The Neuropsychiatry of Parkinson's Disease: Recent Developments

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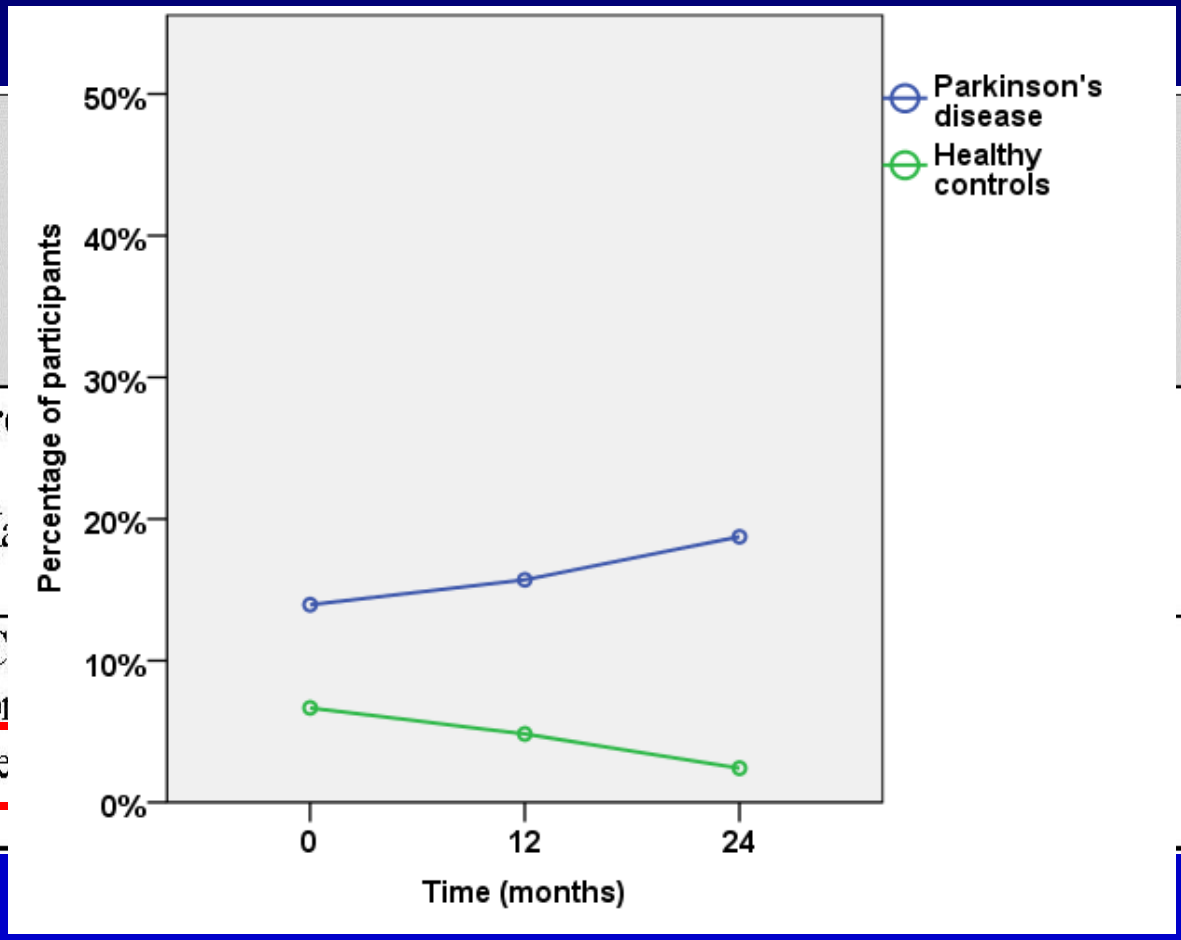
8/16

Depression

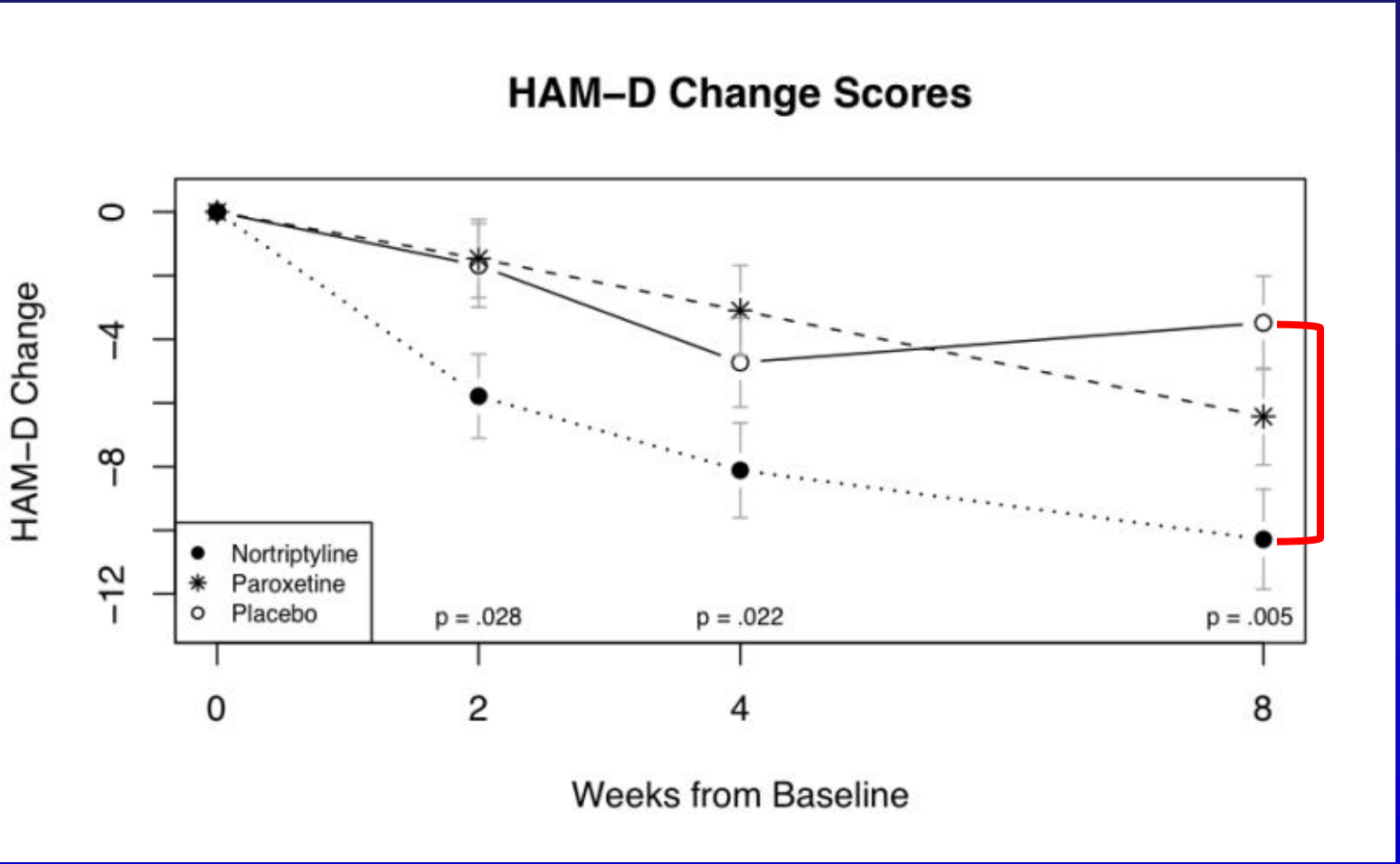
Depressive Symptoms in De Novo and Early PD: PPMI Data

Variable		p-value
GDS Scor		<.001
Mean		
(Min, Ma		
GDS-15 C		0.008
Not Depr		
Depresse		



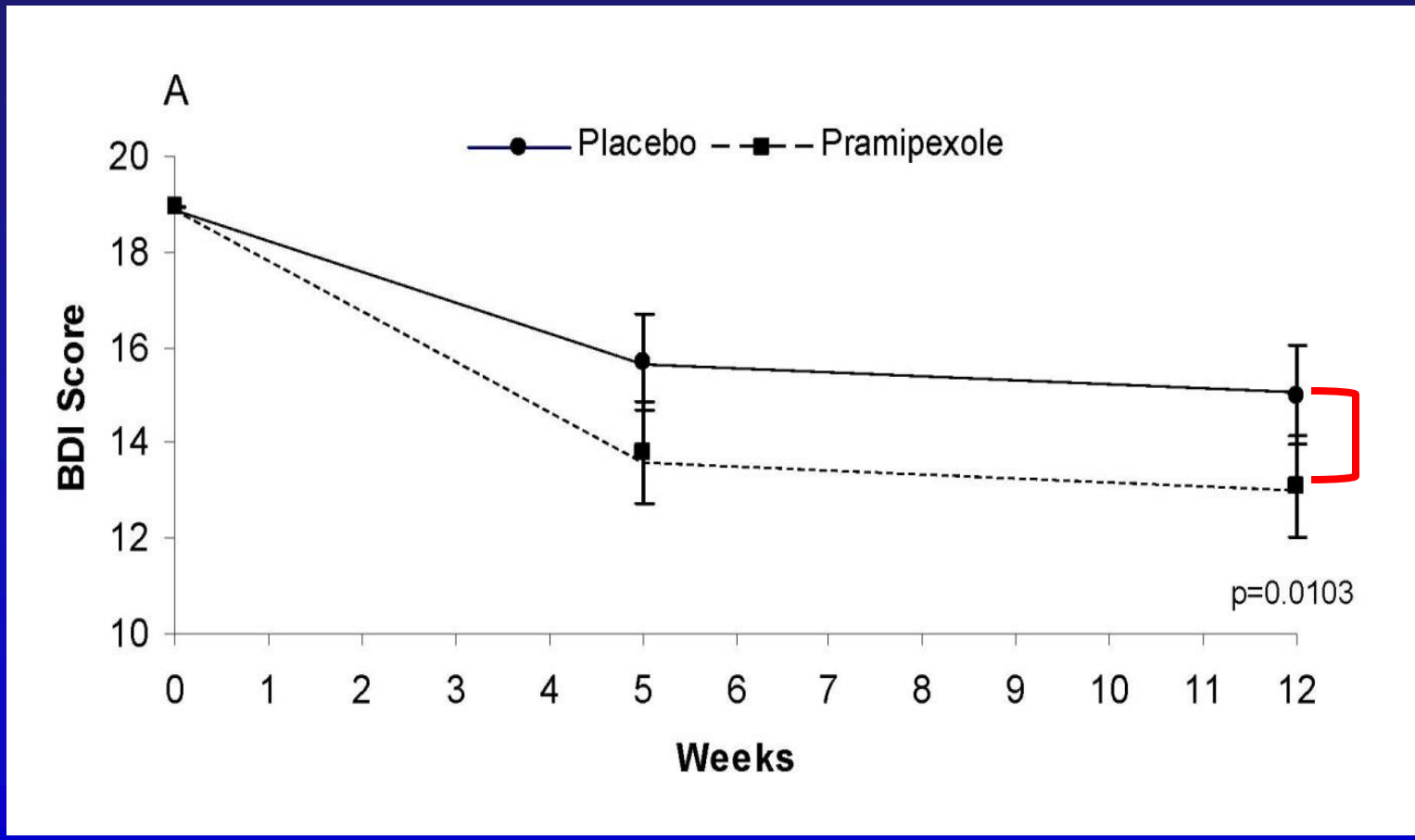
de al Riva et al. *Neurology* 2014;83:1096-1103.

Monoaminergic Basis of Treatment I: **NOREPINEPHRINE**



Menza et al. *Neurology* 2009;72:886-892.

Monoaminergic Basis of Treatment II: **DOPAMINE**



Barone et al. *Lancet Neurology* 2010;9:573-580.

Original Investigation

Combined Rasagiline and Antidepressant Use in Parkinson Disease in the ADAGIO Study

Effects on Nonmotor Symptoms and Tolerability

Kara M. Smith, MD; Eli Eyal, MSc; Daniel Weintraub, MD; for the ADAGIO Investigators

Table 3. Changes in Nonmotor Symptoms Over Time in the Pooled Rasagiline and Placebo Groups

	Estimated Change at Week 36[a]				
	Mean (SE)				
Variable[b]	Pooled Rasagiline	Placebo	Rasagiline-Placebo Difference	95% CI	*P* Value
Depression	0.57 (0.07)	0.76 (0.07)	−0.19 (0.10)	−0.38 to −0.002	.048
Anxiety	0.76 (0.07)	0.87 (0.07)	−0.12 (0.10)	−0.31 to 0.08	.23
Apathy	0.48 (0.07)	0.65 (0.06)	−0.17 (0.09)	−0.35 to 0.02	.07
Cognition	0.31 (0.04)	0.50 (0.03)	−0.20 (0.05)	−0.30 to −0.10	<.001
Daytime sleepiness	0.43 (0.07)	0.68 (0.06)	−0.24 (0.09)	−0.42 to −0.07	.006
PFS score	2.41 (0.06)	2.83 (0.06)	−0.42 (0.09)	−0.59 to −0.24	<.001
Sleep	0.75 (0.07)	0.65 (0.06)	0.10 (0.09)	−0.09 to 0.28	.30

Abbreviation: PFS, Parkinson Fatigue Scale.

[a] Adjusted for baseline score and center.

[b] All items except the PFS score were Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale Nonmotor Experiences of Daily Living items.

Monoaminergic Basis of Treatment III: **SEROTONIN**

SAD-PD: **S**tudy of **A**nti**d**epressants in **P**arkinson's **D**isease

Mean 12 Week Δ in HAM-D Score			
Comparison	Effect	95% CI	P-value
Paroxetine vs. Placebo	-6.2	(-9.7, -2.7)	<0.001
Venlafaxine vs. Placebo	-4.2	(-7.8, -0.6)	0.02

Richard et al. *Neurology* 2012;79:1229-1236.

What is Real Risk for Serotonin Syndrome?

- In A… …ts who… …ibitor + ar… sero… …ent repo…

CVS CAREMARK

Patient Information for Your Consideration

January 24, 2014

Case Number

DANIEL WEINTRAUB MD
3535 MARKET ST
FL 2
PHILADELPHIA, PA 19104

Dear Dr. DANIEL WEINTRAUB:

This confidential drug utilization review program provides educational information concerning potentially serious drug interactions. Our goal is to facilitate optimal, safe, effective, and high quality drug therapy.

Possible Drug Interaction

Our records indicate your patient received the following prescriptions: AZILECT and MIRTAZAPINE. The concomitant administration of serotonergic agents (e.g., SSRIs, SSNRIs) with MAO inhibitors may lead to the development of serotonin syndrome. The syndrome may be manifested by mental status changes, restlessness, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, and or seizures. Concurrent use of these agents is contraindicated.[1]

After evaluating the overall treatment goals for your patient and if medically appropriate, please consider:

•Discontinuing the SRI or MAO inhibitor and continue to appropriately monitor the patient for a sufficient time period to allow for clearance of the agent and any active metabolites

If the medications listed above have been prescribed by different providers, each provider is contacted. If a dispensing pharmacist contacted you regarding this information, please consider this a follow up to that discussion.

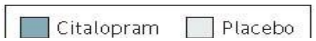
Research

Original Investigation

Effect of Citalopram on Agitation in Alzheimer Disease
The CitAD Randomized Clinical Trial

Anton P. Porsteinsson, MD; Lea T. Drye, PhD; Bruce G. Pollock, MD, PhD; D. P. Devanand, MD; Constantine Frangakis, PhD; Zahinoor Ismail, MD; Christopher Marano, MD; Curtis L. Meinert, PhD; Jacobo E. Mintzer, MD, MBA; Cynthia A. Munro, PhD; Gregory Pelton, MD; Peter V. Rabins, MD; Paul B. Rosenberg, MD; Lon S. Schneider, MD; David M. Shade, JD; Daniel Weintraub, MD; Jerome Yesavage, MD; Constantine G. Lyketsos, MD, MHS; for the CitAD Research Group

Figure 2. Neurobehavioral Rating Scale (NBRS)-Agitation Subscale



Electrocardiogram (ECG) monitoring was initiated after 138 patients were randomized and was available for 48 patients (24 citalopram and 24 placebo). Citalopram was associated with greater increase in QTc interval than placebo (18.1 ms; 95% CI, 6.1-30.1; P = .004), and more participants in the citalopram group showed a QTc increase of greater than 30 ms from enrollment to week 3 than participants in the placebo group (7 vs 1; Fisher exact P = .05). Four participants (3 citalopram and 1 placebo) showed QTc prolongation (>450 ms for men and >475 ms for women).

lower quartile (or the minimum and maximum if within 1.5 × the interquartile range of the quartiles) and data more extreme than the whiskers are plotted individually as outliers.

Porsteinsson et al. *JAMA* 2014;311:682-691.

Differential Effects for STN vs. GPi DBS?

Table 3

Movement disorders

RESEARCH PAPER

Which target is best for patients with Parkinson's disease? A meta-analysis of pallidal and subthalamic stimulation

Wataru Sako,[1] Yoshimichi Miyazaki,[2] Yuishin Izumi,[2] Ryuji Kaji[2]

Outcor						ulation
Neuroc						
Score c						0.02
Total sc						0.29
Score c						
Pro						0.03
Wo						0.27
Verbal l						
Phc						0.33
Semantic (names of animals; range, 0–100)		50.4±10.6	44.7±12.4	47.0±12.4	41.2±13.2	0 (–2.8 to 2.8) 0.99

Hopkins Verbal Learning Test T score§ ††

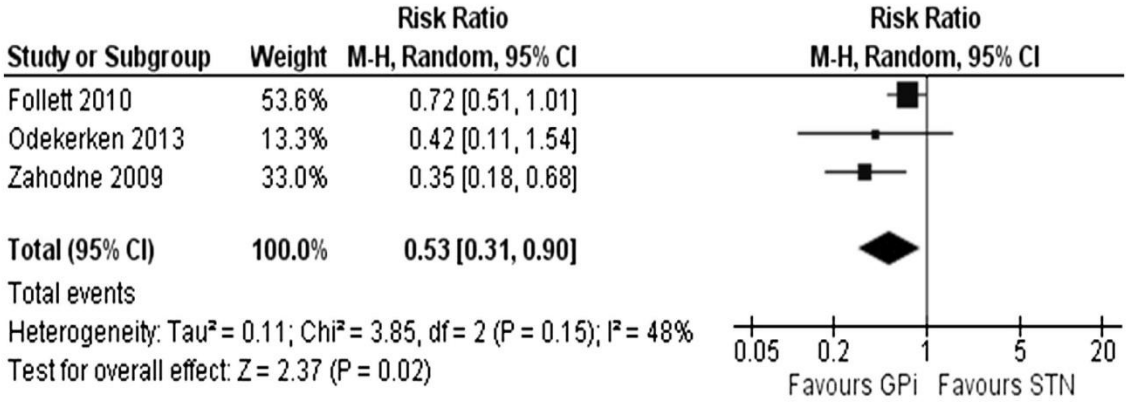


Figure 3 Forest plot of pooled risk ratio (RR) of depression. The summary effect suggested that depression occurred less frequently after pallidal stimulation than subthalamic stimulation. The included studies were homogeneous.

Follett et al. *NEJM* 2010;362:2077-2091.

Sako et al. *JNNP* 2014;85:982-986.

Suicide and DBS: What's the Evidence?

CSP 468 Study

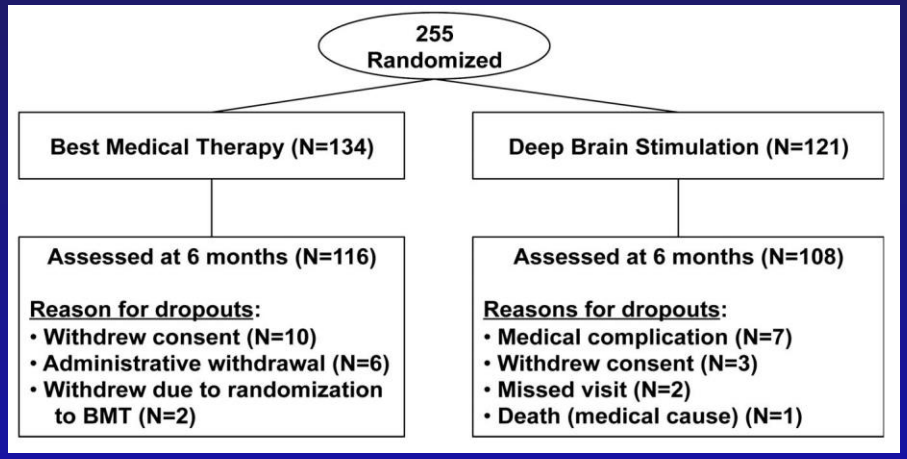


Table 1 Incident suicide ideation and behaviours during controlled phase (DBS vs BMT)

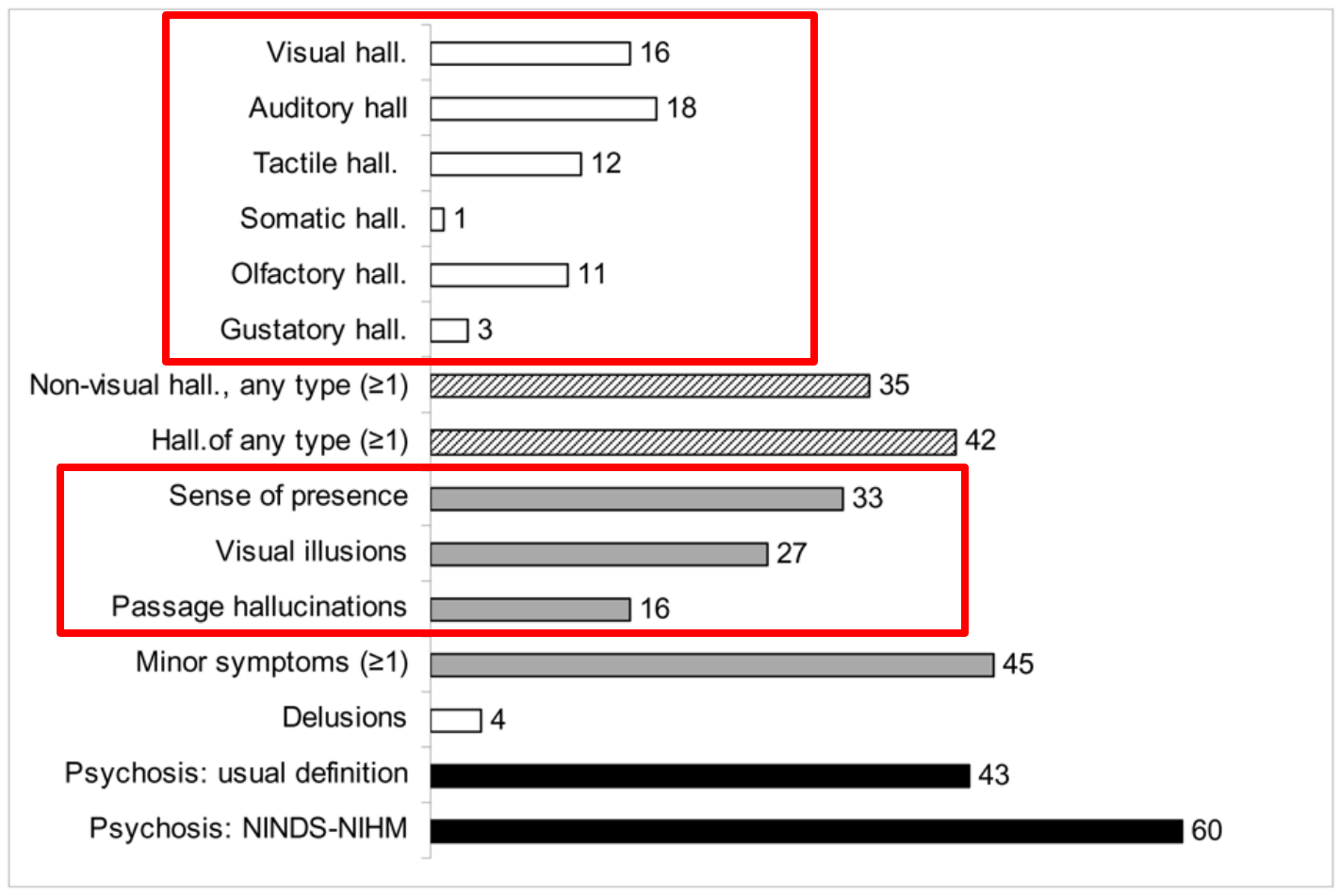
	Baseline		3 Months		6 Months	
	(N=254) Suicide ideation*	(N=255) Suicide behaviours†	(N=224) Suicide ideation	(N=236) Suicide behaviours	(N=224) Suicide ideation	(N=232) Suicide behaviours
DBS	0 (0%)	–	0 (0%)	0 (0%)	2 (1.9%)	0 (0%)
BMT	0 (0%)	–	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)
p Value‡	n/a	–	n/a	n/a	0.61	n/a

*Based on UPDRS Part I depression item, the denominator is the total number of participants who had the complete data for this item.
†Based on adverse event reporting for time period since previous study visit, the denominator is the total number of participants who were at risk during the period.
‡Fisher's Exact Test.

Weintraub et al. *JNNP* 2013;84:1113-1118.

Psychosis

Non-Visual and "Minor" Hallucinations More Common Than Previously Thought



Fenelon et al. *Movement Disorders* 2010; 25: 755–759

RESEARCH ARTICLE

Minor Hallucinations Occur in Drug-Naive Parkinson's Disease Patients, Even From the Premotor Phase

Results: Fifty drug-naive, "de novo" PD patients and 100 controls were prospectively included. Minor hallucinations were experienced in 42% (21 of 50) PD patients and 5% controls ($P < 0.0001$). Coexistence of passage and presence hallucinations was the most common finding. Unexpectedly, 33.3% of patients with minor hallucinations manifested these as a pre-motor symptom, starting 7 months to 8 years before first parkinsonian motor symptoms. The presence of minor hallucinations was significantly associated with presence of rapid eye movement sleep behavior disorder.

Pagonabarraga et al. *Movement Disorders* 2015;10.1002/mds.26432.

Psychosis and Dopamine Replacement Therapy: PPMI Data

Variable UPDRS Part I Hallucinations and Psychosis Item	PD Subjects (N = 423)	Healthy Controls (N = 196)	Statistic (Chi-square)	df	p-value
Negative	410 (97%)	194 (99%)	3.95	1	0.047
Any positive score	**13 (3%)**	**1 (1%)**			

"The frequency of new-onset psychosis was nearly three times as high in the DRT group compared with the untreated group."

de al Riva et al. *Neurology* 2014;83:1096-1103.

Antipsychotic (AP) Prescribing in PD

Antipsychotic Prescribing	PD group (N=2,597)				Non-PD dementia group (N=6,907)		Test of significance
	With dementia[a] (N=793)		Without dementia (N=1,804)				
	N	%	N	%	N	%	
Any AP use	451	56.9	847	47.0	3,350	48.5	$\chi2$ =23.35, df=2, p<0.001[b,c]
Any typical AP	35	4.4	69	3.8	500	7.2	$\chi2$ =33.50, df=2, p<0.00[c]
High potency	32	4.0	56	3.1	456	6.6	$\chi2$ =37.00, df=2, p<0.001[c]
Any atypical AP	437	55.1	814	45.1	3110	45.0	$\chi2$ =29.63, df=2, p<0.001[b,c]
Quetiapine	306	38.6	550	30.5	1,522	22.0	$\chi2$ =139.35, df=2, p<0.001[b,c]
Risperidone	81	10.2	143	7.9	1,282	18.6	$\chi2$ =141.88, df=2, p<0.001[c]
Aripiprazole	41	5.2	116	6.4	273	4.0	$\chi2$ =21.16, df=2, p<0.001
Olanzapine	56	7.1	93	5.2	458	6.6	$\chi2$ =5.87, df=2, p=0.053
Ziprasidone	18	2.3	31	1.7	100	1.4	$\chi2$ =3.44, df=2, p=0.18
Clozapine	5	0.6	18	1.0	4	0.1	$\chi2$ =48.27, df=2, p<0.001[c]

[a] Reference group.
[b] Significant differences between PD patients with and without dementia.
[c] Significant difference between dementia patients with and without PD.

- 50% of PD patients with psychosis prescribed an AP
- Quetiapine most frequently prescribed AP (2/3 of treated patients)
- 1/3 receive high potency APs (typicals + atypicals)
- Clozapine rarely prescribed (<2%)

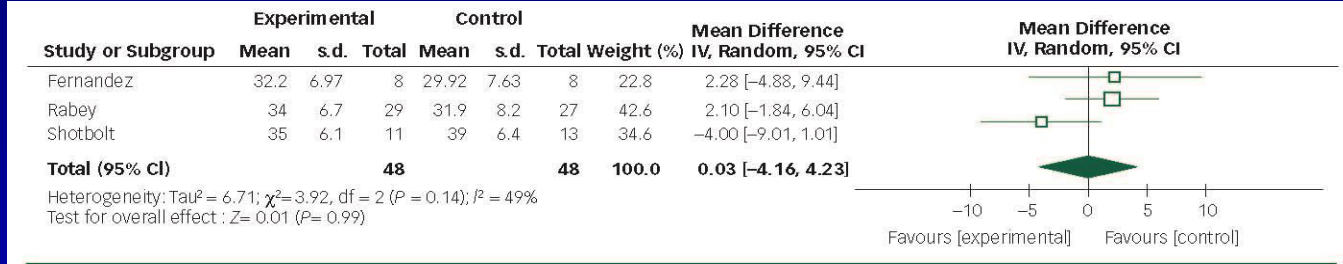
Weintraub et al. *Archives of Neurology* 2011;68:899-904.

BJPsych Open (2015)
1, 27–33. doi: 10.1192/bjpo.bp.115.000927

Review article

Antipsychotics for the management of psychosis in Parkinson's disease: systematic review and meta-analysis

Ketan Dipak Jethwa and Oluwademilade A. Onalaja

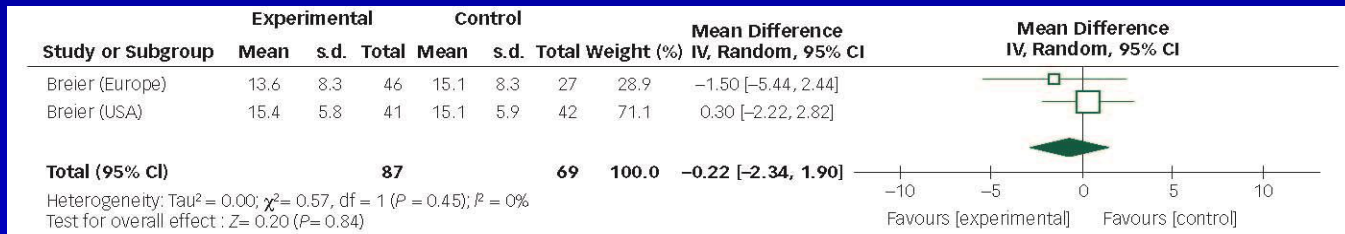


Study or Subgroup	Experimental Mean	s.d.	Total	Control Mean	s.d.	Total	Weight (%)	Mean Difference IV, Random, 95% CI
Fernandez	32.2	6.97	8	29.92	7.63	8	22.8	2.28 [–4.88, 9.44]
Rabey	34	6.7	29	31.9	8.2	27	42.6	2.10 [–1.84, 6.04]
Shotbolt	35	6.1	11	39	6.4	13	34.6	–4.00 [–9.01, 1.01]
Total (95% CI)			**48**			**48**	**100.0**	**0.03 [–4.16, 4.23]**

Heterogeneity: Tau² = 6.71; χ^2 = 3.92, df = 2 (P = 0.14); I^2 = 49%
Test for overall effect : Z = 0.01 (P = 0.99)

Fig. 4 Random effects meta-analysis of the use of quetiapine in the management of Parkinson's disease psychosis, efficacy measure: BPRS.

Quetiapine

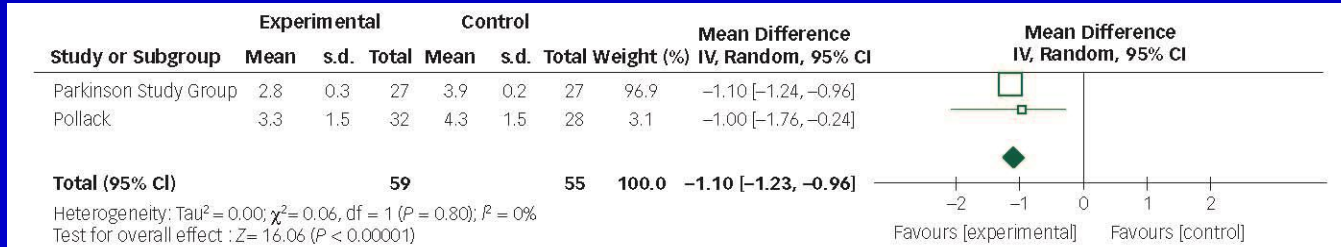


Study or Subgroup	Experimental Mean	s.d.	Total	Control Mean	s.d.	Total	Weight (%)	Mean Difference IV, Random, 95% CI
Breier (Europe)	13.6	8.3	46	15.1	8.3	27	28.9	–1.50 [–5.44, 2.44]
Breier (USA)	15.4	5.8	41	15.1	5.9	42	71.1	0.30 [–2.22, 2.82]
Total (95% CI)			**87**			**69**	**100.0**	**–0.22 [–2.34, 1.90]**

Heterogeneity: Tau² = 0.00; χ^2 = 0.57, df = 1 (P = 0.45); I^2 = 0%
Test for overall effect : Z = 0.20 (P = 0.84)

Fig. 6 Random effects meta-analysis of the use of olanzapine in the management of Parkinson's disease psychosis, efficacy measure: BPRS.

Olanzapine



Study or Subgroup	Experimental Mean	s.d.	Total	Control Mean	s.d.	Total	Weight (%)	Mean Difference IV, Random, 95% CI
Parkinson Study Group	2.8	0.3	27	3.9	0.2	27	96.9	–1.10 [–1.24, –0.96]
Pollack	3.3	1.5	32	4.3	1.5	28	3.1	–1.00 [–1.76, –0.24]
Total (95% CI)			**59**			**55**	**100.0**	**–1.10 [–1.23, –0.96]**

Heterogeneity: Tau² = 0.00; χ^2 = 0.06, df = 1 (P = 0.80); I^2 = 0%
Test for overall effect : Z = 16.06 (P < 0.00001)

Fig. 8 Random effects meta-analysis of the use of clozapine in the management of Parkinson's disease psychosis, efficacy measure: CGI.

Clozapine

What's the Problem? Risks With AP Use in "Dementia-Related Psychosis"

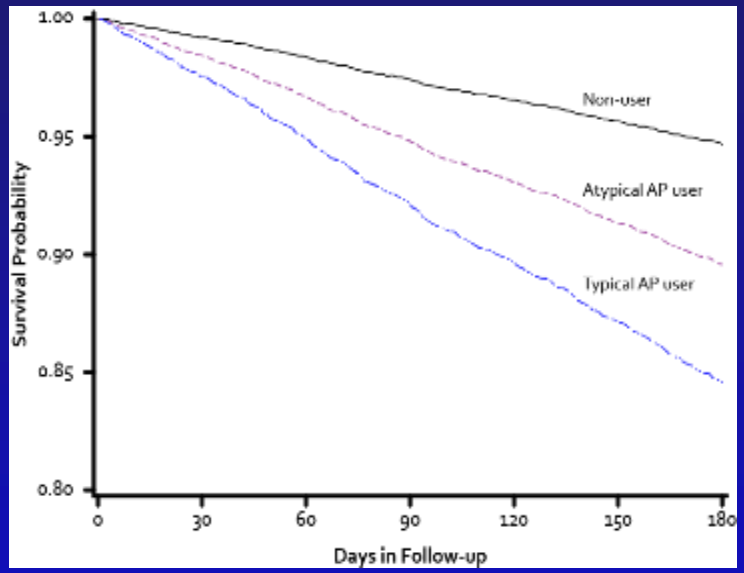
- Increased morbidity and mortality
  - Increased risk of CVAEs and mortality (1.7 times) secondary to CVEs and infections

BLACK BOX WARNING

- Issued for atypical APs in 2005
  - Extended to typical APs in 2008
- Also Type 2 diabetes, orthostatic hypotension, dry mouth, sedation, dizziness, constipation

Mortality Rates by Antipsychotic Exposure in PD

Group	Intention-To-Treat Analysis		Exposure Only Analysis	
	Hazard Ratio (95% CI)	*P*-value	Hazard Ratio (95% CI)	*P*-value
No AP Use	1.0	-	1.0	-
AP User	2.35 (2.08-2.66)	<0.001	2.15 (1.82-2.55)	<0.001
No AP Use	1.0	-	1.0	-
Atypical AP	2.26 (1.98-2.57)	<0.001	2.09 (1.75-2.49)	<0.001
Typical AP	3.65 (2.47-5.39)	<0.001	3.11 (1.72-5.60)	<0.001



<10% of patients diagnosed with dementia

CI=Confidence Interval; AP=Antipsychotic.

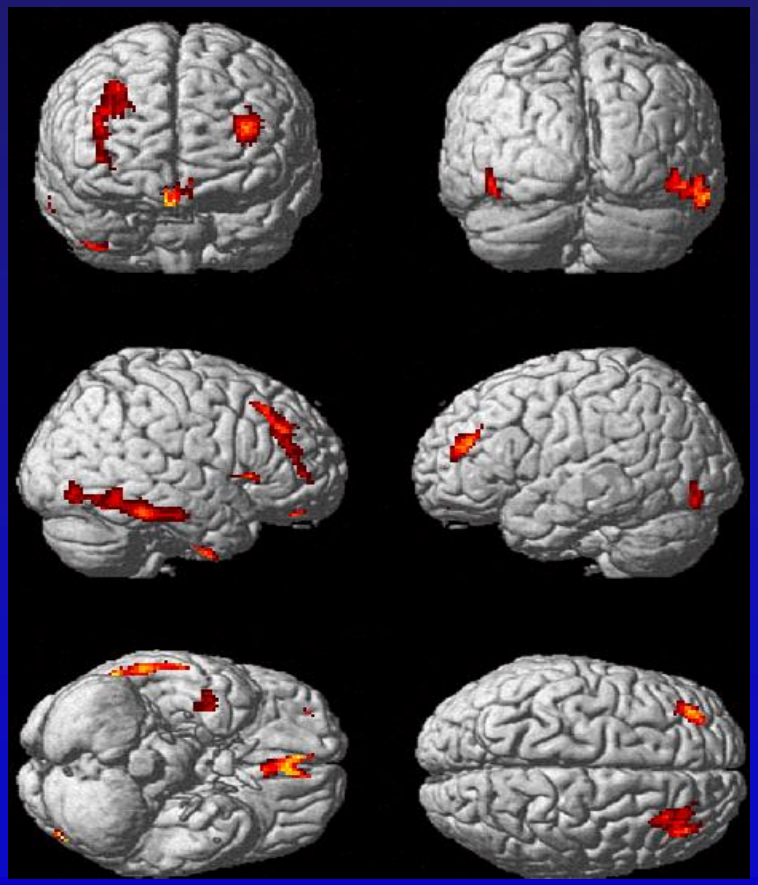
Weintraub et al. *JAMA Neurology* 2016;73(5):535-541.

Morbidity (ER Visits) Outcomes in PD Patients Treated with AP

	ITT		Exposure	
Antipsychotics	Hazard Ratio (95%CI)	P value	Hazard Ratio (95%CI)	P value
AP nonuser[a]	1.0		1.0	
Any AP User	1.64 (1.51-- 1.77)	<.001	1.67 (1.54-- 1.81)	<.001
Atypical AP user	1.63 (1.51-- 1.77)	<.001	1.66 (1.53-- 1.80)	<.001
Typical AP user	1.66 (1.33-- 2.09)	<.001	1.83 (1.37-- 2.44)	<.001
Haloperidol	2.03 (1.52-- 2.71)	<.001	2.91 (1.96-- 4.33)	<.001
Other typical AP	1.15 (0.80-- 1.66)	0.44	0.82 (0.53-- 1.27)	0.37
Olanzapine	1.73 (1.45-- 2.05)	<.001	1.77 (1.46-- 2.15)	<.001
Quetiapine	1.68 (1.55-- 1.82)	<.001	1.69 (1.55-- 1.84)	<.001
Risperidone	1.42 (1.20-- 1.67)	<.001	1.51 (1.27-- 1.80)	<.001
Other atypical AP	1.38 (1.00-- 1.92)	0.05	1.34 (0.91-- 1.98)	0.14

Weintraub et al. (under review).

Links with Serotonin System (5-HT2A Receptor)



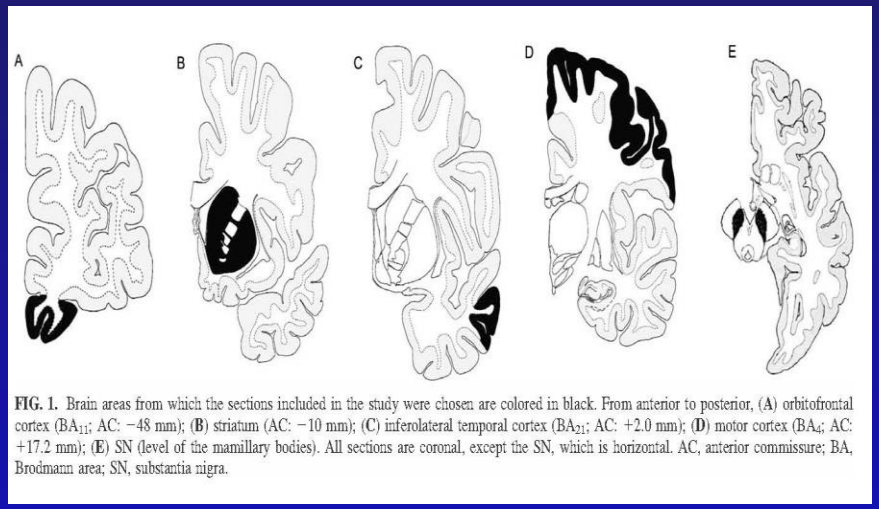
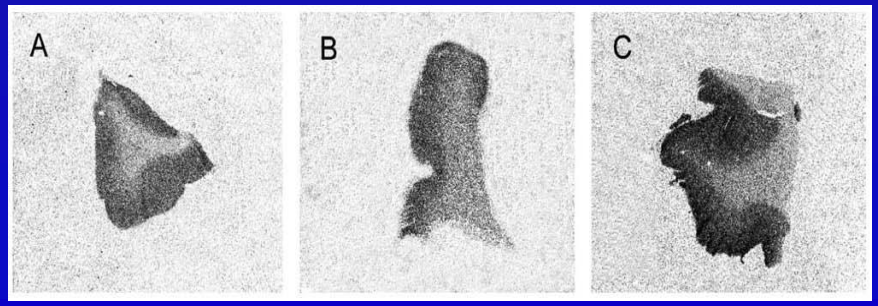
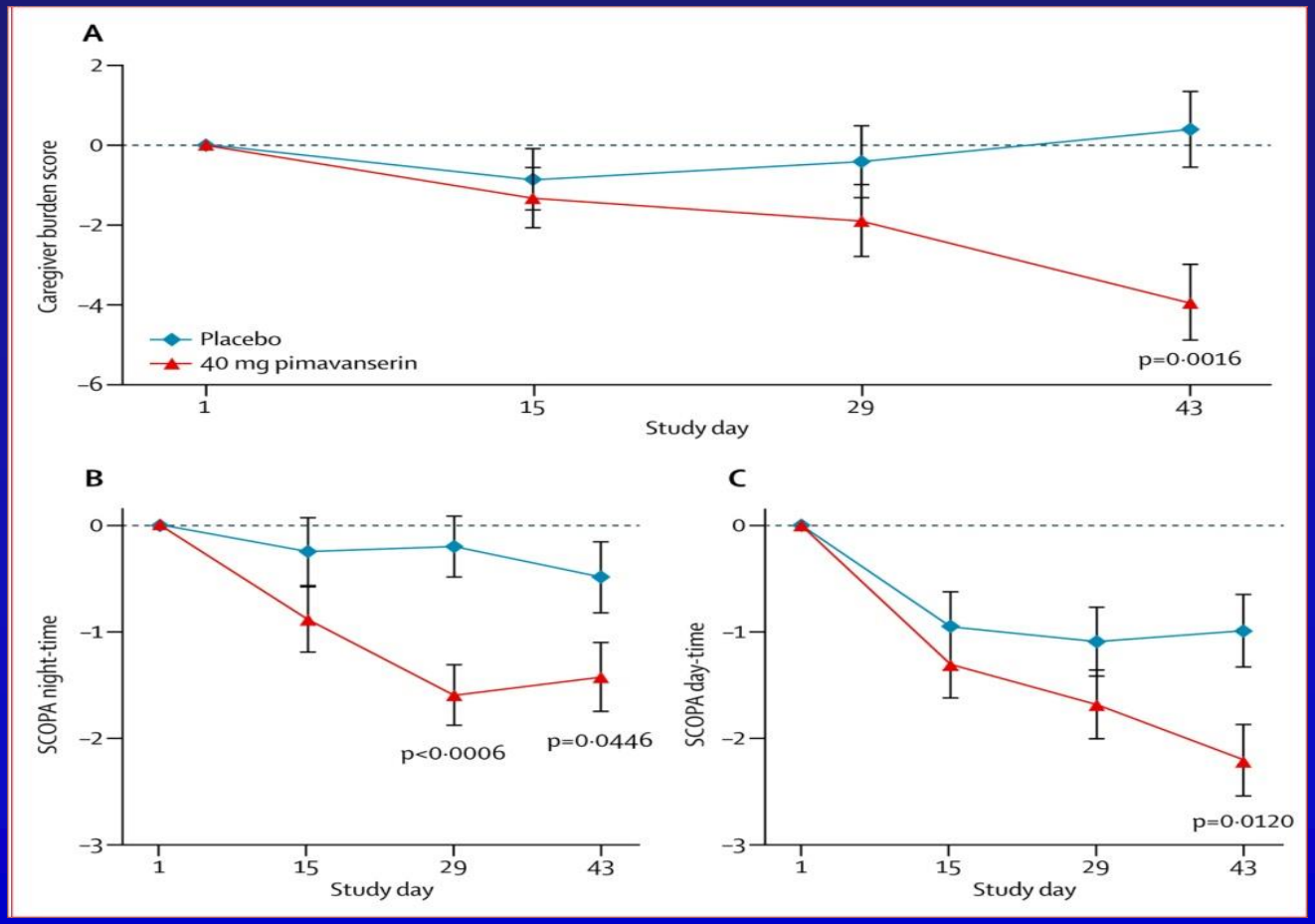


FIG. 1. Brain areas from which the sections included in the study were chosen are colored in black. From anterior to posterior, (**A**) orbitofrontal cortex (BA_{11}; AC: −48 mm); (**B**) striatum (AC: −10 mm); (**C**) inferolateral temporal cortex (BA_{21}; AC: +2.0 mm); (**D**) motor cortex (BA_4; AC: +17.2 mm); (**E**) SN (level of the mamillary bodies). All sections are coronal, except the SN, which is horizontal. AC, anterior commissure; BA, Brodmann area; SN, substantia nigra.



Huot et al. *Movement Disorders* 2010;25:1399-1408.
Ballanger et al. *Arch Neurol* 2010;67:416-421.

New AP for PD Psychosis (Pimavanserin - 5HT-2A inverse agonist)



Cummings et al. *The Lancet* 2013;383:533-540.

Change in SAPS-PD Score For Cognitively Impaired (Baseline MMSE Score <25)

End-of-Study Change	Placebo	Pimavanserin
N	19	27
Mean (SE)	**-0.47 (1.89)**	**-7.11 (1.81)**
Median	2.00	-8.00

Unpublised Data courtesy Acadia Pharmaceuticals and Dr. Clive Ballard.

Cognitive Impairment

Dementia Almost Inevitable Long-Term?

ORIGINAL CONTRIBUTION

Prevalence and Characteristics of Dementia in Parkinson Disease

An 8-Year Prospective Study

Dag Aarsland, MD, PhD; Kjeld Andersen, MD, PhD; Jan P. Larsen, MD, PhD; Anette Lolk, MD, PhD; Per Kragh-Sørensen, MD, DMSc

Background: Few longitudinal studies of dementia in Parkinson disease (PD) have been reported, and the proportion of patients with PD who eventually develop dementia is unknown.

Objective: To examine the 8-year prevalence, characteristics, and risk factors of dementia in patients with PD.

Methods: Patients were recruited from an epidemiological study of PD in the county of Rogaland, Norway, using explicit criteria for PD. Subjects with cognitive impairment at disease onset were excluded. A semistructured caregiver-based interview, cognitive rating scales, and neuropsychological tests were used to diagnose dementia according to criteria from the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* at baseline and 4 and 8 years later. A population-based sample of 3295 subjects in the municipality of Odense, Denmark, was used as a comparison group and examined at baseline and after 2 and 5 years.

Results: We included 224 patients with PD (116 women). At baseline, 51 patients (26%) had dementia. Fifty-five patients died, and 10 refused follow-up without their dementia status known. Forty-three and 28 new cases of dementia were identified at the 4- and 8-year evaluations, respectively. The 4-year prevalence of dementia in PD was nearly 3 times higher than in the non-PD group. The 8-year prevalence in PD was 78.2% (95% confidence interval [CI], 71.1-84.0). Risk factors for dementia were hallucinations before baseline (odds ratio [OR]=3.1; 95% CI, 1.6-6.2) and akinetic-dominant or mixed tremor/akinetic PD (OR=3.3; 95% CI, 1.2-8.5).

Conclusions: More than three quarters of this representative PD cohort developed dementia during the 8-year study period. Early hallucinations and akinetic-dominant PD were associated with an increased risk of dementia.

Arch Neurol. 2003;60:387-392

Cognition in De Novo PD: PPMI Data

Cognitive Domain	Variable	Mean (SD) or N (%)
Global	**MOCA score** (N=423)	27.1 (2.3)
	30 - 26	330 (78%)
	21 - 25	89 (21%)
	<21	4 (1%)
Visuospatial	**Benton Judgment of Line Orientation Score** (N=422)	12.8 (2.1)
	Mild Impairment[a]	30 (7%)
	Moderate Impairment[b]	**14 (3%)**
	Severe Impairment[c]	2 (0%)
Memory	**HVLT Immediate Recall** (N=422)	24.4 (5.0)
	Mild Impairment	131 (31%)
	Moderate Impairment	**73 (17%)**
	Severe Impairment	29 (7%)
	HVLT Delayed Recall (N=422)	8.4 (2.5)
	Mild Impairment	139 (33%)
	Moderate Impairment	**70 (17%)**
	Severe Impairment	26 (6%)
	HVLT Retention (N=422)	0.9 (0.2)
	Mild Impairment	89 (21%)
	Moderate Impairment	**47 (11%)**
	Severe Impairment	21 (5%)
	HVLT Discrimination Recognition (N=421)	9.6 (2.6)
	Mild Impairment	102 (24%)
	Moderate Impairment	**38 (9%)**
	Severe Impairment	13 (3%)
Executive abilities-Working memory	**Letter Number Sequencing Raw Score** (N=422)	10.6 (2.7)
	Mild Impairment	28 (7%)
	Moderate Impairment	**19 (4%)**
	Severe Impairment	4 (1%)
	Semantic Fluency Total Score (N=422)	48.7 (11.6)
	Mild Impairment	61 (14%)
	Moderate Impairment	**22 (5%)**
	Severe Impairment	9 (2%)
Processing speed-Attention	**Symbol Digit Modalities Score** (N=422)	41.2 (9.7)
	Mild Impairment	110 (26%)
	Moderate Impairment	**60 (14%)**
	Severe Impairment	27 (6%)

Weintraub et al. *Movement Disorders* 2015;30:919-927.

Cognition Part of Pre-Motor Syndrome?

Table 3. Logistic regression models of cognitive domains predicting membership in the hyposmia+DAT reduction group (n=38) versus all others (n=187)[a]

Variable	Regression coefficient	Standard error	Wald chi-square	Odds ratio	95% CI	P-value
Global cognition	-0.68	0.24	8.30	0.51	0.32 – 0.81	0.004
Executive function / Working memory	-0.61	0.21	8.18	0.54	0.36 – 0.83	0.004
Language	-0.25	0.20	1.66	0.78	0.53 – 1.14	0.20
Memory	-0.50	0.21	5.52	0.61	0.40 – 0.92	0.02
Processing speed/Attention	-0.43	0.22	3.92	0.65	0.43 – 1.00	0.048
Visuospatial	-0.17	0.21	0.65	0.85	0.56 – 1.27	0.42

[a] Adjusting for age at testing, sex, and education

Chahine and Weintraub et al. *Movement Disorders* 2015; 10.1002/mds.26373.

Heterogeneity in Early Cognitive Deficits

Mild cognitive impairment in Parkinson disease

A multicenter pooled analysis

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K. Bronnick, PhD
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P. Barone, MD
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L. Allcock, MD
G. Santangelo, PhD
T. Foltynie, PhD
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ABSTRACT

Background: In studies of mild cognitive impairment (MCI) in Parkinson disease (PD), patients without dementia have reported variable prevalences and profiles of MCI, likely to be due to methodologic differences between the studies.

Objective: The objective of this study was to determine frequency and the profile of MCI in a large, multicenter cohort of well-defined patients with PD using a standardized analytic method and a common definition of MCI.

Methods: A total of 1,346 patients with PD from 8 different cohorts were included. Standardized analysis of verbal memory, visuospatial, and attentional/executive abilities was performed. Subjects were classified as having MCI if their age- and education-corrected z score on one or more cognitive domains was at least 1.5 standard deviations below the mean of either control subjects or normative data.

Results: A total of 25.8% of subjects (95% confidence interval [CI] 23.5–28.2) were classified as having MCI. Memory impairment was most common (13.3%; 11.6–15.3), followed by visuospatial (11.0%; 9.4–13.0) and attention/executive ability impairment (10.1%; 8.6–11.9). Regarding cognitive profiles, 11.3% (9.7–13.1) were classified as nonamnestic single-domain MCI, 8.9% (7.0–9.9) as amnestic single-domain, 4.8% (3.8–6.1) as amnestic multiple-domain, and 1.3% (0.9–2.1) as nonamnestic multiple-domain MCI. Having MCI was associated with older age at assessment and at disease onset, male gender, depression, more severe motor symptoms, and advanced disease stage.

Conclusions: MCI is common in patients with PD without dementia, affecting a range of cognitive domains, including memory, visual-spatial, and attention/executive abilities. Future studies of patients with PD with MCI need to determine risk factors for ongoing cognitive decline and assess interventions at a predementia stage. *Neurology*® 2010;75:1062–1069

- 25-30% of established non-demented patients with MCI
- Memory impairment common
- Multi-domain impairment common

Frequent and Fast Progression From MCI to Dementia

Long-term o
for incident
establishe

ONLINE FIRST

Prognosis of M
in Early Parkir

The Norwegian ParkW

Kenn Freddy Pedersen, MD, PhD

Importance: Mild cognitive im
mon in Parkinson disease (PD),
of MCI in early PD is unknown

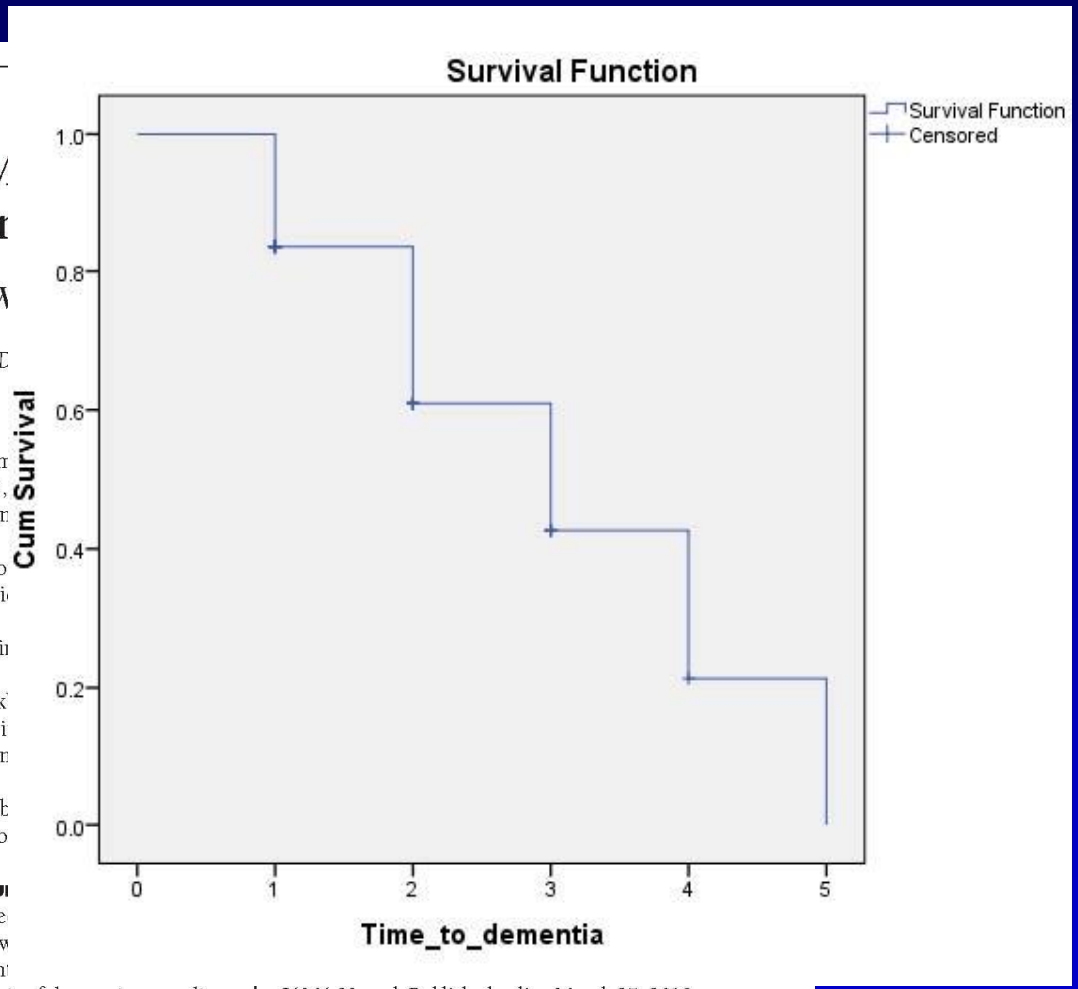
Objective: To examine the co
gression to dementia in an inci

Design: Prospective longitudi

Setting: The Norwegian Park
population-based study of the i
and prognosis of PD in western

Participants: A population-b
tients with incident PD monito

Main Outcomes and Measu
logical tests of attention, exe
memory, and visuospatial skills w
line, 1 year, and 3 years. Patien
ing MCI and received a diagnosis of dementia according
to published consensus criteria.



JAMA Neurol. Published online March 25, 2013.
doi:10.1001/jamaneurol.2013.2110

Pigott et al. *Neurology* 2015;85:1276-1282.

RESEARCH ARTICLE

CME

Dopamine Transporter Imaging Is Associated With Long-Term Outcomes in Parkinson's Disease

Bernard Ravina, MD, MSCE,[1*] Kenneth Marek, MD,[2] Shirley Eberly, MS,[3†] David Oakes, PhD,[3†] Roger Kurlan, MD,[4] Alberto Ascherio, PhD,[5] Flint Beal, MD, PhD,[6] James Beck, PhD,[7] Emily Flagg, BA,[1] Wendy R. Galpern, MD, PhD,[8] Jennifer Harman, PhD,[3] Anthony E. Lang, MD,[9] Michael Schwarzschild, MD, PhD,[5] Caroline Tanner, MD, PhD,[10] and Ira Shoulson, MD[1]

TABLE 3. ORs for dichotomous outcomes by quartiles of baseline mean striatal binding

	Number of Subjects	Outcome Rate (%)	*P* Value for Trend	ORs (95% CI) Q1	Q2	Q3	Q4
MMSE <24	491	19 (3.9)	0.0293	7.6 (0.8, 68.4)	5.8 (0.6, 51.7)	2.3 (0.2, 26.7)	1
MoCA <26	489	137 (28.0)	0.0002	3.3 (1.7, 6.7)	1.7 (0.9, 3.4)	1.4 (0.7, 2.8)	1
Psychosis	491	34 (6.9)	0.0002	12.9 (2.8, 62.4)	6.4 (1.3, 30.9)	3.6 (0.8, 16.5)	1
GDS >=5	490	97 (19.8)	0.0056	2.8 (1.3, 5.7)	1.8 (0.9, 3.6)	1.4 (0.7, 2.8)	1
Postural instability	488	37 (7.6)	0.0018	4.9 (1.6, 15.2)	2.0 (0.7, 6.4)	0.9 (0.2, 3.3)	1
Falling	490	60 (12.2)	0.0089	2.2 (0.9, 5.1)	1.7 (0.7, 3.7)	0.4 (0.1, 1.2)	1
QoL decline	489	122 (25.0)	0.0537	1.8 (0.9, 3.4)	1.3 (0.7, 2.4)	0.9 (0.5, 1.8)	1
S/E ADL decline ≥15	490	67 (13.7)	0.0066	2.8 (1.2, 6.3)	1.1 (0.5, 2.5)	0.7 (0.3, 1.6)	1

ORs (95% CIs) from separate logistic regressions adjusted for age, gender, duration of disease, and PreCEPT study treatment, as well as for use of DAAs and/or L-dopa at most recent visit. S/E ADL analysis was also adjusted for baseline S/E ADL. Mean values for quartiles are shown in Table 2. The highest quartile (4) is the reference category.

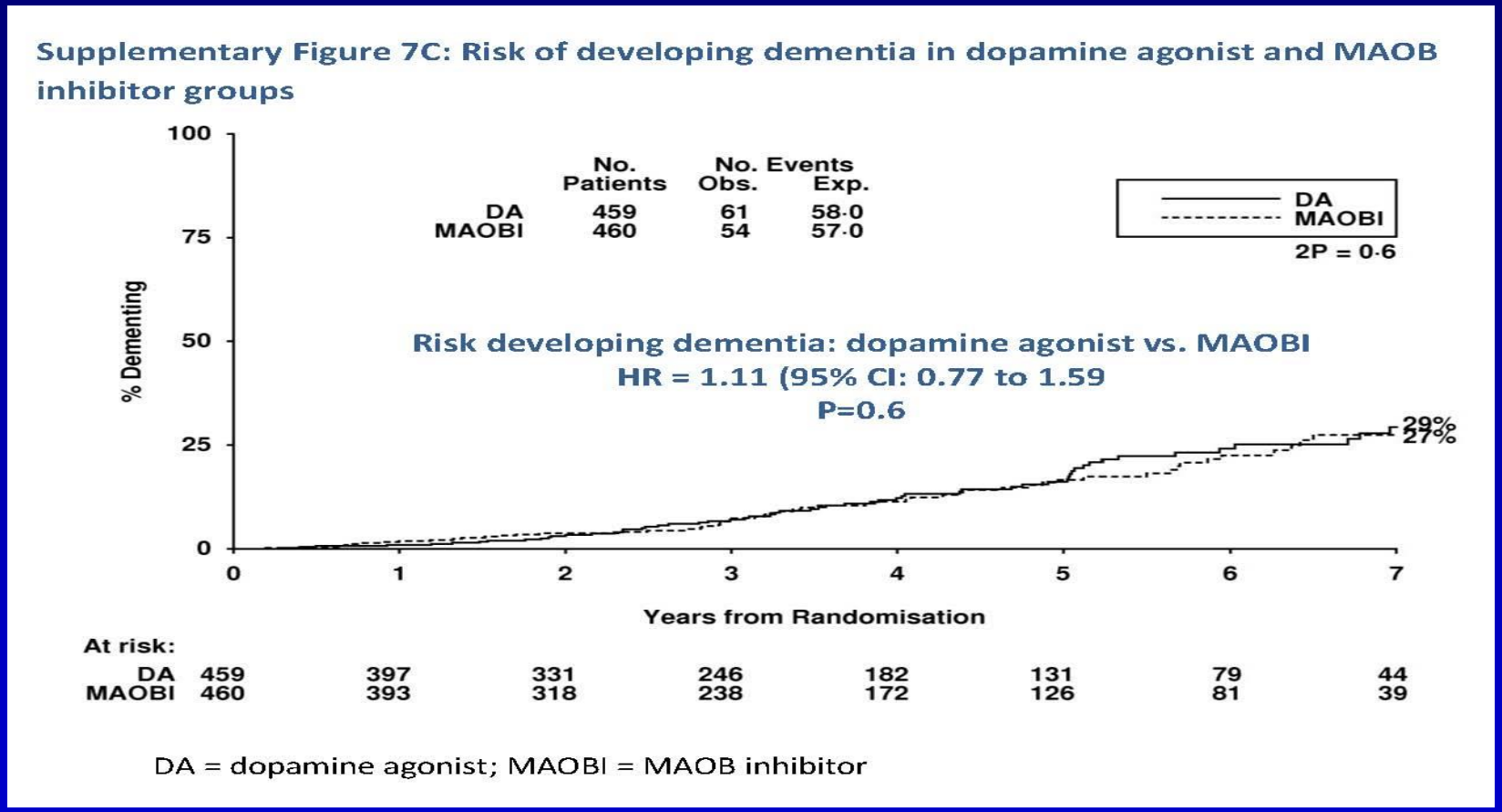
TABLE 5. ORs for dichotomous outcomes by quartiles of annual percentage change in mean striatal binding

	Number of Subjects	Outcome Rate (%)	*P* Value for Trend	ORs (95% CI) Q1	Q2	Q3	Q4
MMSE <24	461	19 (4.1)	0.0385	5.4 (1.2, 23.7)	0.4 (0.0, 4.6)	2.1 (0.4, 10.3)	1
MoCA <26	459	129 (28.1)	0.0278	2.1 (1.1, 3.9)	1.3 (0.7, 2.6)	1.2 (0.6, 2.3)	1
Psychosis	461	32 (6.9)	0.0018	6.4 (1.9, 21.3)	2.5 (0.7, 9.3)	2.4 (0.6, 8.7)	1
GDS >=5	460	90 (19.6)	0.1304	1.6 (0.8, 3.2)	2.0 (1.0, 4.0)	1.3 (0.7, 2.8)	1
Postural instability	459	35 (7.6)	0.5030	1.4 (0.5, 3.7)	0.8 (0.3, 2.5)	0.8 (0.3, 2.3)	1
Falling	460	57 (12.4)	0.0485	2.1 (0.9, 5.3)	3.0 (1.2, 7.1)	1.7 (0.7, 4.1)	1
QoL decline	459	113 (24.6)	0.4453	1.2 (0.7, 2.4)	1.5 (0.8, 2.9)	1.3 (0.7, 2.5)	1
S/E ADL decline ≥15	460	63 (13.7)	<0.0001	6.5 (2.4, 17.8)	6.1 (2.3, 16.7)	2.6 (0.9, 7.5)	1

ORs (95% CIs) from separate logistic regressions adjusted for baseline mean striatum, age, gender, duration of disease, and PreCEPT study treatment, as well as for use of DAAs and/or L-dopa at most recent visit. S/E ADL analysis was also adjusted for baseline S/E ADL. Mean values for quartiles are shown in Table 2. The highest quartile is the reference category.

Ravina et al. *Movement Disorders* 2012;27:1932-1397.

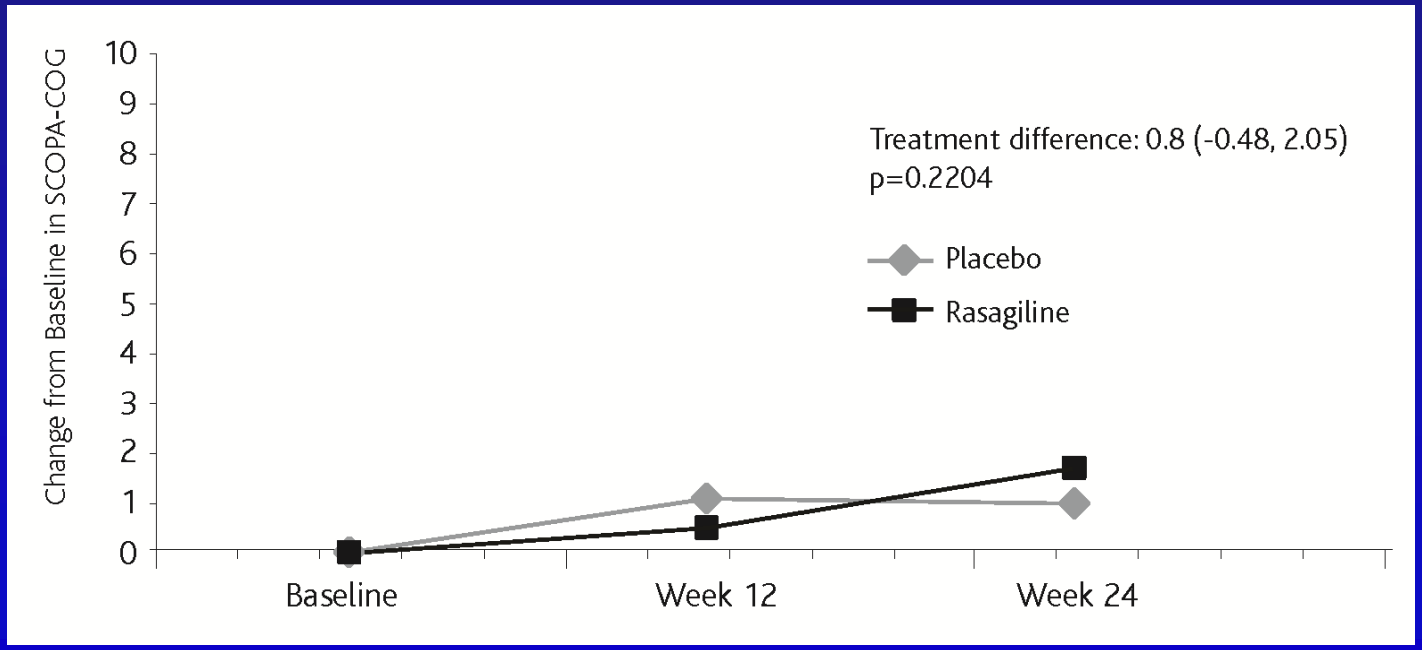
But No Differential Long-Term Effect for PD Medications



PD MED Collaborative Group. *Lancet* 2014;80:792-799.

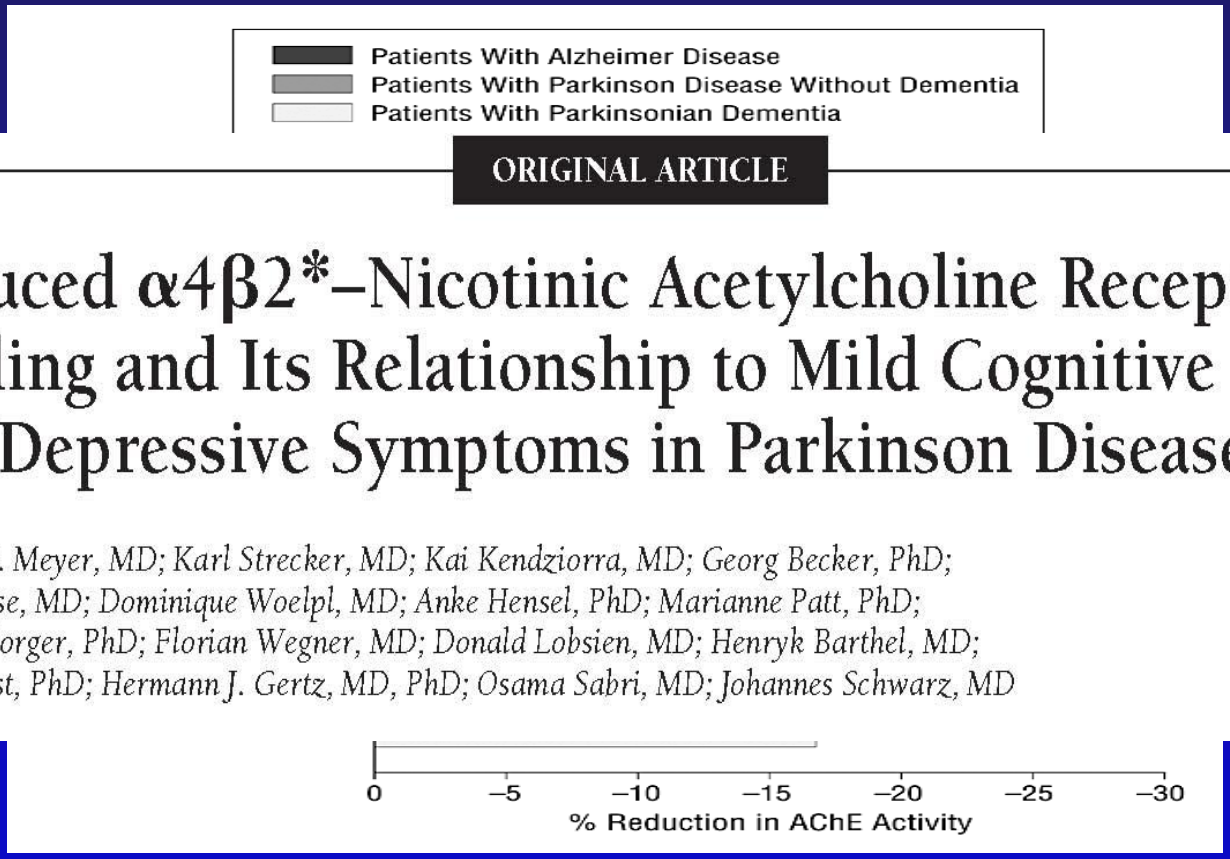
No Effect for MAO-B Inhibitor in PD-MCI

Change from Baseline in SCOPA-COG scores



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

Early, Significant and Widespread Cholinergic Deficits



ORIGINAL ARTICLE

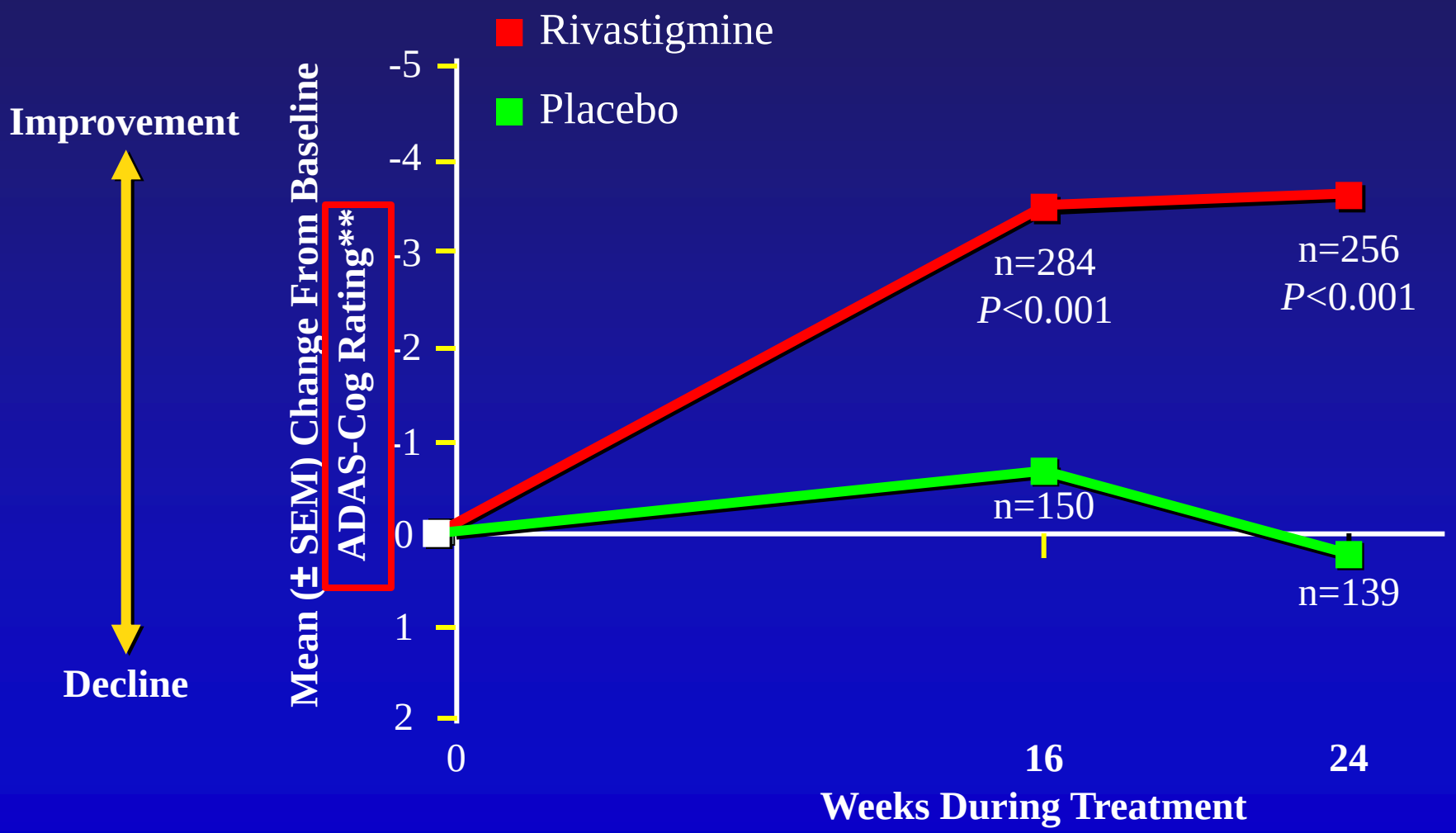
Reduced α4β2*–Nicotinic Acetylcholine Receptor Binding and Its Relationship to Mild Cognitive and Depressive Symptoms in Parkinson Disease

Philipp M. Meyer, MD; Karl Strecker, MD; Kai Kendziorra, MD; Georg Becker, PhD; Swen Hesse, MD; Dominique Woelpl, MD; Anke Hensel, PhD; Marianne Patt, PhD; Dietlind Sorger, PhD; Florian Wegner, MD; Donald Lobsien, MD; Henryk Barthel, MD; Peter Brust, PhD; Hermann J. Gertz, MD, PhD; Osama Sabri, MD; Johannes Schwarz, MD

AChE = acetylcholinesterase activity

Bohnen et al. *Archives of Neurology* 2003;60:1745-1748.
Meyer et al. *Arch Gen Psychiatry* 2009;66:866-877.

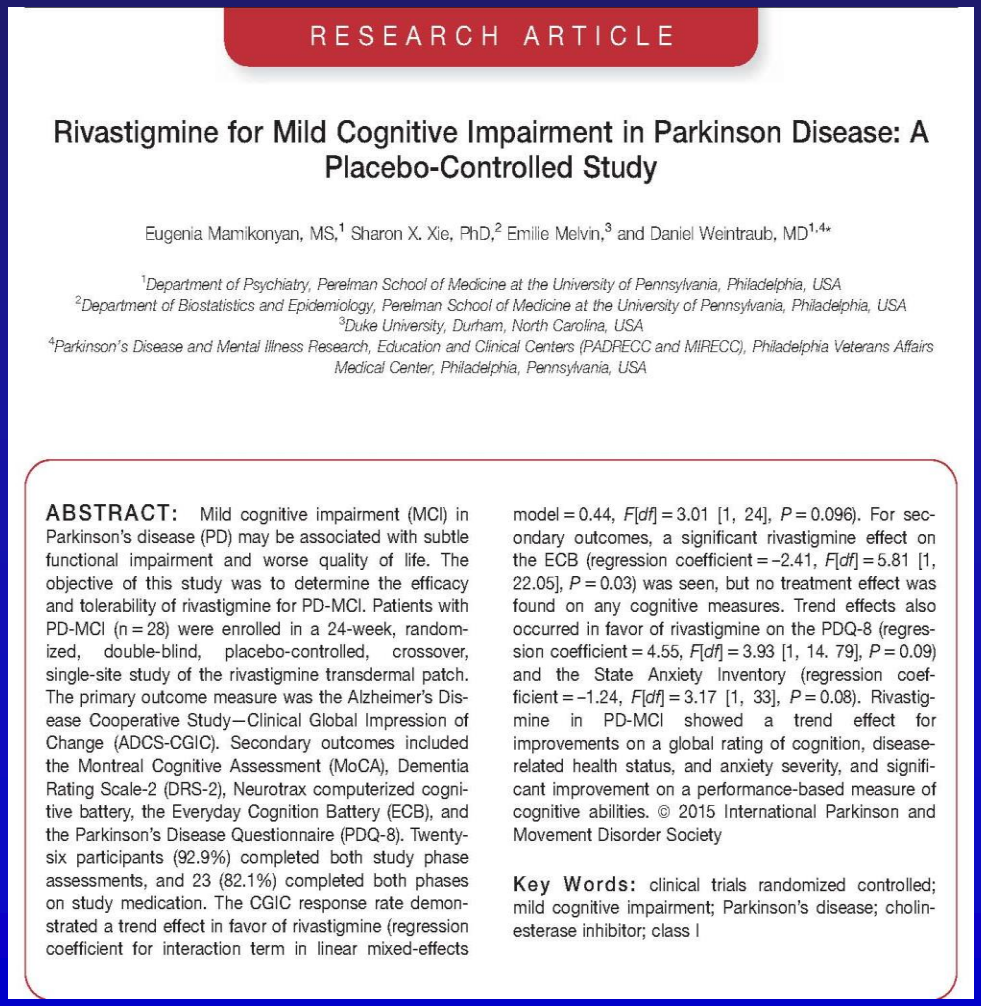
Rivastigmine for PDD



Observed case (OC) analysis

Emre et al. NEJM 2004 351:2509-2518.

Cholinesterase Inhibitors for PD-MCI?



RESEARCH ARTICLE

Rivastigmine for Mild Cognitive Impairment in Parkinson Disease: A Placebo-Controlled Study

Eugenia Mamikonyan, MS,[1] Sharon X. Xie, PhD,[2] Emilie Melvin,[3] and Daniel Weintraub, MD[1,4]*

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[2]Department of Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, USA
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[4]Parkinson's Disease and Mental Illness Research, Education and Clinical Centers (PADRECC and MIRECC), Philadelphia Veterans Affairs Medical Center, Philadelphia, Pennsylvania, USA

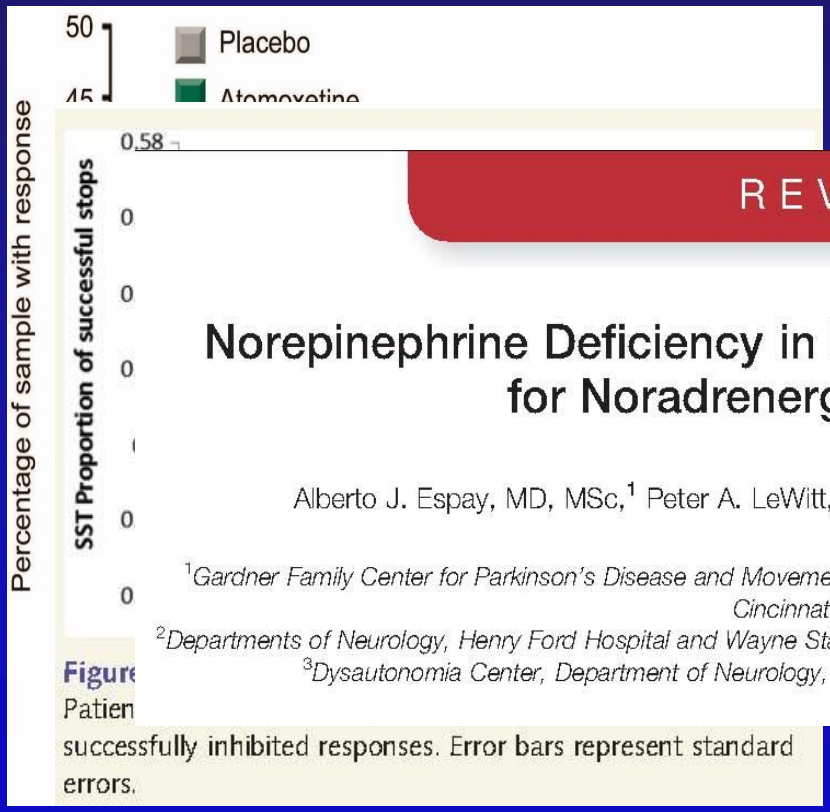
ABSTRACT: Mild cognitive impairment (MCI) in Parkinson's disease (PD) may be associated with subtle functional impairment and worse quality of life. The objective of this study was to determine the efficacy and tolerability of rivastigmine for PD-MCI. Patients with PD-MCI (n = 28) were enrolled in a 24-week, randomized, double-blind, placebo-controlled, crossover, single-site study of the rivastigmine transdermal patch. The primary outcome measure was the Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change (ADCS-CGIC). Secondary outcomes included the Montreal Cognitive Assessment (MoCA), Dementia Rating Scale-2 (DRS-2), Neurotrax computerized cognitive battery, the Everyday Cognition Battery (ECB), and the Parkinson's Disease Questionnaire (PDQ-8). Twenty-six participants (92.9%) completed both study phase assessments, and 23 (82.1%) completed both phases on study medication. The CGIC response rate demonstrated a trend effect in favor of rivastigmine (regression coefficient for interaction term in linear mixed-effects model = 0.44, $F[df] = 3.01$ [1, 24], $P = 0.096$). For secondary outcomes, a significant rivastigmine effect on the ECB (regression coefficient = −2.41, $F[df] = 5.81$ [1, 22.05], $P = 0.03$) was seen, but no treatment effect was found on any cognitive measures. Trend effects also occurred in favor of rivastigmine on the PDQ-8 (regression coefficient = 4.55, $F[df] = 3.93$ [1, 14. 79], $P = 0.09$) and the State Anxiety Inventory (regression coefficient = −1.24, $F[df] = 3.17$ [1, 33], $P = 0.08$). Rivastigmine in PD-MCI showed a trend effect for improvements on a global rating of cognition, disease-related health status, and anxiety severity, and significant improvement on a performance-based measure of cognitive abilities. © 2015 International Parkinson and Movement Disorder Society

Key Words: clinical trials randomized controlled; mild cognitive impairment; Parkinson's disease; cholinesterase inhibitor; class I

- No effect on cognitive measures
- Trend improvement on CGI
- Trend improvement in disease-related function and anxiety
- Significant improvement on performance-based measure of cognitive abilities

Mamikonyan et al. *Movement Disorders* 2015;30:912-918.

The Rise of Norepinephrine



REVIEW

Norepinephrine Deficiency in Parkinson's Disease: The Case for Noradrenergic Enhancement

Alberto J. Espay, MD, MSc,[1] Peter A. LeWitt, MD, MMedSc,[2] and Horacio Kaufmann, MD[3]*

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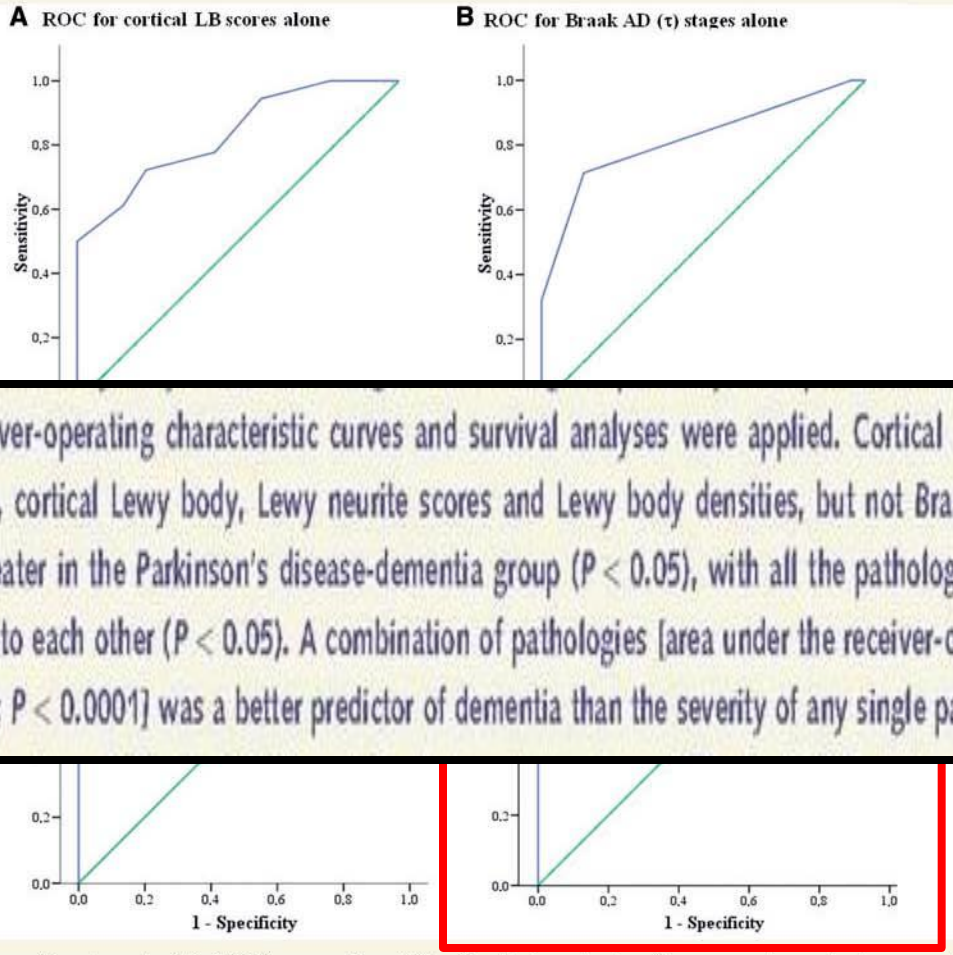
[2]*Departments of Neurology, Henry Ford Hospital and Wayne State University School of Medicine, West Bloomfield, Michigan, USA*
[3]*Dysautonomia Center, Department of Neurology, NYU School of Medicine, New York, New York, USA*

Figure 2 Effects of atomoxetine on the Cambridge Gamble Task. Atomoxetine reduced impulsivity when it was administered on the first session. Patients receiving atomoxetine exhibited **(A)** increased deliberation time and **(B)** more modest increases in betting as the probability of winning increased. Error bars represent standard errors.

Weintraub et al. *Neurology* 2010;75:448-455.
Kehagia et al. *Brain* 2014;137:1986-1997.

doi:10.1093/brain/awr031 Brain 2011: 134; 1493–1505 | 1493

BRAIN



regression models, receiver-operating characteristic curves and survival analyses were applied. Cortical and striatal amyloid-β scores, Braak tau stages, cortical Lewy body, Lewy neurite scores and Lewy body densities, but not Braak α-synuclein stages, were all significantly greater in the Parkinson's disease-dementia group ($P < 0.05$), with all the pathologies showing a significant positive correlation to each other ($P < 0.05$). A combination of pathologies [area under the receiver-operating characteristic curve = 0.95 (0.88–1.00); $P < 0.0001$] was a better predictor of dementia than the severity of any single pathology. Additionally,

Figure 4 Receiver operating characteristic (ROC) curves for ability of pathology to classify cases as demented or non-demented created using the probabilities obtained in the binary regression models. (**A**) Cortical Lewy body (LB) scores alone (area under the curve = 0.83, 95% CI = 0.70–0.97, $P = 0.001$); (**B**) tau stages alone (area under the curve = 0.82, 95% CI = 0.70–0.93, $P = 0.0001$); (**C**) cortical amyloid-β (A-β) scores alone (area under the curve = 0.83, 95% CI = 0.69–0.97, $P = 0.001$); and (**D**) all three pathologies in combination (area under the curve = 0.95, 95% CI = 0.88–1.00, $P = 0.000003$). AD = Alzheimer's disease.

A combination of Lewy- and Alzheimer-type pathologies is a robust pathological correlate of dementia in Parkinson's disease, with quantitative and semi-quantitative assessment of Lewy pathology being more informative than Braak α-synuclein stages. Cortical amyloid-β and age at disease onset seem to determine the rate to dementia.

Negative DBS Effect (Advanced PD)

doi:10.1093/brain/awt151 Brain 2013: 136; 2109–2119 | 2109

BRAIN
A JOURNAL OF NEUROLOGY

Relation of lead trajectory and electrode position to neuropsychological outcomes of subthalamic neurostimulation in Parkinson's disease: results from a randomized trial

Karsten Witt,[1] Oliver Granert,[1] Christine Daniels,[1] Jens Volkmann,[1,*] Daniela Falk,[2] Thilo van Eimeren[1] and Günther Deuschl[1]

Finger tapping[6]	37.6 (12.4)	38.7 (13.2)	1.0 (−0.1 to 2.2)	37.1 (11.4)	36.9 (11.3)	−0.2 (−2.1 to 1.5)	1.3 (−1.2 to 3.8)	.32

group 6 months after surgery ($P = 0.02$). Electrode trajectories intersecting with caudate nuclei increased the risk of a decline in global cognition and working memory performance. Statistically, for every 0.1 ml overlap with a caudate nucleus, the odds for a decline >1 standard deviation increased by a factor of 37.4 (odds ratio, confidence interval 2.1–371.8) for the Mattis Dementia Rating Scale and by a factor of 8.8 (odds ratio, confidence interval 1.0–70.9) for the backward digit span task. Patients with subthalamic nucleus–deep brain stimulation who declined in semantic verbal fluency, Stroop task and the backward digit span task performance showed a position of the active electrode outside the volume built by the active electrodes of stable performers. Passage of the chronic stimulation lead through the head of the caudate increases the risk of global cognitive decline

(0.2 to 4.1) (−3.1 to 1.0) (0.4 to 6.0)

Weaver et al. *JAMA* 2009;301:63-73.
Rothlind et al. *JNNP* 2014;10.1136/jnnp-2014-308119.

No Effect for Memantine?

RESEARCH ARTICLE

International Journal of Geriatric Psychiatry

Memantine improves attention and episodic memory in Parkinson's disease dementia and dementia with Lewy bodies

Keith A. Wesnes[1,2,3], Dag Aarsland[4], Clive Ballard[5] and Elisabet Londos[6]

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[5]Wolfson Centre for Age Related Diseases, Institute of Psychiatry, King's College London, London, UK
[6]Clinical Memory Research Unit, Department of Clinical Sciences, Lund University, Malmö, Sweden
Correspondence to: K. A. Wesnes, E-mail: keith@wesnes.com

Objective: In both dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD), attentional dysfunction is a core clinical feature together with disrupted episodic memory. This study evaluated the cognitive effects of memantine in DLB and PDD using automated tests of attention and episodic memory.

Methods: A randomised double-blind, placebo-controlled, 24-week three centre trial of memantine (20 mg/day) was conducted in which tests of attention (simple and choice reaction time) and word recognition (immediate and delayed) from the CDR System were administered prior to dosing and again at 12 and 24 weeks. Although other results from this study have been published, the data from the CDR System tests were not included and are presented here for the first time.

Results: Data were available for 51 patients (21 DLB and 30 PDD). In both populations, memantine produced statistically significant medium to large effect sized improvements to choice reaction time, immediate and delayed word recognition.

Conclusions: These are the first substantial improvements on cognitive tests of attention and episodic recognition memory identified with memantine in either DLB or PDD.

Key words: memantine; dementia with Lewy bodies; Parkinson's disease dementia; attention; episodic memory; CDR System; automated cognitive tests
History: Received 15 December 2013; Accepted 4 March 2014; Published online in Wiley Online Library (wileyonlinelibrary.com)
DOI: 10.1002/gps.4109

Avoid Anticholinergics?

Research paper

Use of drugs with anticholinergic effect and impact on cognition in Parkinson's disease: a cohort study

Uwe Ehrt,[1] Karl Broich,[4] Jan Petter Larsen,[2,3] Clive Ballard,[5] Dag Aarsland[1,6]

Table 3. Association of Ir

Diagnosis, TSDD[b]		Adjusted[d,e]
Dementia		
	0	1 [Reference]
	1-90	.92 (0.74-1.16)
	91-365	.19 (0.94-1.51)
	366-1095	.23 (0.94-1.62)
	>1095	.54 (1.21-1.96)
AD		
	0	1 [Reference]
	1-90	.95 (0.74-1.23)
	91-365	.15 (0.88-1.51)
	366-1095	.30 (0.96-1.76)
	>1095	.63 (1.24-2.14)

Abbreviations: AD, Alzhein
standardized daily dose.
[a] Observations with missin
(115 observations [3.3%])
[b] Calculation of the TSDD is
[c] Adjusted for age via the ti
[d] $P < .001$, test for trend, fc
each outcome.

ort, age (via the time
evel, body mass index,
ertension, diabetes
ase, history of

p=0.004). In the linear regression analysis, after adjustment for gender, education, age and baseline Hoehn & Yahr stage scores at baseline, the association between AA load and MMSE decline was significant and remained significant after including baseline MMSE and MADRS scores (β 0.162, SE 0.077, standardised β=0.229, p=0.040; total model F=3.1, p=0.010). Similarly, there was a significant association between duration of use of AA drugs and cognitive decline after adjustment for age, education, gender, baseline Hoehn and Yahr stage, and baseline MMSE and MADRS scores in a multivariate linear regression analysis (β=1.8, SE 0.9, standardised β 0.231, p=0.032, total model F=4.9, p<0.001).

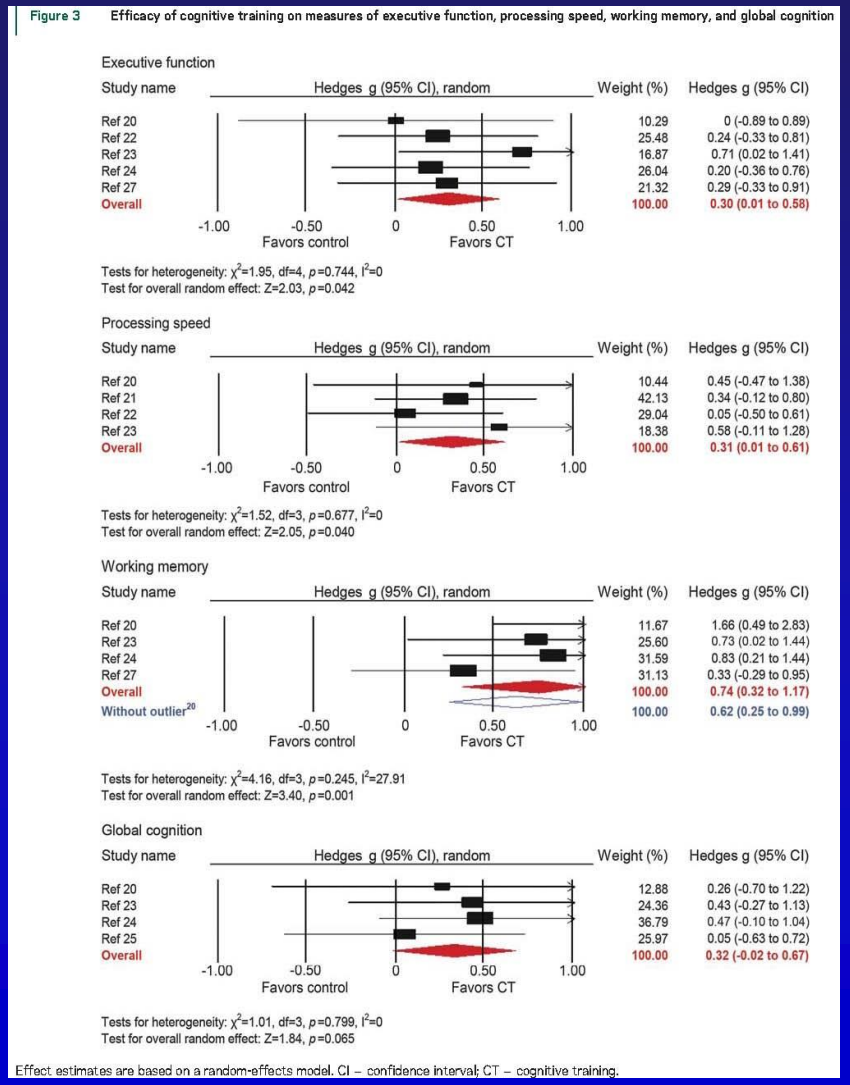
Ehrt et al. *JNNP* 2010;81:160-165.
Gray et al. *JAMA Intern Med* 2015;175:401-407.

Effect of Cognitive Training in PD

Table 1 Characteristics of included studies

Study	Sample characteristics: No. (% male)	Mean (SD) age, y	Mean (SD) MMSE	H&Y range	Mean (SD) years since diagnosis	Study design: program description
Ref. 20	15 (60)	59.70 (10.9)[a]	29.05 (1.1)[a]	1-3	3.35 (0.9)[a]	CT: computerized CT program (RehaCom), 2 × 60 minutes per week for 6 weeks (group-based); control: a simple computerized visuomotor tapping task
Ref. 21	73 (69)	68.78 (8.1)[a]	28.07 (1.5)[a]	1-3	6.94 (5.5)[a]	CT: computerized CT (InSight), 1-3 × 60 minutes per week for 13 weeks (home-based); control: no contact
Ref. 22	42 (68)	67.84 (6.4)[a]	27.05 (2.7)[a]	1-3	6.50 (5.2)[a]	CT: structured paper-pencil tasks that target multiple domains (REHACOP), 3 × 60 minutes session per week for 12 weeks (group-based); control: basic occupational activities
Ref. 23	28 (50)	65.04 (9.2)	27.89 (1.4)	1-3	7.5 (6.8)	CT: multidomain training combining paper-pencil with computerized exercises (SmartBrain Tool), 3 × 45-minute per week for 4 weeks (group-based, in addition to home exercises); control: speech therapy
Ref. 24	43 (69)	69.15 (8.7)	27.9 (2.0)	1-3	5.47 (3.2)	CT: group-based multidomain training (NEUROvitalis), 2 × 90 minutes session per week for 6 weeks; control: no contact
Ref. 25	32 (67)	67.40 (8.1)	26.80 (2.4)[b]	1-2	5 (4.5)	CT: multidomain training with an integrative computerized CT program combining motor training with attention and working memory, 2 × 30 minutes per week for 7 weeks (group-based); control: balance exercises
Ref. 27	39 (68)	68.05 (8.3)	29[c]	2[c]	5.15[d]	CT: multidomain computerized training (CogniPlus), 3 × 40 minutes session per week for 4 weeks (group-based); control: Exergames (Nintendo Wii)

Abbreviations: CT = cognitive training; H&Y = Hoehn & Yahr; MMSE = Mini-Mental State Examination.
[a] Means for the complete sample (comprising subjects who were not included in the final analysis).
[b] Measured with the Montreal Cognitive Assessment (1-30 range).
[c] Average of median scores.
[d] Based on subtracting mean age at diagnosis from mean age at baseline.



Leung et al. *Neurology* 2015;85:1–9.

Does Exercise Improve Cognition in PD?

Phase I/II randomized trial of aerobic exercise in Parkinson disease in a community setting

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ABSTRACT

Objectives: To (1) investigate effects of aerobic walking on motor function, cognition, and quality of life in Parkinson disease (PD), and (2) compare safety, tolerability, and fitness benefits of different forms of exercise intervention: continuous/moderate intensity vs interval/alternating between low and vigorous intensity, and individual/neighborhood vs group/facility setting.

Methods: Initial design was a 6-month, 2 × 2 randomized trial of different exercise regimens in independently ambulatory patients with PD. All arms were required to exercise 3 times per week, 45 minutes per session.

Results: Randomization to group/facility setting was not feasible because of logistical factors. Over the first 2 years, we randomized 43 participants to continuous or interval training. Because preliminary analyses suggested higher musculoskeletal adverse events in the interval group and lack of difference between training methods in improving fitness, the next 17 participants were allocated only to continuous training. Eighty-one percent of 60 participants completed the study with a mean attendance of 83.3% (95% confidence interval: 77.5%–89.0%), exercising at 46.8% (44.0%–49.7%) of their heart rate reserve. There were no serious adverse events. Across all completers, we observed improvements in maximum oxygen consumption, gait speed, Unified Parkinson's Disease Rating Scale sections I and III scores (particularly axial functions and rigidity), fatigue, depression, quality of life (e.g., psychological outlook), and flanker task scores ($p < 0.05$ to $p < 0.001$). Increase in maximum oxygen consumption correlated with improvements on the flanker task and quality of life ($p < 0.05$).

Conclusions: Our preliminary study suggests that aerobic walking in a community setting is safe, well tolerated, and improves aerobic fitness, motor function, fatigue, mood, executive control, and quality of life in mild to moderate PD.

Classification of evidence: This study provides Class IV evidence that in patients with PD, an aerobic exercise program improves aerobic fitness, motor function, fatigue, mood, and cognition.

Neurology® 2014;83:413–425

Value of Good Night Sleep

"95 patients with idiopathic PD…wore actigraphy watch for 2 weeks, from which measure of nocturnal sleep efficiency calculated…Working memory and verbal memory consolidation significantly associated with sleep efficiency. Findings reveal that nocturnal sleep disturbance in Parkinson's disease is associated with specific cognitive difficulties."

Gunn et al. *J of Clin Neuroscience* 2014;21:1112-1115.

Impulse Control Disorders (ICDs)

Screening for impulse control symptoms in patients with de novo Parkinson disease

Case-control study

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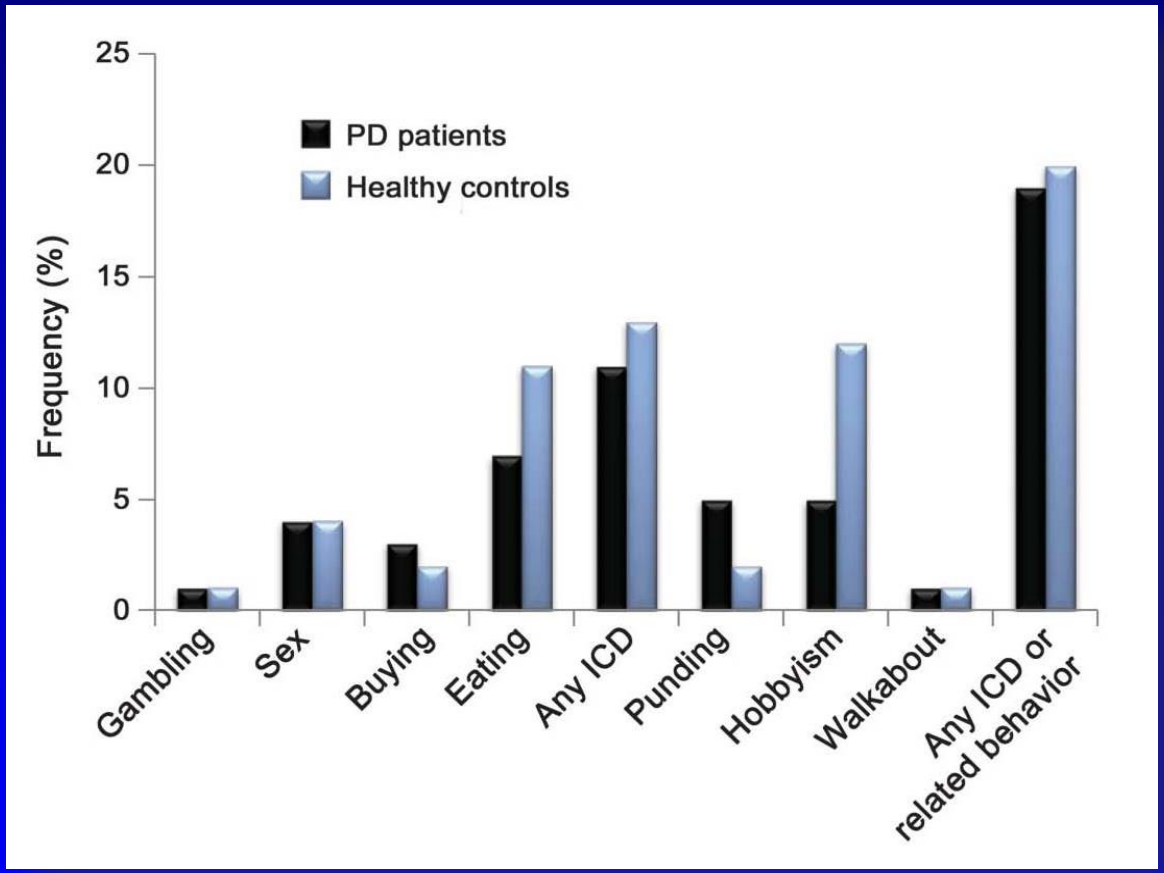
For the Parkinson's Progression Markers Initiative



There were no statistically significant differences found for frequencies of ICD or related behavior symptoms between PD patients and HCs ($p \geq 0.05$), except for obbyism, which was more common in HCs ($p=0.04$).

Weintraub et al. *Neurology* 2013;80:176-180.

ICDs Common in Treated PD: DOMINION Study

5.7%

(7.2%)*

5.0%

(6.4%)*

4.3%

(5.6%)*

3.5%

(4.4%)*

Combined Frequency:
Overall=14%; *On DA=17%; ≥2 ICDs=4%

Weintraub et al. *Archives of Neurology* 2010;67:589-595.

Not Just Dopamine Agonists

Variable*	Entire Study Population (N=3090)		
	Odds ratio [95% CI]	P value	PAR%&
Age (≤65 years vs. >65 years)	2.50 [1.98; 3.15]	<0.001	41.2%
Marital status (not married vs. married)	1.48 [1.16; 1.89]	0.002	7.4%
Country (living in United States)	1.62 [1.25; 2.10]	<0.001	27.9%
Current smoking (yes vs. no)	1.70 [1.07; 2.70]	0.02	2.9%
Family history gambling problems (yes vs. no)	2.08 [1.33; 3.25]	0.001	1.5%
DA treatment (yes vs. no)	2.72 [2.07; 3.57]	<0.001	49.3%
Levodopa treatment (yes vs. no)	1.51 [1.09; 2.09]	0.01	9.6%

* Clinical and demographic variables included were those with P value <0.10 on univariate analysis; data presented for significant results only; & **PAR% (population attributable risk percentage) for exposure variable = ([prevalence in the entire population – prevalence in unexposed population] / prevalence in entire population) x 100**. The PAR% is a univariate calculation, so the sum of the PAR% for multiple variables can exceed 100%.

Amantadine Too

TABLE 1: Impulse Control Disorder Frequencies by Amantadine Treatment Status

	Amantadine use	32 (4.4)	696 (95.6)	1.03 (0.68–1.54)

[a]Stratified by country.
CI = confidence interval; CMH = Cochran-Mantel-Haenszel test.

TABLE 3: Multivariable Logistic Regression Model (Stepwise Selection) of ICD Correlates

Step	Variable[a]	Model	
		Odds ratio (95% CI)	*p*
1	Age (≤65 years vs >65 years)	2.40 (1.91–3.02)	<0.0001
2	DA use (yes vs no)	2.64 (2.01–3.46)	<0.0001
3	Levodopa LEDD (median ≥ 450mg/day)	1.50 (1.21–1.86)	0.0002
4	Amantadine use (yes vs no)	1.29 (1.02–1.63)	0.0342

[a]Clinical and demographic variables included were those with $p < 0.10$ on univariate analysis, only data for significant results presented. Other variables included in model were PD duration, Hoehn and Yahr stage, history deep brain stimulation, education, and family history of alcohol abuse.

Weintraub et al. *Annals of Neurology* 2010;68:963-968.

Rasagiline Too

- Multicentre, r… D symptoms in PD patients (N… onths) with single nonerg… le, or rotigotine)
- ICD assessme… ire (QUIP)
- ICDs were ho… exuality=28, buying=16, ga… ler=6, walkabout=3
- In univariate a… e, and rasagiline use significan…
- On multivaria… use, and rasagiline use… CD symptoms

Table 4 Association of clinical features and ICD

	ICD + (n: 91)	ICD − (n: 142)	p (univariant)	p (multivariant regression analysis)
Male	62 (68.1)	83 (58.5)	0.1370 (NS)	–
Age (years)	63.9±9.3	67.3±9.7	0.0084	p=0.028, OR 0.96, 95% CI 0.93 to 0.99
Total UPDRS	30.2±13.4	29.6±12.9	0.7293 (NS)	NS
UPDRS III	20.2±9.2	20.3±9.2	0.9423 (NS)	NS
Fluctuations	39 (42.9)	57 (40.1)	0.6811 (NS)	–
Exposure time (years)	6.1±4.4	5.8±3.9	0.6024 (NS)	NS
Oral DA	84 (92.3)	113 (79.6)	0.0087	p=0.014, OR 3.14 (95% CI 1.26 to 7.83)
Transdermal DA	7 (7.7)	29 (20.4)		
DA-LEDD (mg)	207.5 ±89.2	198.55±96	0.4770 (NS)	–
LD-LEDD (mg)	617.1±337	591.3±307.	0.6078 (NS)	–
MAOI:	67 (76.6)	87 (61.3)	0.0519 (NS)	–
Rasagiline	66 (72.5)	82 (57.8)	0.0222	p=0.032, OR 2.12, 95% CI 1.07–4.21
Selegiline	1 (1.1)	5 (3.7)	0.2548 (NS)	
Amantadine	7 (7.7)	8 (5.6)	0.5322 (NS)	–
TOTAL LEDD (mg)	707.6±433	734.2 ±416.4	0.6401 (NS)	–

Data are shown as number and percentage for qualitative variables and mean±SD for quantitative variables.
DA-LEDD, dopamine agonist levodopa equivalent daily dose; ICD, impulse control disorder; MAOI, monoaminooxidase-B inhibitor; UPDRS, Unified Parkinson's Disease Rating Scale.

Garcia-Ruiz et al. *JNNP*. 2014;85:840-844.

Decreased Dopamine Transporter Availability Associated With Incident Behaviors in Early PD

	All subjects		Subjects on DRT	
	OR	P	OR	P
Baseline DAT binding				
Right caudate	1.07	.82	1.12	.71
Left caudate	.905	.70	.94	.84
Right putamen	.77	.58	.99	.99
Left putamen	.55	.18	.78	.63
Mean total striatal	.82	.64	.99	.98
Change in DAT binding (baseline-year 1)				
Right caudate	**2.75**	**.08**	**4.03**	**.01**
Left caudate	1.58	.35	1.78	.26
Right putamen	2.37	.33	3.28	.25
Left putamen	1.66	.48	2.52	.24
Mean total striatal	**4.04**	**.14**	**6.90**	**.04**
DAT binding (post-baseline)				
Right caudate	.66	.31	.47	.07
Left caudate	.66	.31	.62	.32
Right putamen	**.17**	**.04**	**.06**	**.01**
Left putamen	.17	.03	.15	.07
Mean total striatal	**.36**	**.09**	**.25**	**.04**

Smith et al. *JNNP*. 2016;87:864-870.

Association of single nucleotide polymorphisms with impulse control disorder incidence : A candidate gene study in the PPMI cohort

DRD2_factor3	-16.93521	2048.69466	-0.008	0.99340	
DRD3_factor2	0.63760	0.61115	1.043	0.29682	
DRD3_factor3	0.83669	1.02747	0.814	0.41546	
COMT_factor2	0.51970	0.68212	0.762	0.44613	
COMT_factor3	0.75652	0.79409	0.953	0.34075	
OPRM1_factor2	0.48013	0.83127	0.578	0.56354	
OPRM1_factor3	16.98528	6522.63873	0.003	0.99792	
DAT1_factor2	-0.79391	0.65237	-1.217	0.22362	
DAT1_factor3	0.14309	1.66148	0.086	0.93137	
GRIN2B_factor2	-0.64069	0.65719	-0.975	0.32961	
GRIN2B_factor3	-0.09186	0.83815	-0.110	0.91273	
HTR2A_factor2	2.08480	0.74418	2.801	0.00509	**
HTR2A_factor3	0.33744	0.82963	0.407	0.68420	
SERT_factor2	0.21533	0.66206	0.325	0.74500	
SERT_factor3	0.08592	0.86960	0.099	0.92129	
TPH2_factor2	0.59166	0.65999	0.896	0.37000	
TPH2_factor3	0.48228	0.94625	0.510	0.61028	
OPRK1_factor2	-2.07457	1.03999	-1.995	0.04606	*
OPRK1_factor3	-17.41113	3923.99764	-0.004	0.99646	
ADRA2C_factor2	-0.20366	0.62171	-0.328	0.74323	
ADRA2C_factor3	-18.02403	2666.66023	-0.007	0.99461	
DDC_factor2	2.79361	1.18644	2.355	0.01854	*
DDC_factor3	3.44081	1.98590	1.733	0.08316	.
DDC14_factor2	-1.58370	0.93377	-1.696	0.08988	.
DDC14_factor3	-3.67783	1.62418	-2.264	0.02355	*
AGE	-0.05271	0.03036	-1.736	0.08255	.
GENDER	-1.79254	0.77467	-2.314	0.02067	*
EDUCYRS	-0.11375	0.10121	-1.124	0.26106	
MCATOT.0	0.03504	0.14900	0.235	0.81408	
CAUCASIAN	1.42237	1.92334	0.740	0.45958	
AGONISTvsNOPDMED	3.17872	0.98832	3.216	0.00130	**

- Heritability of symptom = 57%
- Adding 13 candidate SNPs increased ICD prediction in DA-treated patients (AUC from 71% to 87%)
- Strongest SNP predictors
  - Serotonin 2A receptor
  - Kappa opioid receptor
  - Dopamine decarboxylase

Kraemmer et al. *JNNP*. 2016;10.1136/jnnp-2015-312848.

Current Management Options

- Do nothing
  - Assess significance
- Alterations to PD pharmacotherapy
  - Discontinue, lower or switch DA therapy
  - But dopamine agonist withdrawal syndrome (DAWS)
- Psychosocial treatment (CBT)
- Psychopharmacology
  - Antidepressants (SSRIs), antipsychotics, and mood stabilizers (anticonvulsants) used clinically
- Consider deep brain stimulation (DBS)

Table 2 Ardouin scale percentage of prevalence of each disorder (patients with a score ⩾2) before (baseline) and 1 year after surgery

Ardouin Scale (n = 62)	Baseline (%)	One year (%)	P-value
Mood evaluation			
Depressive mood	8.1	11.3	0.774
Hypomaniac mood, mania	12.9	0	0.008
Anxiety	22.6	11.3	0.092
Irritability, aggressiveness	14.5	6.5	0.227
Hyperemotivity	35.5	24.2	0.189
Psychotic symptoms	0	0	1.000
Functioning on an apathetic mode	4.8	21	0.013
Non-motor fluctuations			
ON	35.5	6.5	⩽0.001
OFF	41.9	14.5	⩽0.001
Hyperdopaminergic behaviours			
Nocturnal hyperactivity	30.6	3.2	⩽0.001
Diurnal somnolence	17.5	4.8	0.022
Excessive eating behaviour	37.1	12.9	0.002
Creativity	19.4	6.5	0.008
Hobbyism	33.9	1.6	⩽0.001
Punding	3.2	0	0.500
Risk-taking behaviour	4.8	4.8	1.000
Compulsive shopping	8.1	1.6	0.219
Pathological gambling	4.8	0	0.250
Hypersexuality	3.2	0	0.500
Dopaminergic compulsive medication use	19.4	1.6	0.003
Functioning on an appetitive mode	46.8	3.2	⩽0.001

Statistical values were obtained using exact McNemar test.

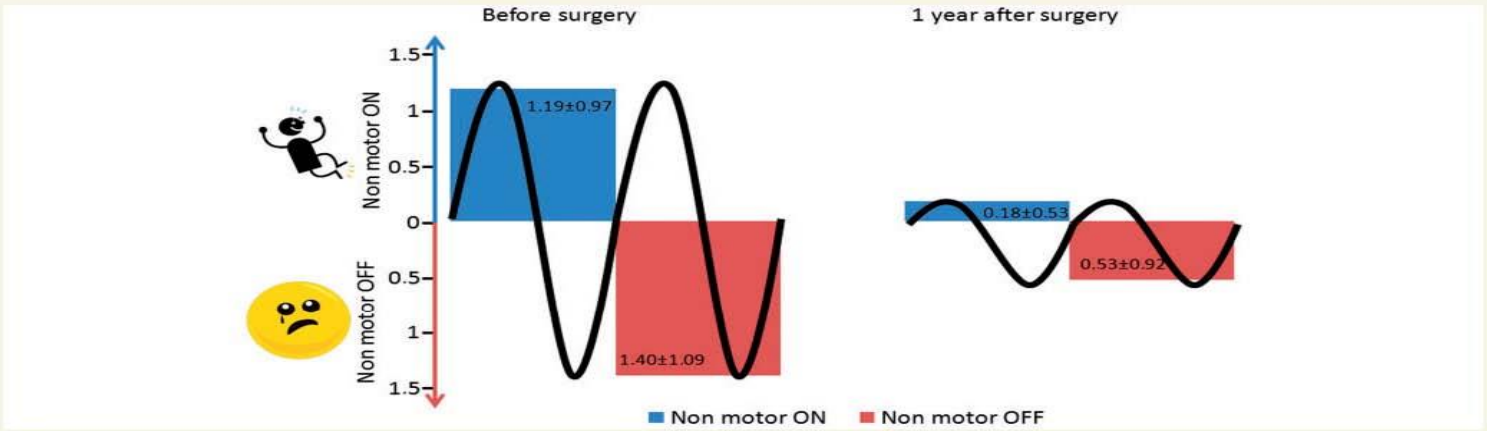


Figure 1 Non-motor fluctuations, Ardouin scale mean (±SD) severity scores (max = 4) at baseline and 1-year follow-up.

Lhommée et al. *Brain*. 2012;135:1463-1477.

Recent Complexity: Answer in Postoperative Dopaminergic Dosing?

OPEN ACCESS Freely available online

PLoS one

Effects of STN and GPi Deep Brain Stimulation on Impulse Control Disorders and Dopamine Dysregulation Syndrome

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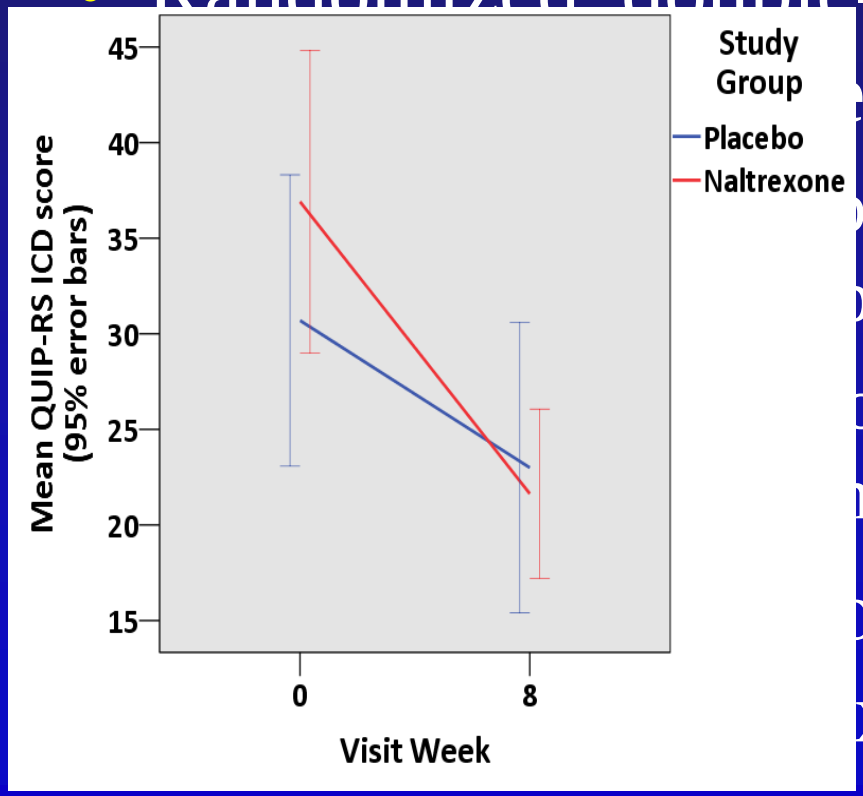
Clinical Study

Dopamine dysregulation syndrome, impulse control disorders and punding after deep brain stimulation surgery for Parkinson's disease

Shen-Yang Lim [a], Sean S. O'Sullivan [b], Katya Kotschet [c], David A. Gallagher [d], Cameron Lacey [e], Andrew D. Lawrence [f], Andrew J. Lees [b], Dudley J. O'Sullivan [g], Richard F. Peppard [c], Julian P. Rodrigues [h], Anette Schrag [d], Paul Silberstein [i], Stephen Tisch [j,†], Andrew H. Evans [a,*]

Benefit for Opioid Antagonist

- Randomized, double-blind, placebo-controlled
- Mixed-effects model



Model[a]	Regression coefficient	df	F	P value
Intercept	10.745	1, 59	12.744	0.001
Co-morbid ICDs	1.626	1, 46	0.871	0.36
History of DBS	-4.648	1, 43	2.760	0.10
Baseline QUIP-RS ICD score	0.805	1, 46	317.457	<0.001
Visit week	-1.865	1, 49	39.643	<0.001
Treatment group	-2.307	1, 88	0.954	0.33
Visit week*treatment group	0.920	1, 49	4.263	0.04

Papay et al. *Neurology* 2014;83:826-33.

Long-Acting, Transdermal Dopamine Agonist Treatment

- Post-hoc analysis of pooled data from 6 long-term, open-label extension studies of rotigotine in PD
  - Patients received optimal dose rotigotine (up to 16mg/24h); concomitant levodopa permitted
- ICD behavior type AEs analyzed for subgroup of patients who (1) received rotigotine for ≥180 days, and (2) were administered modified Minnesota Impulse Disorders Interview (mMIDI)
  - MIDI modified to add eating and punding to gambling, sex and buying
- AEs then categorised according to the 5 mMIDI diagnostic categories (by medical review) based on comments from external advisors

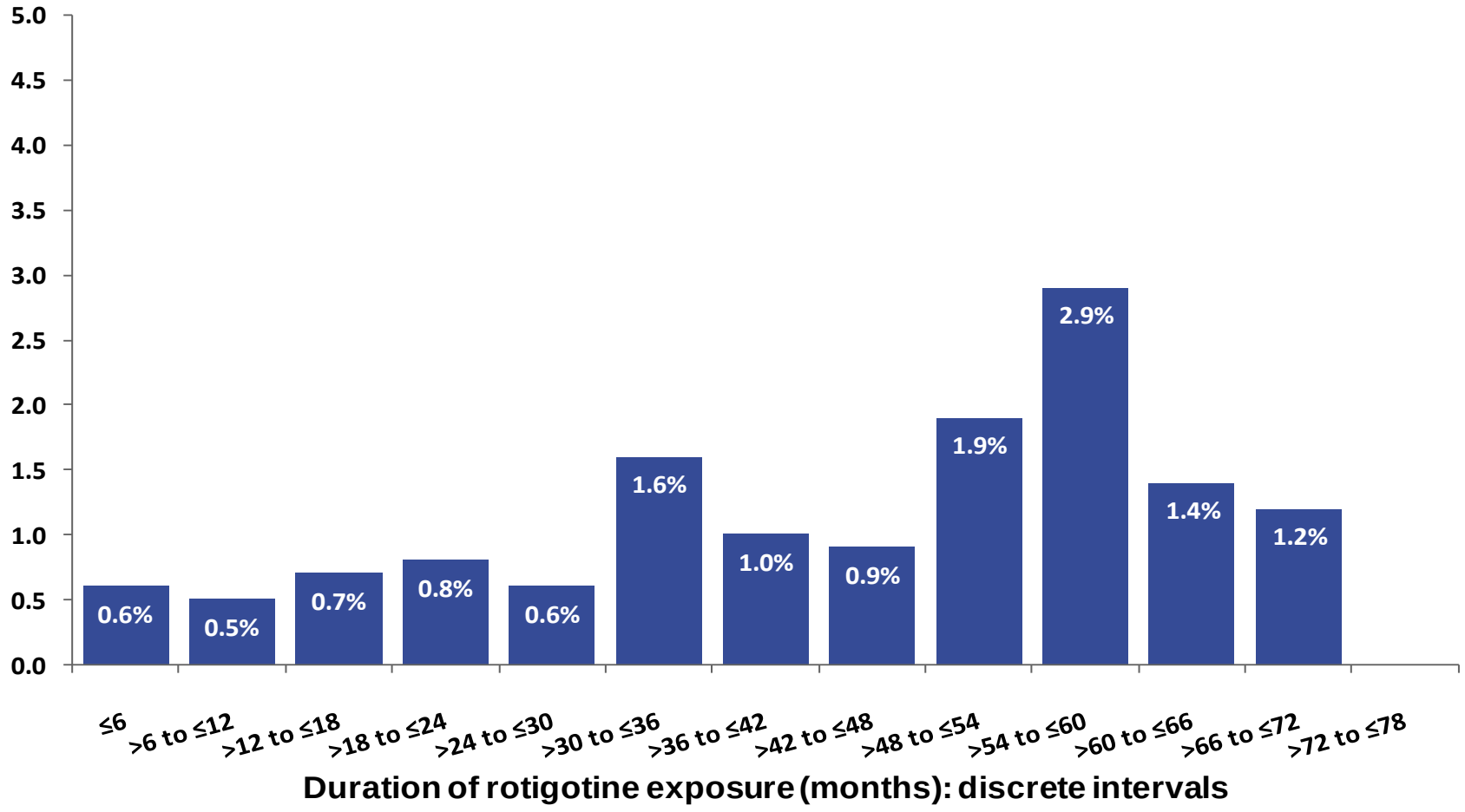
Antonini et al. *Eur J Neurology* 2016;0.1111/ene.13078.

Incidence of ICD Behaviors By Dose at ICD Onset

	Rotigotine dose at AE ONSET mg/24 h; n (%) [AE]							
	2 n=403	4 n=737	6 n=743	8 n=730	10 n=622	12 n=543	14 n=409	16 n=310
Any ICD behavior reported as AEs	6 (1.5) [6]	6 (0.8) [9]	8 (1.1) [9]	16 (2.2) [18]	13 (2.1) [15]	12 (2.2) [15]	13 (3.2) [22]	11 (3.5) [12]
Buying disorder	2 (0.5)	0	3 (0.4)	2 (0.3)	3 (0.5)	1 (0.2)	6 (1.5)	2 (0.6)
Compulsive gambling	2 (0.5)	2 (0.3)	1 (0.1)	6 (0.8)	2 (0.3)	3 (0.6)	1 (0.2)	1 (0.3)
Compulsive sexual behaviour	1 (0.2)	0	2 (0.3)	3 (0.4)	3 (0.5)	5 (0.9)	6 (1.5)	2 (0.6)
Compulsive eating	0	3 (0.4)	1 (0.1)	1 (0.1)	2 (0.3)	1 (0.2)	3 (0.7)	2 (0.6)
Punding behaviour	1 (0.2)	2 (0.3)	1 (0.1)	1 (0.1)	1 (0.2)	3 (0.6)	2 (0.5)	3 (1.0)
Other[b]	0	2 (0.3)	1 (0.1)	4 (0.5)	3 (0.5)	2 (0.4)	3 (0.7)	2 (0.6)

[a]ICD behavior reported as AEs categorized according to mMIDI module were defined by Medical Review.
[b]"Other" includes Reported Terms: compulsive behaviour/s, compulsive disorder, impulse control disorder, impulsive behaviour, impulsive control behaviour/s, obsessive compulsive behaviour, obsessive compulsive disorder, poor impulse control.
Six patients had AEs indicative of compulsive-impulsive behaviour after the end of treatment, the last rotigotine dose has been imputed as the onset dose for these cases.

Incidence of ICD Behaviors Reported By Duration of Rotigotine Exposure



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