Assessment and Management of Psychiatric & Cognitive Complications in Parkinson's Disease

Daniel Weintraub, M.D.

Assistant Professor of Psychiatry,
University of Pennsylvania;
Parkinson's Disease and Mental Illness Research, Education and Clinical Centers (PADRECC and MIRECC),
Philadelphia VA

Introduction

Common Psychiatric and Cognitive Disorders

- Depression
- Psychosis
- Cognitive impairment / dementia
- Impulse control disorders (ICDs) and related behaviors
- Anxiety
- Disorders of sleep and wakefulness
- Pseudobulbar affect (i.e., IEED)

Depression

Prevalence

- Widely varying estimates
  - Neurology clinics vs. population-based
- Fluctuating course in some
- **20-40%** is accepted range for all types of depression
    - Major depression ≈ 5-20%
    - Other forms of depression ≈ 10-30%
  - Higher than in elderly in general, and *probably* than in other neurodegenerative or chronic diseases

Impact of Depression on Functional Ability (UPDRS ADL Score)

Variable	Coefficient b	Standard error (b)	t	P
Constant	47.5	9.1	5.2	<.001
HDRS	**0.5**	**0.1**	**4.4**	**<.001**
MMSE	-1.4	0.3	-4.2	<.001

Forward stepwise regression method **including UPDRS motor score**, Hoehn and Yahr stage, and duration of PD in model

Weintraub et al. *Journal of the American Geriatrics Society* 2004;52:784-788.

Suicidal and Death Ideation in Parkinson's Disease

Variable	Death or Suicide Ideation (n=35)		
	Odds Ratio (Exp[B])	95% Confidence Interval for Odds Ratio	P value
IDS score	**2.76**	**1.88 – 4.07**	**<.001**
Psychosis	1.12	0.37 – 3.43	.84
History of ICD	2.27	0.49 – 10.04	.30

IDS = Inventory of Depressive Symptomatology

Weintraub et al. *Movement Disorders* (in press).

Under- Recognition and Treatment

N=106	Depressed (n=31)	Not Depressed (n=75)
Current Antidepressant Treatment (n=24)	**10 (9%*)**	14 (13%)
No Antidepressant Treatment (n=82)	**21 (20%)**	61 (58%)

*Percentage of entire sample.

Modified data from Weintraub et al. *Journal of Geriatric Psychiatry and Neurology* 2003;16:178-183.

Is Depression in PD Different? Heterogeneity is the Rule

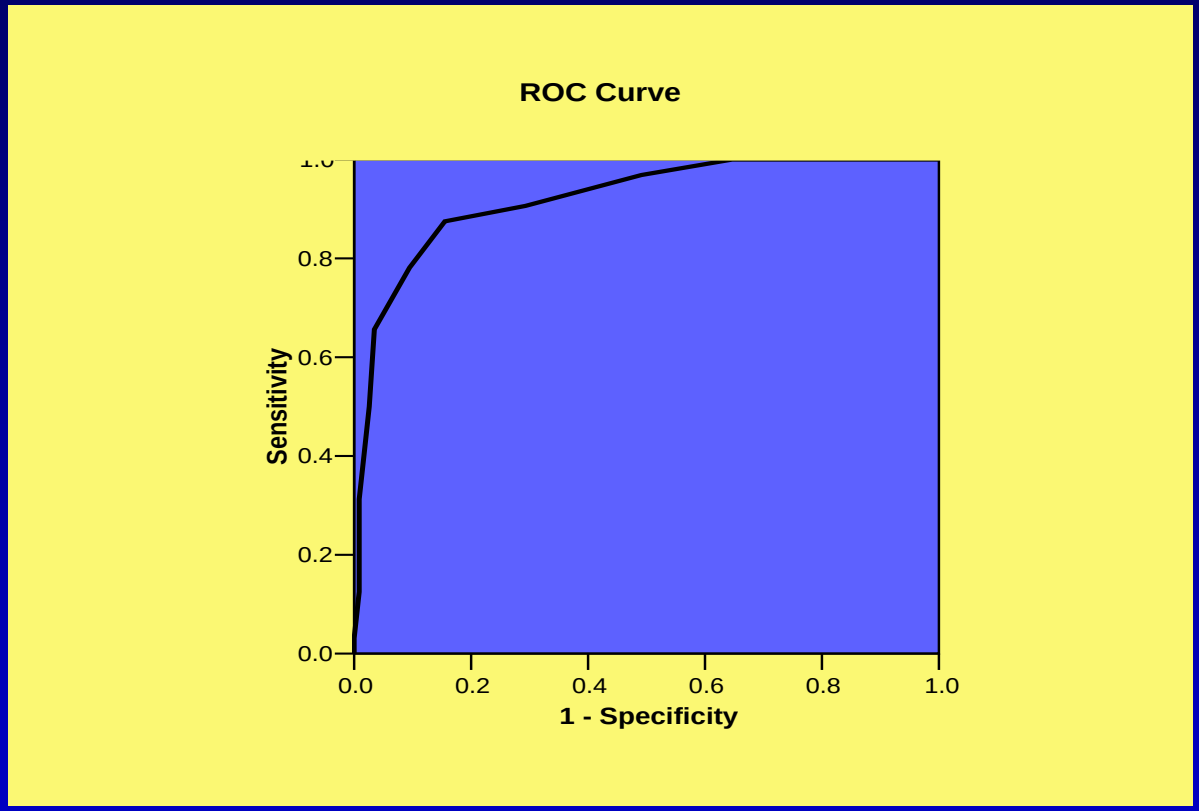
- Stage and severity of PD
- Mix of motor symptoms
- Age
- Cognitive impairment
- Psychiatric co-morbidity
- Range of depression severity
- Specific depressive symptoms
- Treatment effects

The difficulty in distinguishing PD depression from depression in general is in trying to define a single construct of PD depression.

Diagnosing Depression in PD

- Symptom overlap on 5/9 DSM-IV items
  - Sleep (hypersomnia and insomnia)
  - Appetite change / weight loss
  - Psychomotor changes
  - Fatigue
  - Changes in concentration and thinking
- Inclusive vs. etiologic criteria when rating?
  - Applies to both diagnostic criteria and rating scales

GDS-15 for Depression Screening in PD



- GDS-15 score of 5 best cut-off under ROC curve
- 88% sensitivity and 85% specificity

Weintraub et al. *American Journal of Geriatric Psychiatry 2006;*14:169-175.

Meta-Analysis of Antidepressant Studies in PD

Treatment	k	d_+	95% CI	Q_w
Active Treatment	11	+0.93	+0.73<δ<+1.13	29.80*
Placebo	2	+1.18	+0.55<δ<+1.81	0.47

Note: Q_B=0.59, p=0.44

*p<0.001

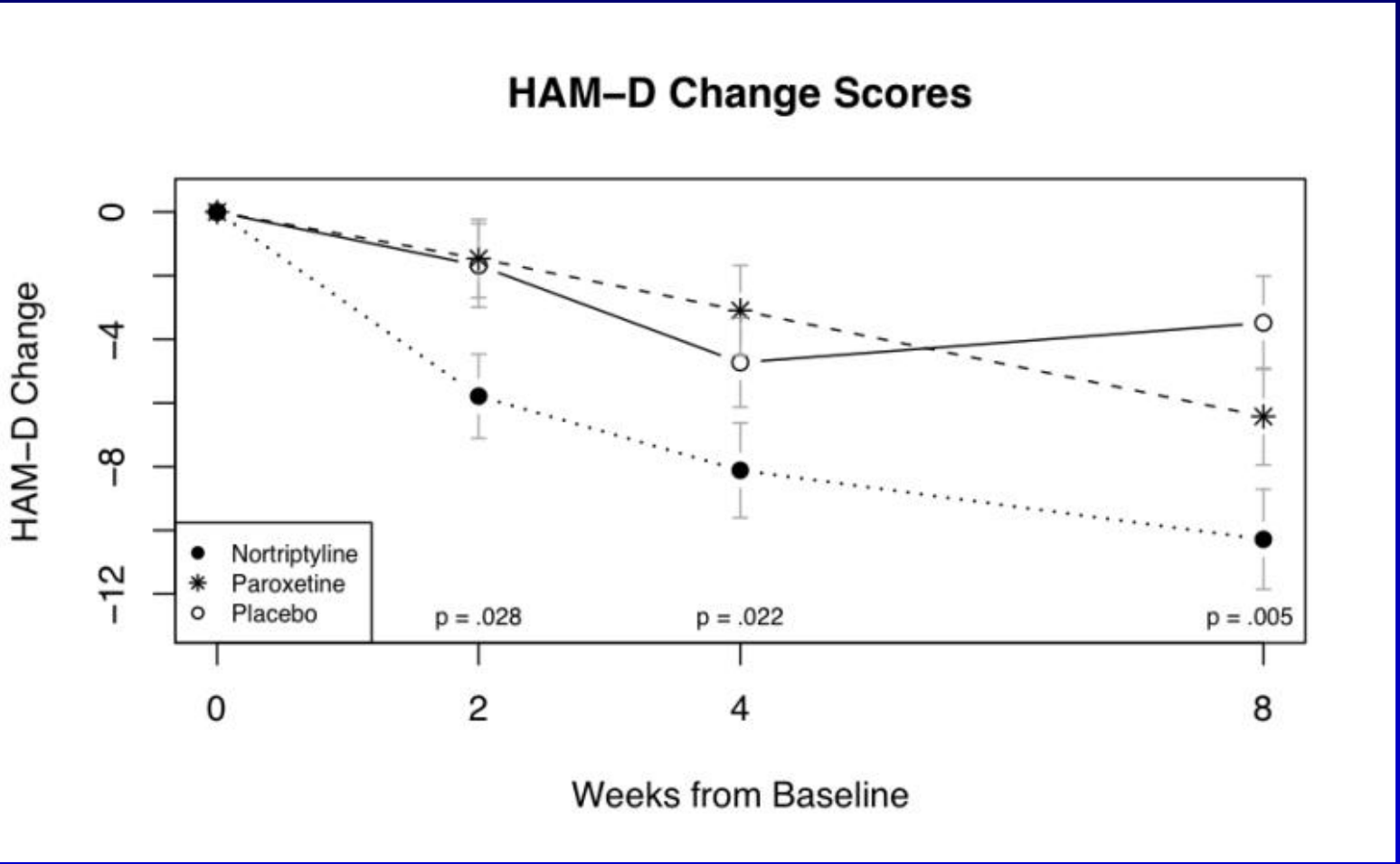
Key: Treatment = active treatment versus placebo administration
k = number of studies in analysis
d_+ = mean weighted effect size
95% CI = 95 percent confidence interval for d_+
Q_w = within-class effect (test for homogeneity)
Q_B = between-class effect

Weintraub et al. *Movement Disorders* 2005;20:1161-1169.

Possible Reasons for Limited SSRI Response in PD

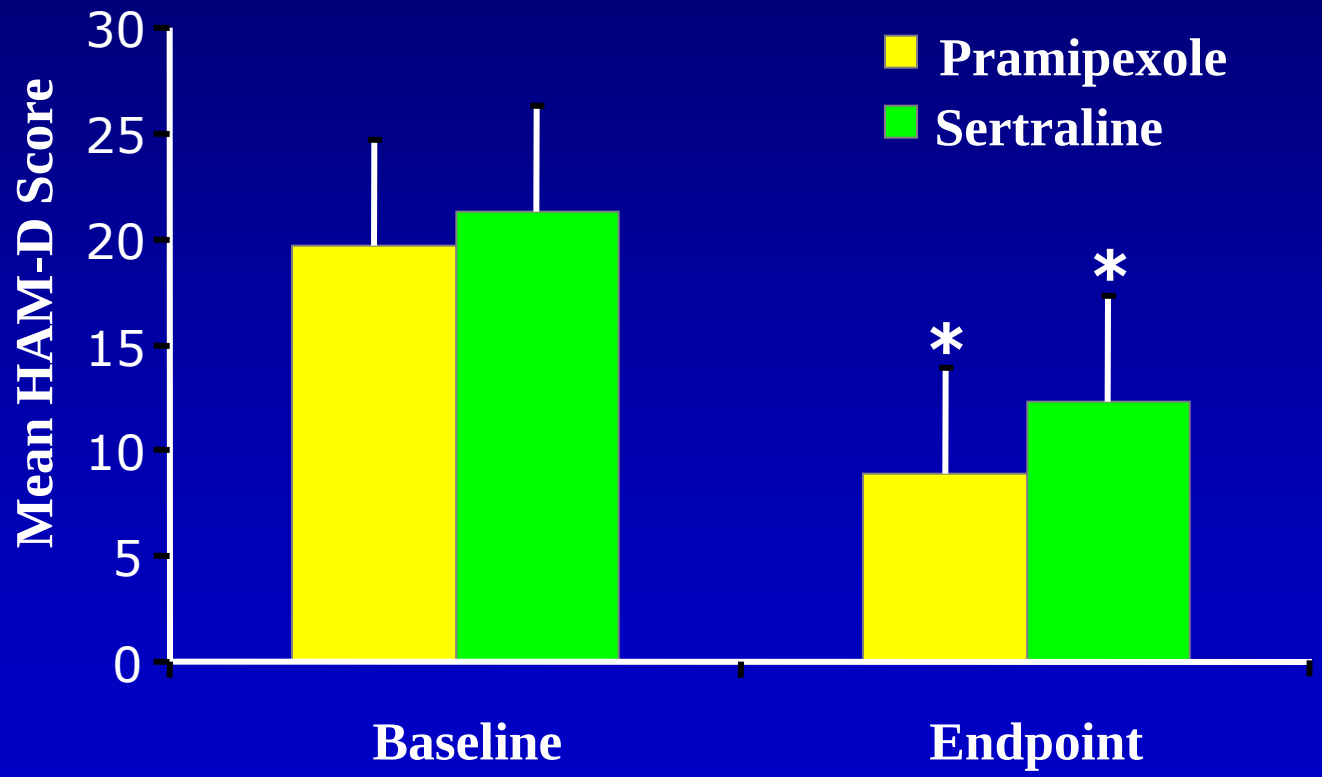
- Misdiagnosis
  - Apathy (instead of anhedonia)
  - Symptom overlap
- Serotonergic impairments in PD
- Pan-neurotransmitter impairments
  - Dopamine + norepinephrine + cholinergic impairment
- Executive impairment
- Impairments in neural circuitry
- Psychiatric co-morbidity
  - Psychosis, anxiety, disorders of sleep and wakefulness

Placebo-Controlled Trial of Nortriptyline vs. Paroxetine



Menza et al. *Neurology* (in press).

Randomized Study of Pramipexole vs. Sertraline for Depression in PD



*Significant changes ($P < .001$) from baseline to endpoint.

Barone et al. *Journal of Neurology* 2006;253:601-607.

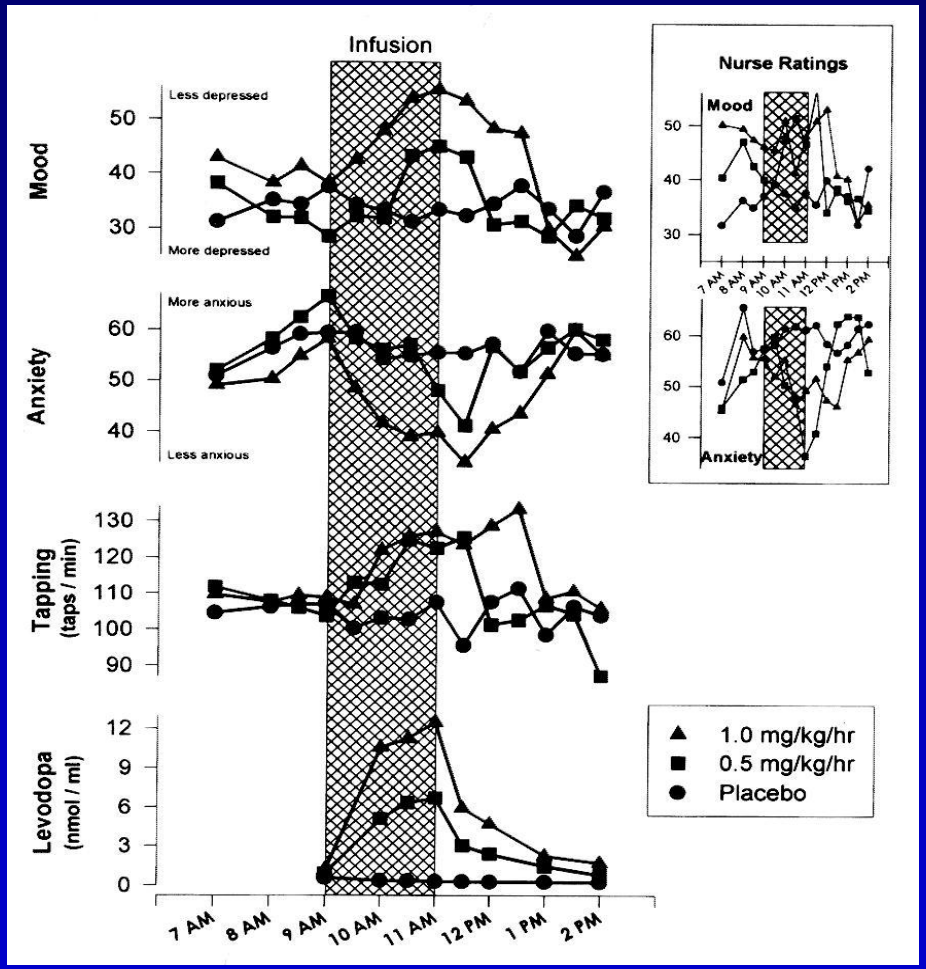
Anxiety – The Neglected Affective Disorder in PD

- Up to 40% of PD patients experience an anxiety disorder
- **Most patients with anxiety disorder also have depression diagnosis, and vice versa**
- Anecdotally, anxiety often more disabling than depression
  - Can be more distressing both psychologically and physically

Presentation

- Anxiety attacks (i.e., panic attacks)
  - Often associated with “off” periods or part of “non-motor fluctuations”
- Generalized anxiety disorder (GAD)
- Social phobia symptoms also common

Correlation Between Mood, Motor Function and Levodopa Levels



"Mood changes and tapping speed were somewhat discordant, which argues that mood changes are not simply a consequence of improved motor function."

Maricle et al. *Neurology* 1995;45:1757-1760.

Treatment

- No existing treatment studies
- Newer antidepressants also have anti-anxiety effects in non-PD patients
- Sometimes need to use low doses of benzodiazepines
  - Lorazepam, alprazolam, clonazepam
  - Beware of (1) cognitive side effects, (2) sedation, and (3) changes in balance / gait

Psychosis

Prevalence

- Hallucinations in **15-40%** of PD patients
  - Typically visual, other modalities less common
  - ≈5% of patients also experience delusions
- PD psychosis may serve as model for delirium
  - Induced / reversible (PD medications)
  - Fluctuations in attention and alertness
  - Visual hallucinations

Multifactorial Etiology

- Factors commonly associated with psychosis:
  - **PD medications**
    - Controversy about role of specific agents
  - **Cognitive impairment**
  - Increasing age
  - Increasing severity and duration of PD
  - Visual impairment
  - Co-morbid psychiatric disorders
    - Including vivid dreaming
- Likely complex interaction of above factors

Risk Factors - PD Medications

Variable (Mean [SD] or %)	Psychosis			Depression		
	No Psychosis N=96 (74%)	Psychosis N=34 (26%)	*P* value	Non-Depressed N=83 (64%)	Depressed N=47 (36%)	*P* value
Age (# years)	71.9 (8.6)	69.9 (9.2)	.25	72.6 (7.6)	69.5 (10.2)	.08
Education (# years)	14.6 (3.3)	14.2 (3.4)	.52	14.7 (3.5)	14.1 (3.1)	.35
Duration of PD (# years)	6.5 (4.9)	8.5 (6.2)	.05	7.1 (5.6)	6.9 (5.0)	.81
Sidedness (% right-sided PD)	42.7	41.2	.99	42.2	42.6	.79
Levodopa dosage (mg/day)	**392 (312)**	**579 (406)**	**<.01**	376 (312)	555 (381)	<.01
Dopamine agonist use (% yes)	**44.1**	**72.7**	**<.01**	54.4	46.8	.41
UPDRS score	22.1 (11.2)	24.8 (11.0)	.26	22.4 (12.0)	23.3 (9.6)	.70
MMSE score	28.1 (1.8)	27.6 (2.7)	.24	28.3 (1.6)	27.3 (2.6)	.03
ESS score	10.0 (5.3)	10.5 (4.5)	.67	9.8 (5.2)	10.7 (4.7)	.35

Weintraub et al. *Parkinsonism and Related Disorders* 2006;12:427-431.

Risk Factors – Cognitive Impairment

	PD without Dementia (N=83)	PD with Dementia (N=48)
Hallucinations	**14%**	**54%**
Delusions	**7%**	**29%**
Major Depression	9%	13%
Non-major Depression	29%	29%

Aarsland et al. *International Journal of Geriatric Psychiatry* 2001;16:528-536.

Treatment - Antipsychotics

- Balancing benefits (antipsychotic effects) and risks (worsening parkinsonism)
- Atypical antipsychotics
  - Concerns about worsening parkinsonism
  - Quetiapine medication of choice (range 25-200 mg/day)
    - **However, only two efficacy studies were negative**
- Clozapine
  - Efficacious in three randomized studies
  - Low doses (mean of 25-36 mg/day)

Other Treatments

- Concern about atypical antipsychotic use in neurodegenerative diseases
  - Increased morbidity and mortality risks
    - Increased risk of CVAs and increased mortality risk (1.6-1.7 times) secondary to cardiovascular events and infections
    - Hyperglycemia/Type 2 diabetes, hematologic abnormalities, orthostatic hypotension, cataracts, hyperlipidemia, dry mouth, sedation, dizziness, constipation
- Cholinesterase inhibitors
  - In DLB study, rivastigmine improved Neuropsychiatric Inventory (NPI) subscale including psychosis
  - In PDD study, rivastigmine group less likely to report psychosis as an adverse event

McKeith et al. *The Lancet* 2000:356:2031-2036.

Cognitive Impairment and Dementia

Cumulative Prevalence Rate of Dementia in PD

- Study controlled for survival bias and was longitudinal
- 8-year community-based PD study in Norway
  - Large Danish non-PD control group of similar age
- 224 PD patients
  - Mean age = 73 years and PD duration = 10 years
- Dementia rates
  - 22% at baseline
  - 4-year prevalence rate of 52%
    - 19% of controls with dementia at 5 yrs
  - 8-year prevalence rate of 78%

Aarsland et al. *Arch Neurol*. 2003;60:387-392

Risk Factors for PD Dementia

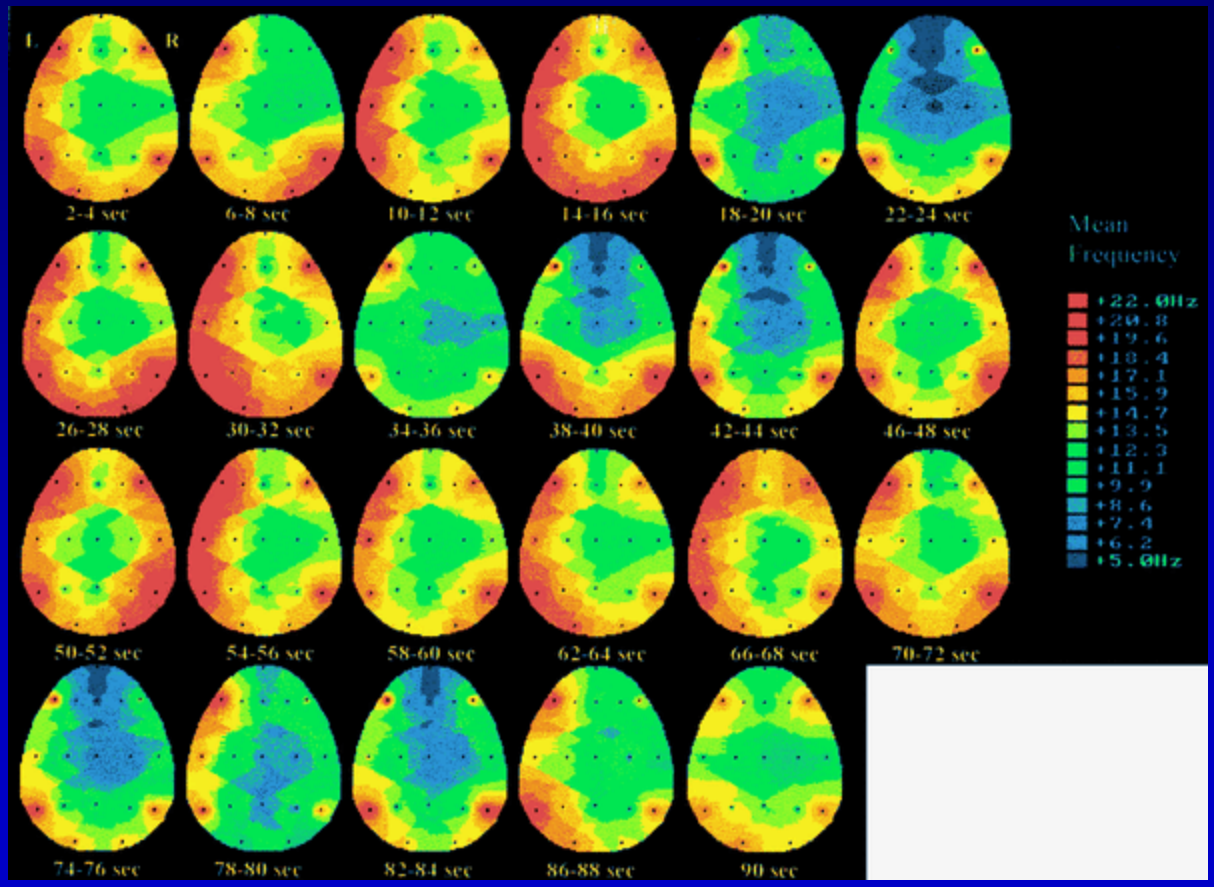
- **Increasing age**
- **Male sex**
- Lower education
- Non-tremor predominant features
  - Rigidity, gait imbalance, postural instability
- Psychiatric symptoms
  - Depression and psychosis
- Increasing severity of PD
  - Neuropathology, longer duration of PD
- Older age of PD onset

Some of the variables confounded by age

“Classical” Cognitive Profile in PD

- Executive dysfunction
  - Concept formation, problem solving, set shifting
  - Tasks that require planning and sequencing
- Attention impairment
  - Reaction times and vigilance
  - Fluctuations
- Visuospatial impairment
- Impaired **memory** (retrieval vs. **encoding deficits**)
  - Preserved recognition
  - Benefit from external cues
- **Language skills** and **praxis** relatively less affected

Electrophysiologic Characterization of Fluctuating Cognition in DLB



Walker et al. *Neurology* 2000;54:1616-1625.

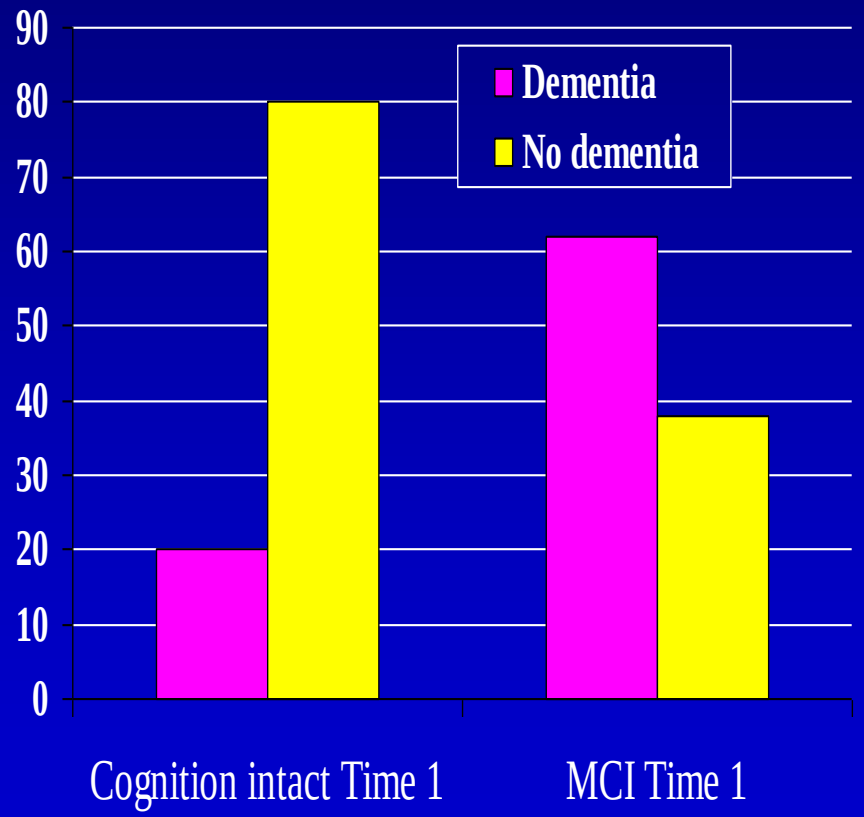
Proposed Diagnostic Criteria for PDD

- Impairment in ≥2 core cognitive domains
  - Impaired attention, executive, visuospatial, and free recall memory abilities, the latter usually improves with cueing
  - Shifts focus away from memory impairment
- Presence of at least one behavioral symptom (apathy, depressed or anxious mood, hallucinations, delusions, excessive daytime sleepiness) supports diagnosis
  - Emphasize behavioral symptoms
- End result
  - More sensitive
  - Bring in line with existing criteria for DLB

Emre et al. *Movement Disorders* 2007;22:1689-1707.

MCI and Progression to Dementia in PD

- Population-based PD sample without dementia (N=72) followed for 4 years (N=60)
- Baseline status
  - Cognition intact = 47%
  - MCI = 53%
- 4-year follow-up
  - Dementia = 42%
- MCI predicted dementia:
  - OR 4.8 (95% CI=1.6-14.8)

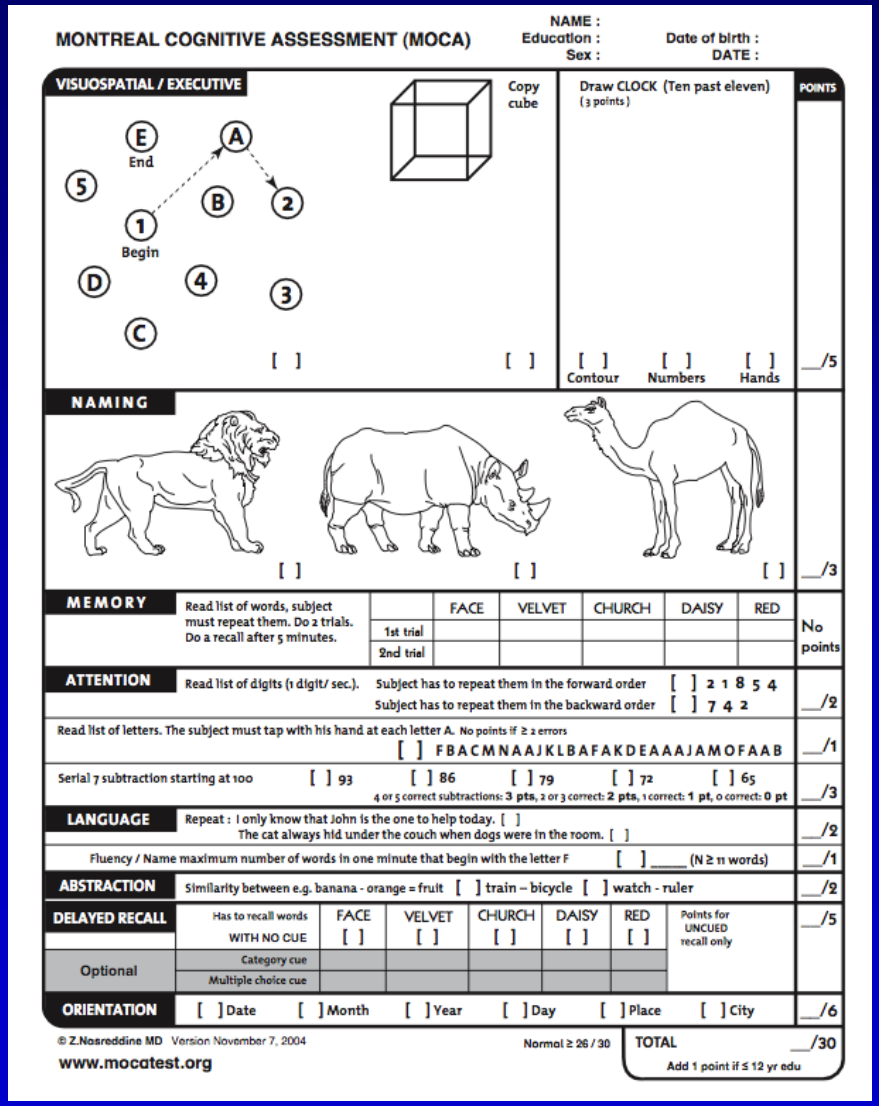


Janvin et al. *Movement Disorders* 2006;21:1343-1349.

Montreal Cognitive Assessment (MoCA)

- Assesses a broad range of cognitive domains
  - Attention/concentration (5 points)
  - Executive function (4 points)
  - Memory (5 points)
  - Language (6 points)
  - Visuospatial skills (4 points)
  - Orientation (6 points)
- Education adjusted
  - +1 point if ≤ 12 years
- Maximum possible score = 30 points
- **Total score <26 indicative of at least MCI**

Nasreddine et al. *Journal of the American Geriatrics Society* 2005;53:695-699.



MONTREAL COGNITIVE ASSESSMENT (MOCA)

NAME :
Education :
Sex :
Date of birth :
DATE :

VISUOSPATIAL / EXECUTIVE — Copy cube; Draw CLOCK (Ten past eleven) (3 points); POINTS

E End, A, 5, B, 2, 1 Begin, D, 4, 3, C

[ ] [ ] [ ] Contour [ ] Numbers [ ] Hands /5

NAMING /3

[ ] [ ] [ ]

MEMORY — Read list of words, subject must repeat them. Do 2 trials. Do a recall after 5 minutes. No points

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

ATTENTION — Read list of digits (1 digit/ sec.). Subject has to repeat them in the forward order [ ] 2 1 8 5 4. Subject has to repeat them in the backward order [ ] 7 4 2 /2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors [ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B /1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65. 4 or 5 correct subtractions: 3 pts, 2 or 3 correct: 2 pts, 1 correct: 1 pt, 0 correct: 0 pt /3

LANGUAGE — Repeat : I only know that John is the one to help today. [ ] The cat always hid under the couch when dogs were in the room. [ ] /2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] ____ (N ≥ 11 words) /1

ABSTRACTION — Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler /2

DELAYED RECALL — Points for UNCUED recall only /5

	Has to recall words WITH NO CUE	FACE	VELVET	CHURCH	DAISY	RED
		[ ]	[ ]	[ ]	[ ]	[ ]
Optional	Category cue					
	Multiple choice cue					

ORIENTATION — [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City /6

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Normal ≥ 26 / 30

TOTAL /30. Add 1 point if ≤ 12 yr edu

MoCA Study

- 103 idiopathic PD outpatients administered MoCA and MMSE
  - Counterbalanced administration
- Only patients with a MMSE score in the top 75th percentile (age- and education-corrected) were included in the analyses
  - 77% (N=79) of original sample
  - **Mean (SD) MMSE = 28.9 (1.1)**

Nazem et al. Annual Symposium on Etiology, Pathogenesis, and Treatment of Parkinson's Disease and Other Movement Disorders 2007 meeting (oral presentation).

MoCA Performance in PD & Controls

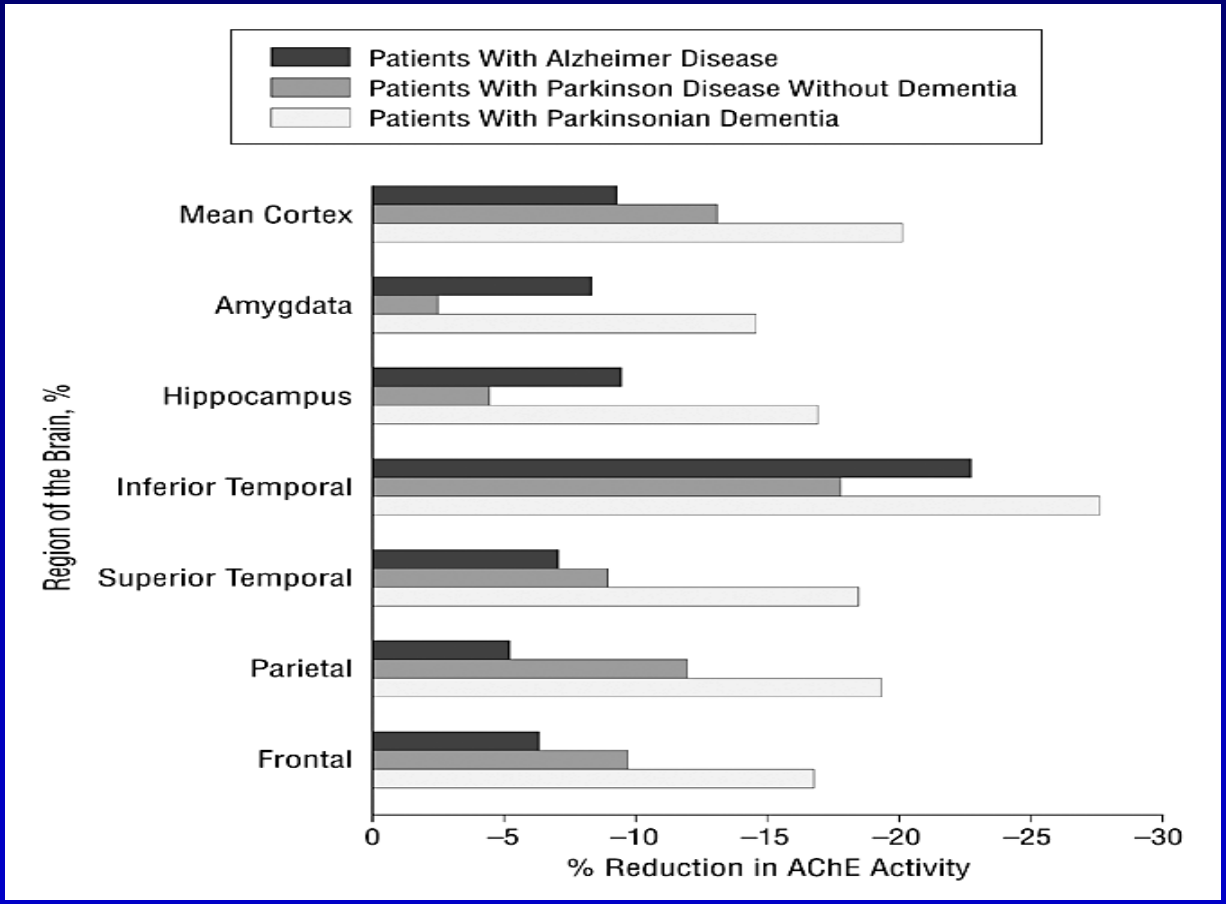
	PD Patients	Controls
Impaired (MoCA <26)	**42 (53.2%)**	**12 (13.5%)**
Unimpaired (MoCA ≥26)	37 (46.8%)	77 (86.5%)

X^2 (df=1) = 30.21, P< .001

PD Performance on MoCA Subscores by Impairment Status

MoCA Subscore	Mean (SD)		t (df)	P value
	PD Impaired	PD Non-Impaired		
Visuospatial/Executive	**3.6 (1.0)**	**4.4 (0.7)**	**4.35 (73.93)**	**<.001**
Naming	**2.7 (0.5)**	**3.0 (0.2)**	**3.14 (61.21)**	**.003**
Attention	**5.4 (0.8)**	**5.9 (0.4)**	**3.65 (57.75)**	**.001**
Language	**1.5 (1.0)**	**2.7 (0.5)**	**6.62 (64.70)**	**<.001**
Abstraction	1.4 (0.7)	1.7 (0.6)	1.64 (77)	.11
Delayed Recall	**1.8 (1.5)**	**3.9 (1.0)**	**7.35 (71.10)**	**<.001**
Orientation	**5.9 (0.3)**	**6.0 (0.0)**	**2.08 (41.00)**	**.04**

Cholinergic Function in PD, PDD, and AD



AChE = acetylcholinesterase activity

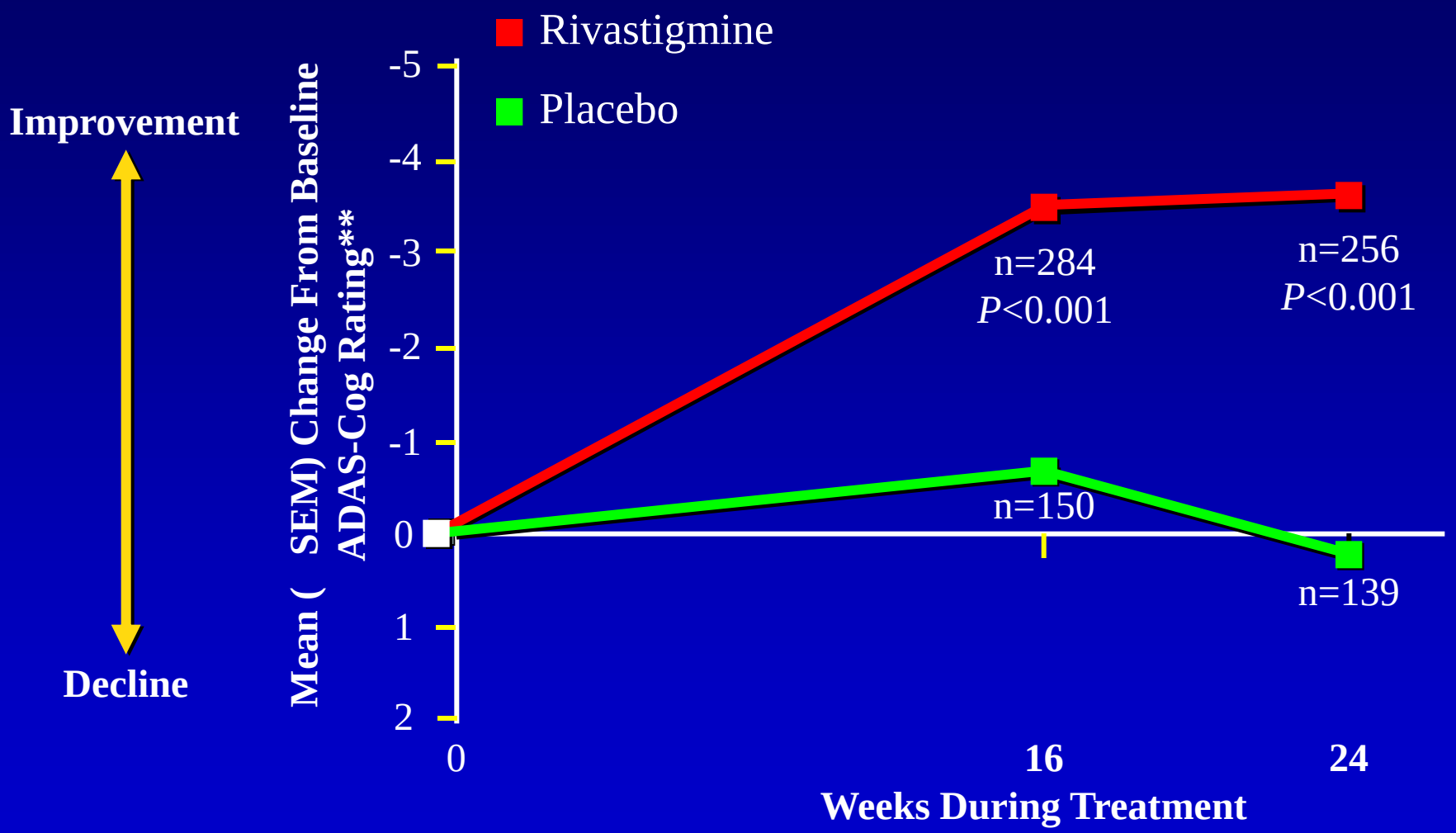
Bohnen et al. *Archives of Neurology* 2003;60:1745-1748.

Rivastigmine Study for PDD

- Objective
  - Evaluate the efficacy and safety of cholinesterase inhibitor (rivastgimine) in patients with PDD
- Study design
  - 24-wk, double-blind, randomized, placebo-controlled, parallel-group, multicenter study in Europe and Canada
  - 541 patients
  - Randomized 2:1 (rivastigmine: placebo)
  - 3 to 12 mg/day

Emre et al. *New England Journal of Med*icine 2004;351:2509-2518.

Cholinesterase Inhibitor Treatment for PDD*



* Observed case (OC) analysis.

** ADAS-Cog = Alzheimer's disease Assessment Scale – Cognitive

Study Conclusions

- Efficacy demonstrated for cholinesterase inhibitor for PDD
- Clinically meaningful improvement in only 20% of subjects (15% of placebo)
  - Based on CGI (global improvement) score
- AD measures used to assess outcomes
  - ADAS-Cog primarily assesses memory, language and praxis
- Well tolerated overall
  - Tremor significantly more common in active treatment group, but no significant differences in UPDRS motor score

Impulse Control Disorders

Presentation in PD

- Compulsive
  - Gambling
    - Can involve frequent low stakes (slots, scratch cards)
  - Sexual behavior
    - Internet, sex clubs, same sex
  - Buying
  - Eating
    - Cravings for certain foods, overnight eating
- Related behaviors
  - Punding (fascination with meaningless objects or activities)
  - Task preoccupation (“hobbyism”)
  - “Dopamine dysregulation syndrome” (DDS)
    - Akin to substance abuse disorder

DOMINION Study

- Study of frequency and correlates of 4 ICDs in PD
  - MAGS for gambling, MIDI for buying and sexual behavior, and DSM-IV criteria for binge-eating
- 46 PD centers in US and Canada
- 3090 patients completed the ICD assessments
- 66.0% of patients were taking a dopamine agonist
  - Overall, 86.8% of patients were taking levodopa

Weintraub D, Koester J, Potenza MN, Siderowf AD, Stacy MA, Whetteckey J, Wunderlich GR, Lang AE, for the DOMINION Study Group. Dopaminergic therapy and impulse control disorders in Parkinson's disease: top line results of a cross-sectional study of over 3,000 patients. Poster presentation at the Movement Disorder Society 12th International Congress of Parkinson's Disease and Movement Disorders: Chicago, Illinois: June 25, 2008.

ICD Frequencies

- At least one ICD identified in 13.6% of patients
  - 36.0% of ICD patients had >1 ICD
- Frequencies of single ICDs were:
  - problem/pathological gambling - 5.0%
  - compulsive sexual behavior - 3.5%
  - compulsive buying - 5.7%
  - binge-eating disorder - 4.3%

Current ICD Frequencies in DA- vs. Non-DA-Treated Patients

ICD type	DA treatment status	Current ICD N (%)	No current ICD N (%)	P value (CMH-test); odds ratio [95% CI]
Any ICD	No dopamine agonist	72 (6.9)	978 (93.1)	<.001
	Dopamine agonist	348 (17.1)	1692 (82.9)	2.72 [2.08;3.54]
Problem/pathological gambling	No dopamine agonist	24 (2.3)	1026 (97.7)	<.001
	Dopamine agonist	130 (6.4)	1910 (93.6)	2.82 [1.81;4.39]
Pathological gambling only	No dopamine agonist	17 (1.6)	1033 (98.4)	.004
	Dopamine agonist	72 (3.5)	1968 (96.5)	2.15 [1.26;3.66]
Compulsive sexual behaviour	No dopamine agonist	18 (1.7)	1032 (98.3)	<.001
	Dopamine agonist	90 (4.4)	1950 (95.6)	2.59 [1.55;4.33]
Compulsive buying	No dopamine agonist	30 (2.9)	1020 (97.1)	<.001
	Dopamine agonist	147 (7.2)	1893 (92.8)	2.53 [1.69;3.78]
Binge-eating disorder	No dopamine agonist	18 (1.7)	1032 (98.3)	<.001
	Dopamine agonist	114 (5.6)	1926 (94.4)	3.34 [2.01;5.53]

Current ICD Frequencies by DA Type

ICD type	Specific DA	Current ICD N (%)	No current ICD N (%)	P value (CMH-test); odds ratio [95% CI]
Any ICD	Ropinirole	101 (15.5)	550 (84.5)	.14
	Pramipexole	228 (17.7)	1058 (82.3)	1.22 [0.94;1.57]
Problem/pathological gambling	Ropinirole	37 (5.7)	614 (94.3)	.44
	Pramipexole	83 (6.5)	1203 (93.5)	1.17 [0.78;1.76]
Pathological gambling only	Ropinirole	24 (3.7)	627 (96.3)	.69
	Pramipexole	42 (3.3)	1244 (96.7)	0.90 [0.54;1.51]
Compulsive sexual behaviour	Ropinirole	28 (4.3)	623 (95.7)	.75
	Pramipexole	58 (4.5)	1228 (95.5)	1.08 [0.68;1.71]
Compulsive buying	Ropinirole	51 (7.8)	600 (92.2)	.58
	Pramipexole	87 (6.8)	1199 (93.2)	0.90 [0.63;1.30]
Binge-eating disorder	Ropinirole	28 (4.3)	623 (95.7)	.06
	Pramipexole	80 (6.2)	1206 (93.8)	1.53 [0.98;2.39]

22% of patients on pergolide (N=50) had an ICD.

Multivariate Analysis of ICD Correlates

Variable	Odds ratio [95% CI]	P value
Age (≤65 years vs. >65 years)	2.39 [1.90;3.00]	<.001
Dopamine agonist LEDD (>150mg vs. ≤150mg)	2.15 [1.73;2.68]	<.001
Levodopa LEDD (>450mg vs. ≤450mg)	1.45 [1.18;1.80]	<.001
Marital status (not married vs. married)	1.47 [1.15;1.88]	.002
Family history gambling problems (yes vs. no)	2.21 [1.42;3.44]	<.001

ICD Assessment Instruments

- No screening instruments developed or used for ICDs in PD
- Lack of established, formal diagnostic criteria for some of the ICDs seen in PD
- No rating scales have been tested in PD to determine changes in ICD severity over time

Weintraub D, Stewart S, Potenza M, Siderowf A, Duda J, Hurtig H, Colcher A, Horn S, Stern M. Validation of the Parkinson's Disease Impulsive-Compulsive Disorders Screening Questionnaire (PICS). Poster presentation at the Movement Disorder Society 12th International Congress of Parkinson's Disease and Movement Disorders: Chicago, Illinois: June, 26, 2008.

Questionnaire for **I**mpulsive-Compulsive Disorders in **P**arkinson's Disease **(QUIP)**

- Guiding principles
  - Draw on existing questionnaires to extent possible
  - Comprehensive for ICDs and other compulsive disorders
  - Brief (several minutes to complete)
  - Simple and clear
  - Self-administered
  - Consistency between disorders
  - For use in clinical or research settings
  - Meant to be screening questionnaire (maximize sensitivity)

Validation Study*

- 31.2% of patients had a history of ≥1 ICD, other compulsive disorder, or compulsive medication use sometime during PD
  - Half of those subjects (15.3%) had a history of two or more disorders
- Diagnostic interview results:
  - Gambling 7.0%
  - Sexual behavior 8.9%
  - Buying 6.4%
  - Eating 4.5%
  - Hobbyism 14.6%
  - Punding 10.2%
  - Walkabout 3.2%
  - Compulsive medication use <0.1%

*N=157 at 4 PD centers (Penn, Philadelphia VA, U. of Kansas, Mayo Phoenix)

Validation Brief ICD Section

	Cutoff Points[a]							
	Gambling (N=11)		Sex (N=14)		Buying (N=10)		Eating (N=7)	
	1	2	1	2	1	2	1	2
Sensitivity	**91**	73	**100**	64	**80**	40	**86**	43
Specificity	**95**	99	**90**	96	**91**	99	**85**	96
PPV	**59**	89	**48**	60	**38**	80	**21**	40
NPV	**99**	98	**100**	96	**99**	96	**99**	98
AUC (95% CI)	.95 (.84-1.05)		.96 (.93-.99)		.87 (.72-1.02)		.88 (.72-1.04)	

[a] 2 questions per ICD, 8 questions in total

Validation Other Compulsive Disorders

	Gateway Questions		
	Hobbyism (N=23)	**Punding (N=16)**	**Walkabout (N=5)**
Sensitivity	96	63	60
Specificity	90	93	97
PPV	61	50	43
NPV	99	96	99
AUC (95% CI)	.93 (.87-.98)	.78 (.63-.92)	.79 (.52-1.05)

Only 1 subject diagnosed with compulsive medication use

Study Conclusions

- QUIP valid as self-administered screening instrument for ICDs and other compulsive disorders that occur in PD
- QUIP is simple and brief (median completion time <5 minutes), so appropriate for use in clinical care and research
- Brief QUIP (13 questions in total) may perform as well as the full QUIP (30 questions in total)
- QUIP validated as screening instrument, so clinical interview needed for patients who screen positive
- Clinical interview should focus on all ICDs and related behaviors
- There remains need to develop: (1) rating scales to assess the severity of ICDs and other compulsive disorders, and (2) consensus diagnostic criteria for some of these disorders

Current Management Options

- Do nothing
  - Assess clinical significance
  - Some patients unable or reluctant to make adjustments to PD pharmacotherapy
- Alterations to PD pharmacotherapy
- Consider DBS
- Psychopharmacology
- Psychosocial treatments

Long-Term Follow-Up of ICDs

- 15 ICD subjects completed f/u telephone interview
  - Mean time period = 29 months after ICD identification
- 12 (80.0%) patients discontinued or significantly decreased (>30% reduction) DA treatment
  - 83.3% (10/12) no longer met diagnostic criteria for an ICD

  BUT
- 26.7% of subjects overall still met ICD criteria, including 50% of subjects who continued DA treatment

Mamikonyan et al. *Movement Disorders* 2008;23:75-80.

Changes in Dopaminergic Therapy and UPDRS Motor Score Over Time

	Time 1 (mean [SD])	Time 2 (mean [SD])	Average % Change	Statistic (Z score [P value])[1]
Dopamine agonist LEDD	358.7 (179.4)	170.2 (233.3)	- 52.6%	-3.1 (.002)
Levodopa LEDD	349.7 (381.3)	482.3 (358.9)	+ 37.9%	-1.9 (.05)
Total LEDD	708.3 (482.9)	652.5 (465.3)	- 7.9%	-0.5 (.64)
UPDRS motor score[2]	22.6(8.7)	24.6(10.2)	+8.8%	-1.3(.19)

[1] Wilcoxon Signed Ranks Test

[2] N=14 (UPDRS scores unavailable for 1 patient)

Deep Brain Stimulation?

- Seven patients with pathological gambling underwent DBS
- Pre-surgery levodopa equivalent dose = 1,390 mg/day
  - Post-surgery 74% reduction in overall LEDD
- PG resolved postoperatively in all patients over mean of 18 months
- Conclusions:
  - "Dopaminergic dysregulation commonly attributed to pulsatile overstimulation of the limbic dopaminergic system may be subject to desensitization on chronic subthalamic stimulation, which has a relative motor selectivity and allows for decrease in dopaminergic treatment."
- However, emerging case literature of ICDs starting post-DBS surgery

Ardouin C et al. *Movement Disorders* 2006;21:1941-1946.

Psychopharmacology

- Antidepressants (SSRIs), atypical antipsychotics, and mood stabilizers (anticonvulsants) used clinically
  - Case reports for atypical antipsychotics in treatment of ICDs in PD
- Need for medications that will allow patients to stay on PD medications and not worsen parkinsonism
  - Specific D_3-receptor antagonists?
  - Partial dopamine agonist + 5-HT_{1A} agonist?
  - Medications targeting opioid and glutamate systems

Conclusions

1. PD is a neuropsychiatric/cognitive disease
2. Multi-morbidity of psychiatric disorders is the norm
3. Need for PD-specific screening instruments, diagnostic criteria, and rating scales
4. Under-recognition and under-treatment of most disorders
5. Lack of evidence for efficacy of almost all existing treatments
6. Existing PD treatments may have mixed effects for psychiatric and cognitive complications

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