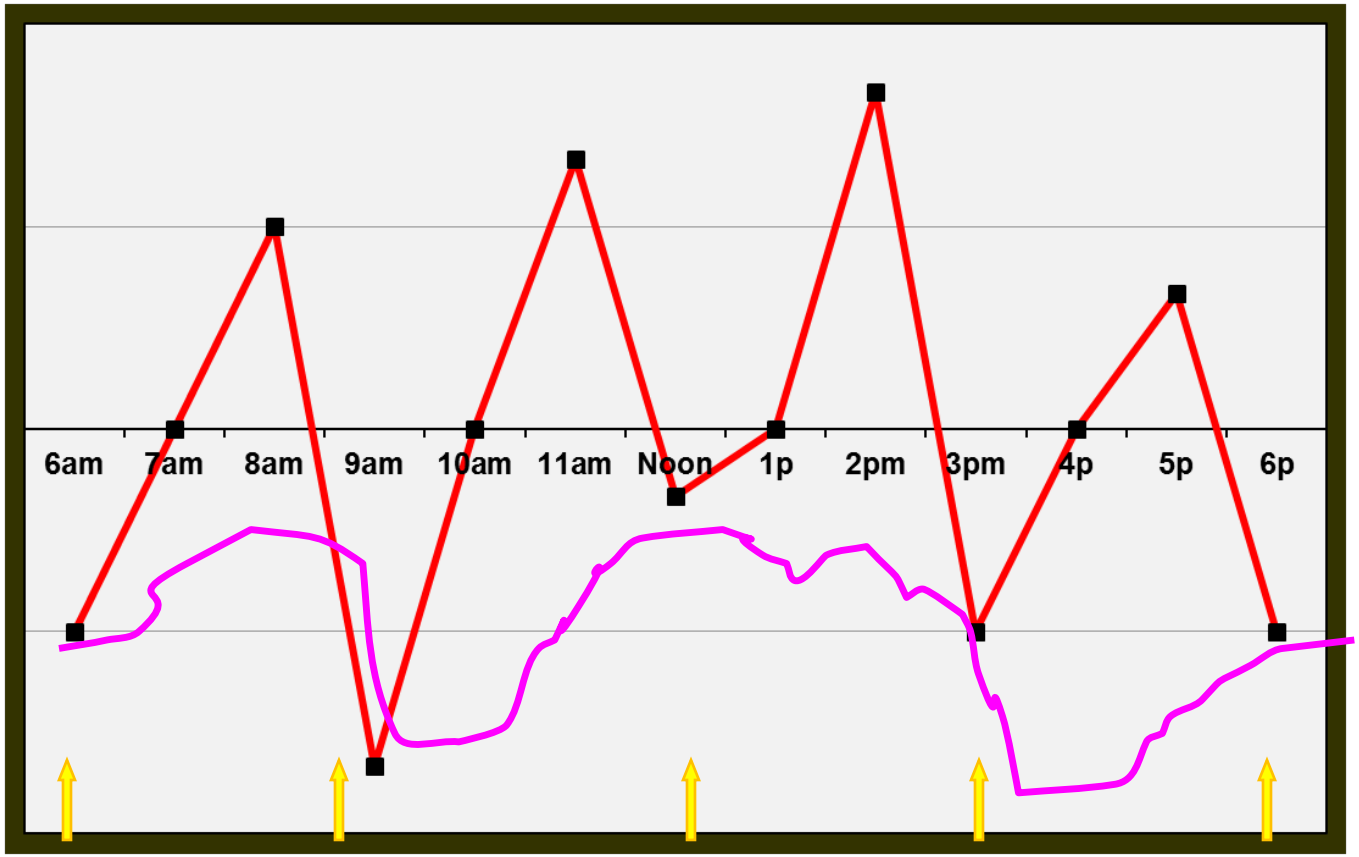
- Slowed thinking, mental hyperactivity, impaired memory, mental emptiness
- Off-Anxiety (81%), Off-depression (63%), On-hypomania (24%), irritability, psychosis

Sensory/Vegetative

- Fatigue, akathisia, tightening sensations, tingling, pain

Witjas et al, Neurology 2002; 59: 408-413; Racette et al., J Neuropsychiatry Clin Neurosci 2002; 14: 438-442.

Fluctuating Motor and Non-Motor Symptoms



Levodopa dose

Motor state

Mood

Richard et al, 2004

Anxiety Disorders Non-Psychiatric Impact

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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

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	Depression	Anxiety
Parkinsonism	Decreased facial expression Psychomotor changes – Slowness, motor restlessness	On-off fluctuations Restlessness Insomnia
Somatic	Pain, Muscle tension Fatigue, energy loss Insomnia, Decreased appetite Weight Loss	Muscle tension, Fatigue Autonomic Symptoms Insomnia
Cognitive Impairment	Executive dysfunction Decreased memory & Concentration	Executive dysfunction Decreased concentration
Other Psychiatric Symptoms	Anxiety, ICDS, Apathy, Psychosis	Depression, ICDs, Psychosis

Psychological Features of Anxiety

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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, Benzodiazapines

Clinical Features

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

Psychosis (Hallucinations and Delusions)

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I. Prevalence

- Depends on definition of psychosis, PD, and cognitive impairment
- ~ 8%–40% reported rates[1]
  - ~ 5%–17% without significant dementia
  - ~ 42%–81% with significant dementia
- Persistent and progressive[3]

II. Impact[2]

- 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

Greene P, et al. 1993; 60:703-706; [2] Factor SA, et al. 2003; [d]de Maindreville AD et al. 2005

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)

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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

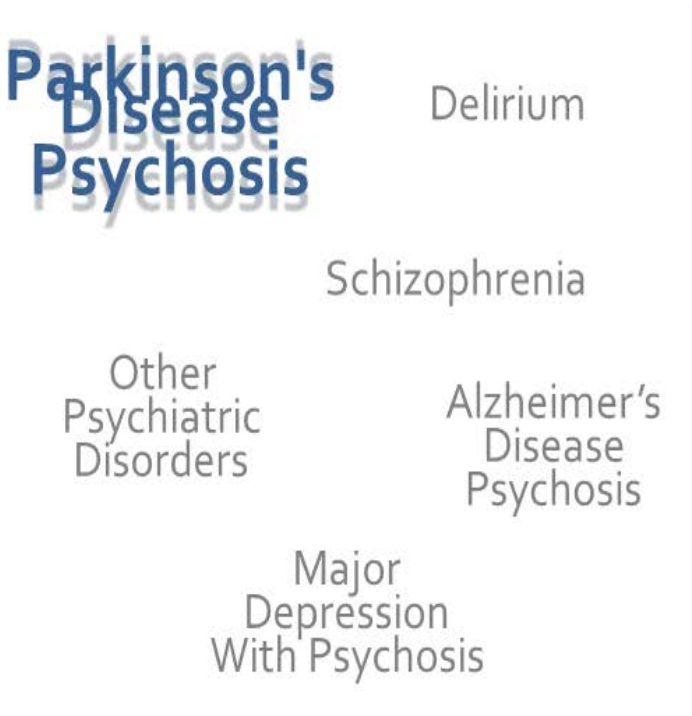
– Recurrent or continuous for ≥ 1 month

Other causes excluded

– Differential diagnosis

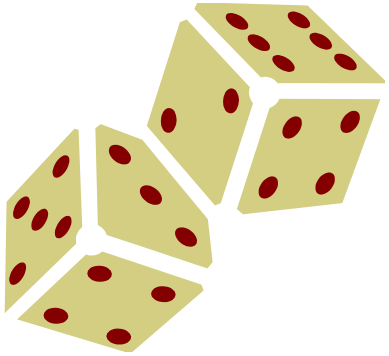
Associated features

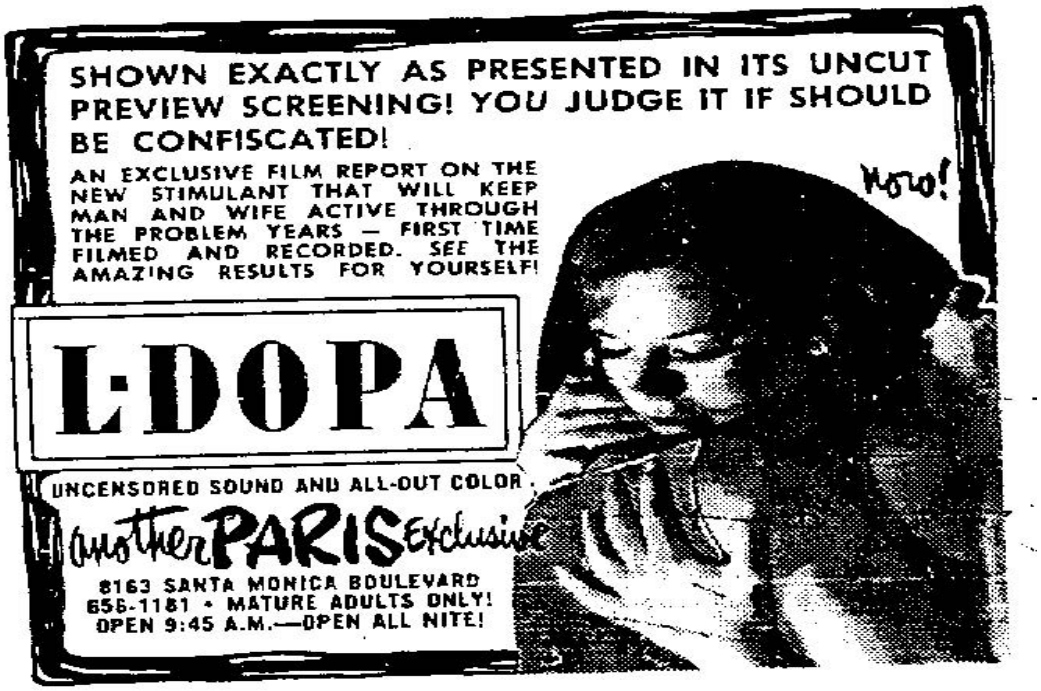
– With or without insight, dementia, or Parkinson's disease treatment



Ravina B, et al. *Mov Disord*. 2007;22(8):1061-1068.

PD-Specific Disturbances





(NEJM, 1970)

Risk Factors for PDP

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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

1. Connolly B, Fox SH. *Neurotherapeutics*. 2014;11(1):78-91. 2. Goldman JG, et al. *Expert Opin Pharmacother*. 2011;12(13):2009-2024. 3. Huot P, et al. *Mov Disord*. 2010;25(10):1399-1408.
4. Ballanger B, et al. *Arch Neurol*.. 2010;67(4):416-421. 5. Marsh L, et al. *Neurology*. 2004;63(2):293-300. 6. Lenka A, et al. *Parkinsonism Relat Disord*. 2016;22:1-8.
7. [illegible] *Curr Treat Options Neurol*. 2010;12(3):200-211. 8. Marsh L. *Primary Psychiatry*. 2005;12(7):56-62. 9. Fénelon G, et al. *Mov Disord*. 2010;25(6):768-766.

PD-specific Medication-related Mood Syndromes

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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

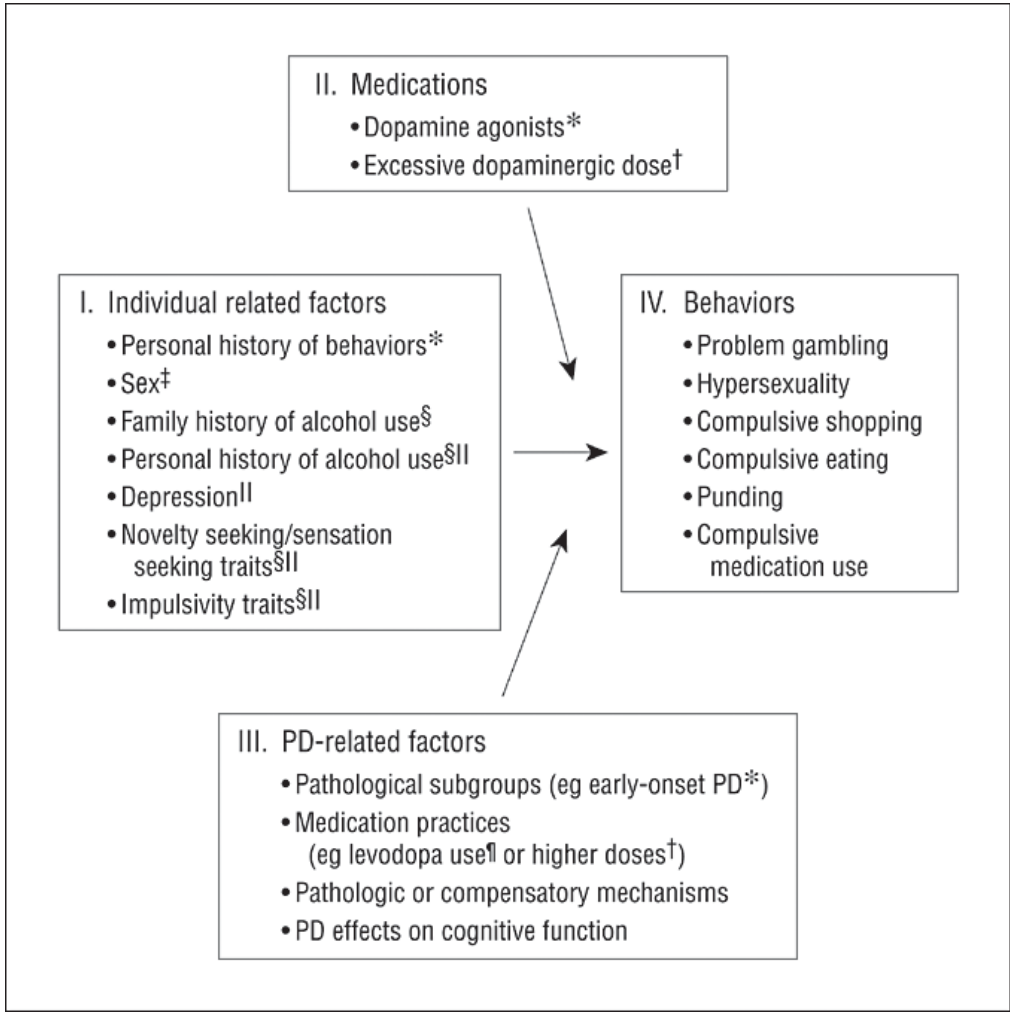
3) On-off Motor and Non-motor fluctuations (Racette 2002)

Impulse Control and Behavioral Disorders

Disturbance	Prevalence
Pathological Gambling	3-8%
Hypersexuality	2.5%
Pathological Shopping	0.4-1.5%
Punding	1.5-14%
Compulsive Dopaminergic Med Use	3.4-4%

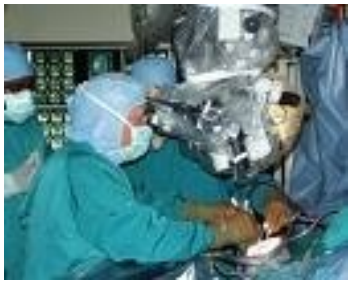
Voon, V. et al. Arch Neurol 2007;64:1089-1096.

Factors associated with Impulse Control Disorders



Treatment

Treatment
General Approaches



1. Treatment Works - People Recover

2. Targeted and Individualized Approach

Targeted and Individualized Treatment

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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)

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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

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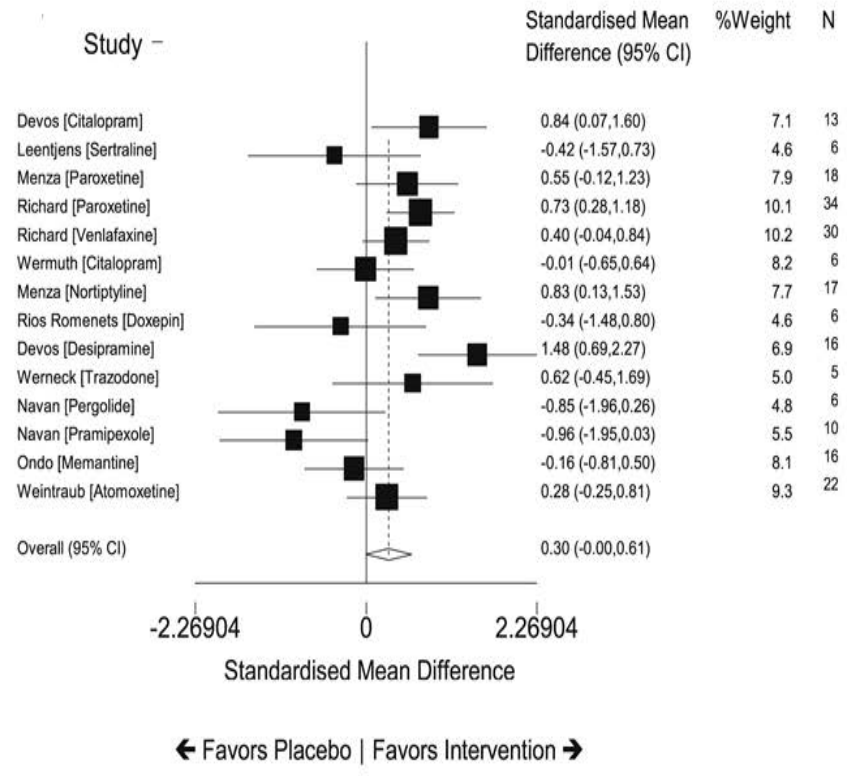
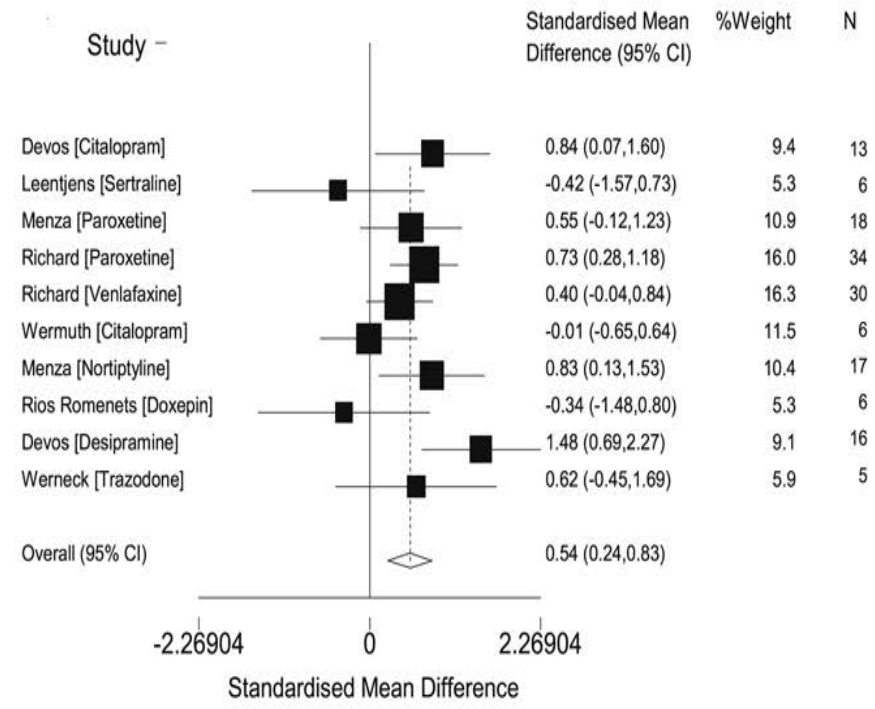
ALL INTERVENTIONS SMD=.30



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

ANTIDEPRESSANTS SMD=.56



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

Bomasang-Layno 2015

Residual Symptoms Can Persist Despite Antidepressant Medication Response

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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

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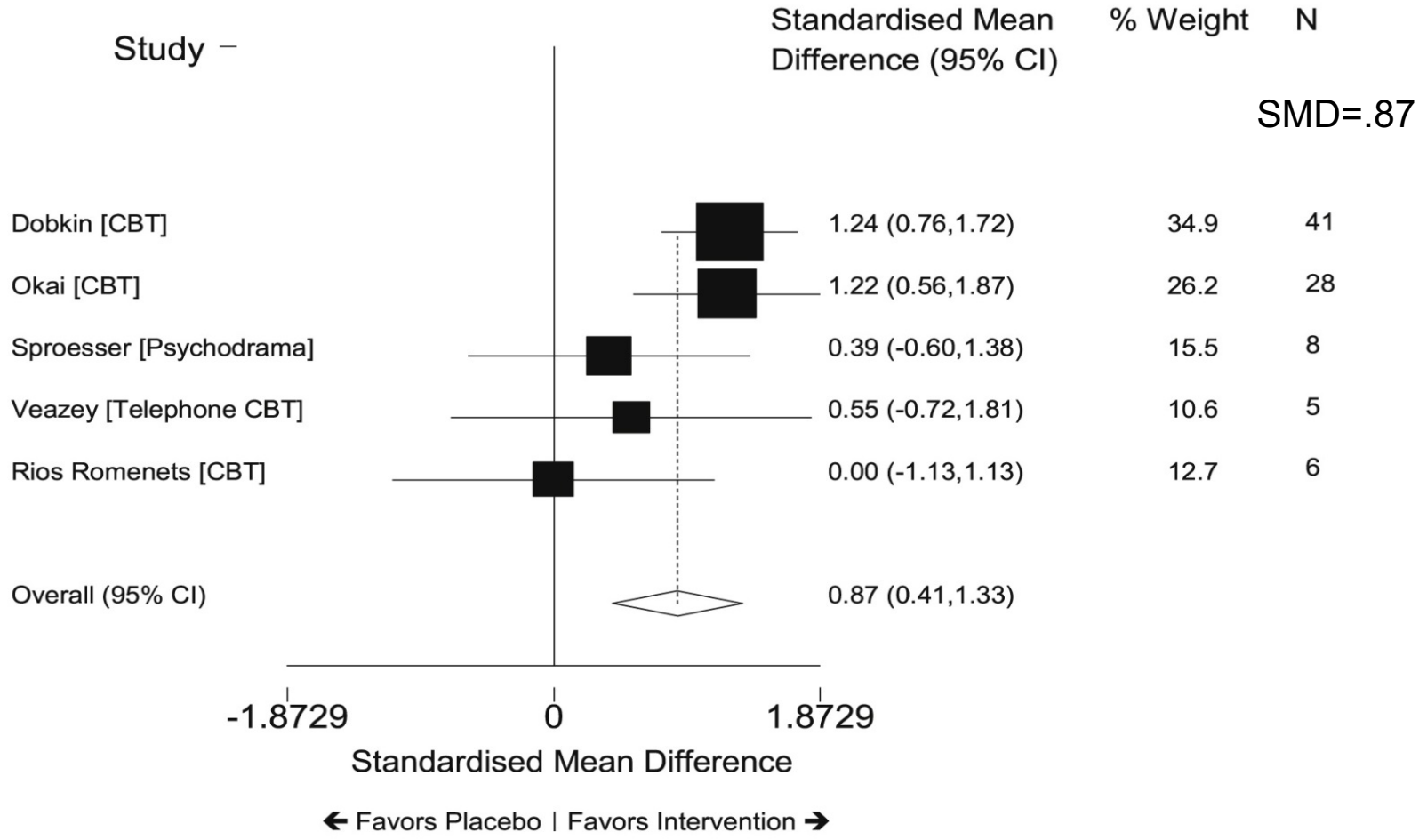

Test of SMD=0 : z= 3.72 p = 0.000

Bomasang-Layno 2015

Psychosis Treatment
Adjust/Eliminate Select PD Meds

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Discontinue First

Anticholinergics
Selegiline/Rasagaline
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*

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Treatment for Psychosis		Efficacy	Safety	Practice Implications
MDS evidence-based medicine review designations (2011)[1]	Clozapine	Efficacious	Acceptable risk with specialized monitoring	Clinically useful†
	Olanzapine	Unlikely efficacious	Unacceptable risk	Not useful†
	Quetiapine	Insufficient evidence	Acceptable risk without specialized monitoring	Investigational†
FDA- approved for PDP (2016)[2]	Pimavanserin	Efficacious[3]	No treatment-related impairment of motor function[3]; increase in QT interval without association to cardiac events[3]	Clinically useful

* Black box warning for typical and atypical antipsychotics in elderly patients who have dementia-related psychosis[4]

† Not FDA approved for the treatment of PDP

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

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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!

- **M**edication, **E**ducation, **S**kills, **S**upport **(MESS)**
- Treat assiduously and to remission to reduce excess disability
- Address caregiver burden and quality of life
- Interdisciplinary coordinated teams


Thank You

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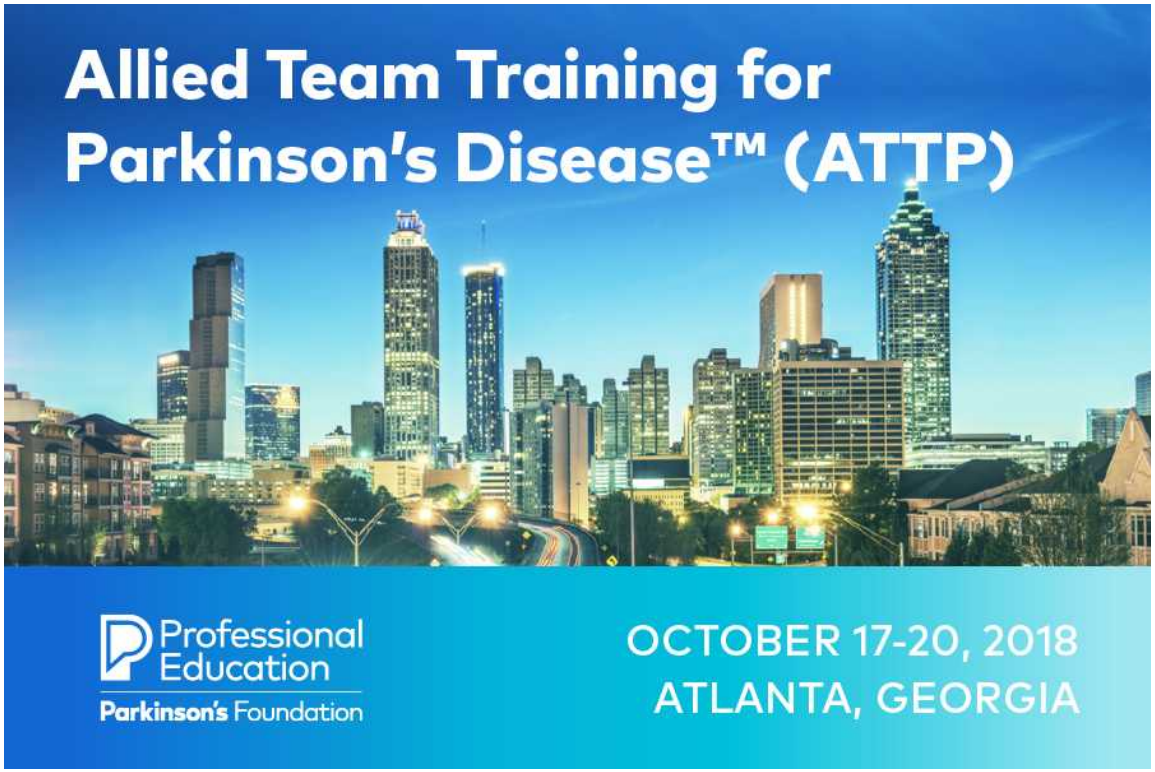

Resources

Expert Briefings
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National Helpline

Available at
1-800-4PD-INFO or
Helpline@Parkinson.org
Monday through Friday
9:00 AM – 6:00 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