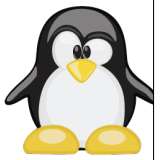
Parkinson's disease

Parnsiri Chairangsaris, MD
Phramongkutklao Hospital and College of Medicine

Issues to consider in the management of PD

- Efficacy
- Safety
- Simplicity
- Drugs availability and Costs
- MD experience



- At risk populations (age, comorbidities, ….)
- Patient preferences, needs, expectations, awareness, information

Costs

Levodopa	Inexpensive
Anticholinergics	Inexpensive
Dopamine agonists	Some are expensive
MAO-B inhibitors	Some are expensive
COMT inhibitors	Expensive

Initiation of symptomatic therapy

- Neuroprotective or disease-modifying?
- Therapy does not need to be started at time of diagnosis for all patients.
- Treatment should be initiated when symptoms cause the patient disability or discomfort.
- GOAL: improving function and quality of life.

Initial symptomatic therapy of PD

Level A

- Levodopa
- Dopamine against
- MAOB inhibitors

Need to consider

- Efficacy
- Complications with L-dopa
- Complications with DA and MAOB-I

5

Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial

PD MED Collaborative Group*

Lancet, 2014

- Open label, pragmatic, randomized newly diagnosed PD patients 1:1:1 into levodopa, DA agonist, MAO-BI. N=1620
- After initial Rx, patients and doctors were free to use any additional medications or stop the medications.
- Followed for up to 7yrs, median = 3yrs. Primary outcome = PDQ-39 scores. Pre-specified 6 pts as a meaningful difference.

Methods In this pragmatic, open-label randomised trial, patients newly diagnosed with Parkinson's disease were randomly assigned (by telephone call to a central office; 1:1:1) between levodopa-sparing therapy (dopamine agonists or MAOBI) and levodopa alone. Patients and investigators were not masked to group assignment. Primary outcomes were the mobility dimension on the 39-item patient-rated Parkinson's disease questionnaire (PDQ-39) quality-of-life scale (range 0–100 with six points defined as the minimally important difference) and cost-effectiveness.

Interpretation Very small but persistent benefits are shown for patient-rated mobility scores when treatment is initiated with levodopa compared with levodopa-sparing therapy. MAOBI as initial levodopa-sparing therapy was at least as effective as dopamine agonists.

6

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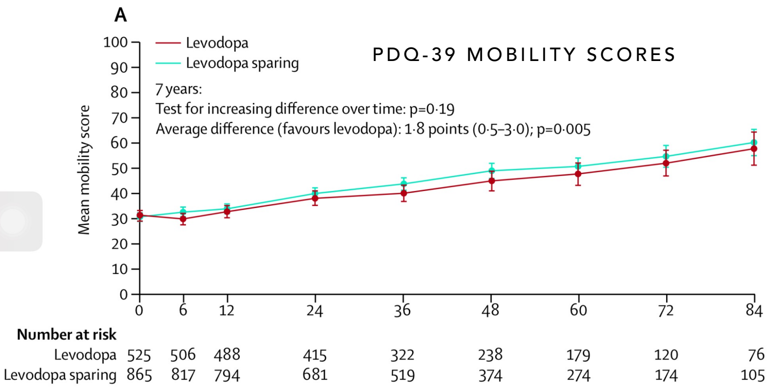
Lancet, 2014



Interpretation Very small but persistent benefits are shown for patient-rated mobility scores when treatment is initiated with levodopa compared with levodopa-sparing therapy. MAOBI as initial levodopa-sparing therapy was at least as effective as dopamine agonists.

7

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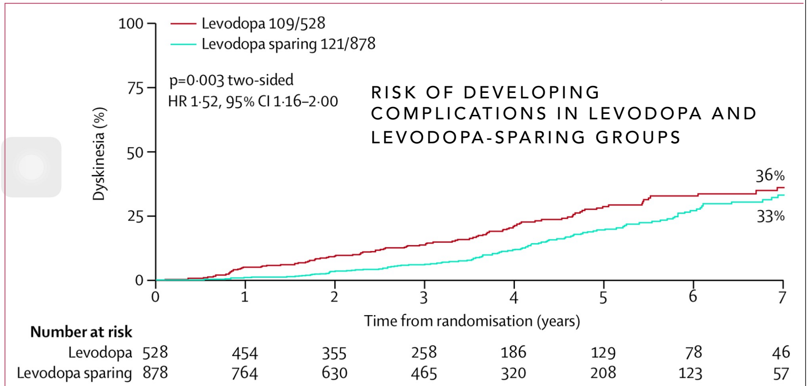
Lancet, 2014

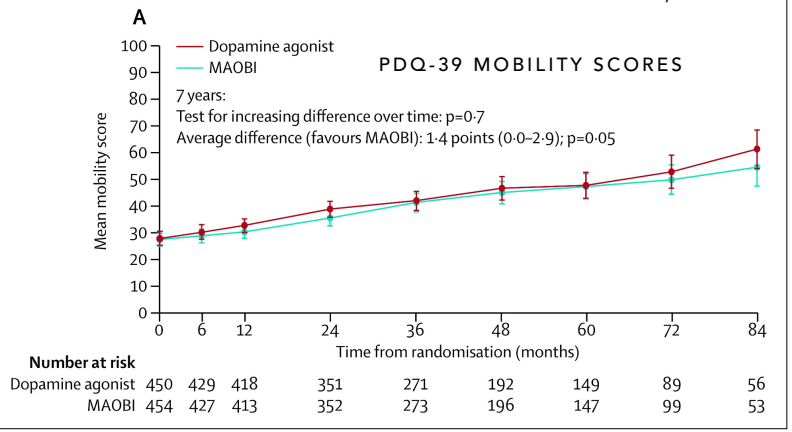


8

Long-term effectiveness of dopamine agonists and monoamine oxidase B inhibitors compared with levodopa as initial treatment for Parkinson's disease (PD MED): a large, open-label, pragmatic randomised trial

PD MED Collaborative Group*

Lancet, 2014



9

- No short-term or "long-term" benefit from using L-dopa-sparing therapy (dopamine agonists or MAOBI) vs. L-dopa
  - Despite L-dopa-treated patients developing more dyskinesias, patients reported **better QoL**, vs. patients on L-dopa-sparing therapies (but this difference was **small**)
  - But: **Few (12%) were <60 y/o at randomization**
- MAOBI as initial therapy as effective as dopamine agonists
  - But: The study design **permitted omission** of the L-dopa or the MAOBI arm
- 28% of patients allocated DAs and 23% of patients allocated MAOBI discontinued allocated treatment because of **side-effects**, compared with 2% allocated L-dopa (p<0.0001)

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Risk factors for motor complications from L-dopa

Disease severity	Yes
Duration of treatment	Yes/No
Dose of Levodopa	Yes
Young age	Yes
Female gender	Yes
Pulsatility	Uncertain

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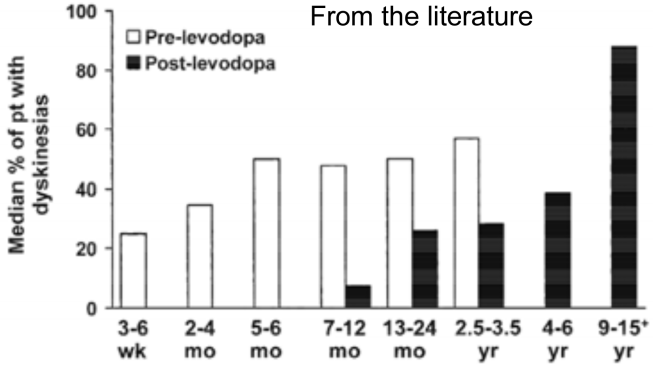
Differences between the two groups can be explained by disease severity. Within the "post" group differences are explained by duration of Rx.

From the literature



Ahlskog and Muenter, 2001

12

Adverse effects from Sinemet in DATATOP extension studies

Duration of Rx

	6 months	12 months	18 months
Wearing off	23%	39%	51%
Dyskinesias	9%	17%	26%
On-Off	2%	3%	5%
Freezing	12%	23%	26%

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BRAIN
A JOURNAL OF NEUROLOGY

Brain. 2014 Oct;137(Pt 10):2731-42.

The modern pre-levodopa era of Parkinson's disease: insights into motor complications from sub-Saharan Africa

Roberto Cilia,[1] Albert Akpalu,[2] Fred Stephen Sarfo,[3] Momodou Cham,[4] Marianna Amboni,[5,6] Emanuele Cereda,[7] Margherita Fabbri,[8] Patrick Adjei,[2] John Akassi,[3] Alba Bonetti[1] and Gianni Pezzoli[1]

1 Parkinson Institute, Istituti Clinici di Perfezionamento, Milan, Italy
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doi:10.1093/brain/awu

BRAIN
A JOURNAL OF NEUROLOG

Brain. 2014 Oct;137:2731-42.

The mod
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Roberto Cilia,[1] A
Emanuele Cered
Gianni Pezzoli[1]

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Table 4 Logistic regression analysis for predictors of motor complications

	Model prediction (AUC)[a]	
Set of variables[b,c]	**Motor fluctuations**	**Dyskinesias**
A + B + C	0.77[d]	0.79[e]
B + C + D	0.71	0.75
Model for motor fluctuations[d]	**OR (95%CI)**	***P*-value**
Levodopa dose (mg/kg)	1.33 (1.05–1.68)	**0.019** ←
Duration of levodopa at occurrence (years)	1.09 (0.80–1.48)	0.606
Disease duration at onset of motor fluctuations (years)	1.36 (1.01–1.83)	**0.040** ←
Model for dyskinesias[e]		
Levodopa dose (mg/kg)	1.19 (1.00–1.42)	**0.045** ←
Duration of levodopa at occurrence (years)	0.93 (0.73–1.18)	0.550
Disease duration at onset of motor fluctuations	1.42 (1.07–1.87)	**0.014** ←

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doi:10.1093/brain/awu195 Brain 2014: Page 1 of 12 | 1

BRAIN
A JOURNAL OF NEUROLOGY

Brain. 2014 Oct;137(Pt 10):2731-42.

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Amboni,[5,6] and

1 Parkinso
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6 IDC Her
7 Nutrition
8 IRCCS Institute of Neurological Sciences, Bologna, Italy

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We conclude that motor fluctuations and dyskinesias are not associated with the duration of levodopa therapy, but rather with longer disease duration and higher levodopa daily dose.

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A JOURNAL OF NEUROLOGY

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E-mail: roberto.cilia@gmail.com.

The practice to withhold levodopa therapy with the objective of delaying the occurrence of motor complications is not justified.

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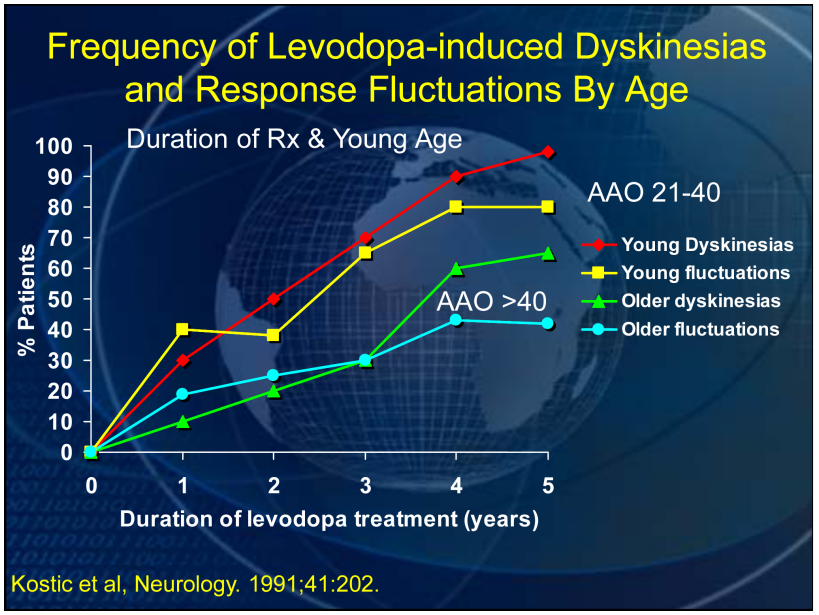

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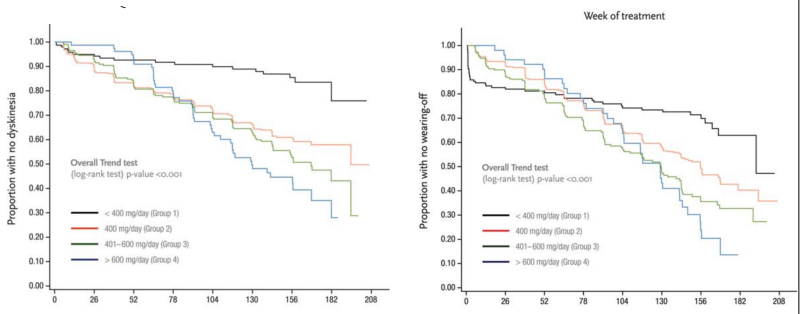
RESEARCH ARTICLE

Factors Predictive of the Development of Levodopa-Induced Dyskinesia and Wearing-Off in Parkinson's Disease

C. Warren Olanow, MD, FRCPC,[1,2*] Karl Kieburtz, MD, MPH,[3] Olivier Rascol, MD, PhD,[4] Werner Poewe, MD,[5] Anthony H. Schapira, MD, DSc, FRCP, FMedSci,[6] Murat Emre, MD,[7] Helena Nissinen, MD, PhD,[8] Mika Leinonen, MSci,[9] Fabrizio Stocchi, MD, PhD,[2] for the Stalevo Reduction in Dyskinesia Evaluation in Parkinson's Disease (STRIDE-PD) Investigators

Movement Disorders, Vol. 28, No. 8, 2013



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RESEARCH ARTICLE

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TABLE 3. Summary of multivariate model for predictive factors of the time to dyskinesia and the time to wearing-off (N=723)[a]

Step[b]	Factor	χ^2 Statistic	*P* value	Effect on dyskinesia (higher risk)
A. Time to dyskinesia				
1	Age at onset of PD	36.09	<0.001	Lower age
2	Nominal L-dopa dose	31.55	<0.001	Higher dose
3	Region (North America/Europe)	12.82	<0.001	North America
4	Weight	10.05	0.002	Lower weight
5	Treatment allocation (LCE/LC)	8.80	0.003	LCE
6	Gender	4.46	0.035	Females
7	UPDRS Part II score at baseline	3.88	0.049	Higher scores

Step[b]	Factor	χ^2 Statistic	*P* value	Effect on wearing-off (higher risk)
B. Time to Wearing Off				
1	Age at onset of PD	63.04	<0.001	Lower age
2	UPDRS Part II score	21.72	<0.001	Higher score
3	Region (North America/Europe)	33.81	0.001	North America
4	Nominal L-dopa dose	25.04	<0.001	Higher dose
5	Gender	8.84	0.003	Females
6	UPDRS Part III score	3.98	0.05	Higher score

PD, Parkinson's disease; LCE, L-dopa/carbidopa/entacapone; LC, L-dopa/carbidopa; UPDRS, Unified Parkinson's Disease Rating Scale.
[a]In total, 723 of 745 patients had no missing data on any of the potential factors and were included in the multivariate analysis.
[b]The steps are listed in the order in which the factors were selected for the model.

Movement Disorders, Vol. 28, No. 8, 2013

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When using levodopa, does "continuous dopaminergic stimulation" help?

- No benefit of levodopa CR versus IR
- No benefit of levodopa with entacapone versus levodopa without entacapone

Initiating therapy with these formulations did not reduce motor complications

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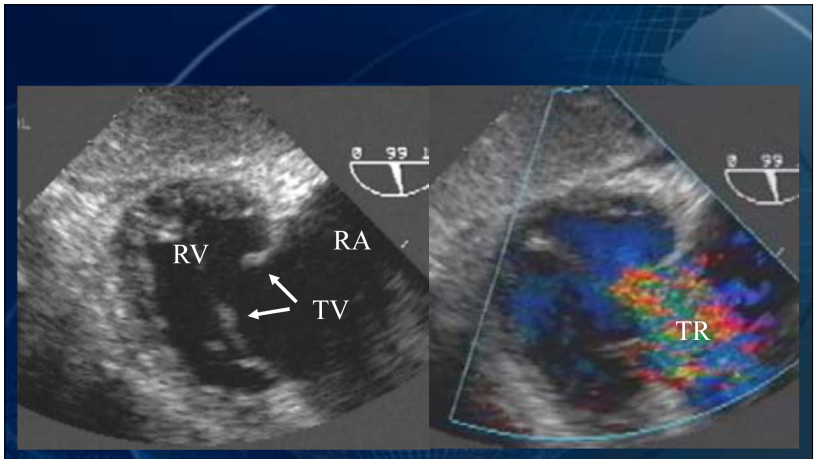


Pergolide-induced RestrictiveValvulopathy

Van Camp et al Lancet April 10, 2004

22

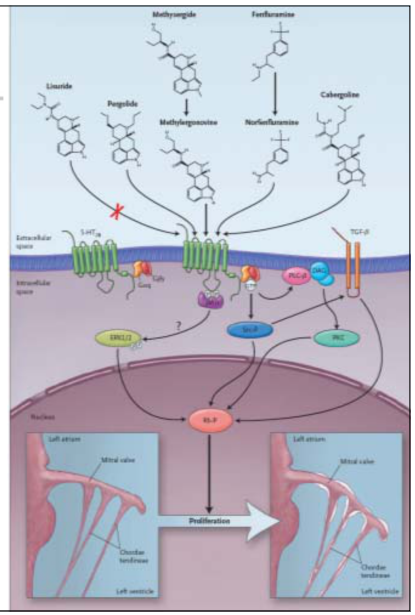
FOCUS ON RESEARCH

Drugs and Valvular Heart Disease

Bryan L. Roth, M.D., Ph.D.

NEJM 2007;356:6-9.

Pergolide and cabergoline, but not bromocriptine or lisuride, are 5HT2B agonists.



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Fibrosis Associated With Dopamine Agonist Therapy in PD

Term	Bromocriptine	Pergolide	Piribedil	Pramipexole
Alveolitis	1	-	-	-
Alveolitis fibrosing	2	1	-	-
Atelectasis	1	-	-	-
Fibrosis mediastinal	1	-	-	-
Pleural pain	2	1	-	-
Pleural fibrosis	40	21	-	-
Pleurisy	81	25	-	-
Pleural effusion	59	38	1	-
Pericardial effusion	-	2	-	-
Periocarditis	-	6	-	-
Retroperitoneal fibrosis	29	19	1	-
Pulmonary fibrosis	30	18	-	-
Total	246	131	2	0

Muller T, Fritze J. Clin. Neuropharmacol. Vol. 26, No. 3, 2003

24

Adverse Events by Treatment Groups in CALM-PD

Adverse Event	Prami %	Levo %	p-value
Somnolence	32.4	17.3	<0.01
Hallucinations	9.3	3.3	<0.05
Peripheral Edema	14.6	4.0	<0.01
Postural Hypotension	5.9	10.0	ns
Nausea	36.4	36.7	ns
Dizziness	25.5	24.0	ns

25

SURVEY ON SLEEP ATTACKS

Korner Y, Meindorfner C, Moller JC, Stiasny-Kolster K, Haja D, Cassel W, Oertel WH, Kruger HP. Predictors of sudden onset of sleep in Parkinson's disease. Mov Disord 2004;19(11):1298-1305.

- Sent a questionnaire to 12,000 patients and received responses from 63%,
- 42% reported they had experienced sudden onset of sleep.
- 10% of these had not experienced sleepiness before their first sleep attack.
- Predicting factors were nonergoline dopamine agonists, age less than 70, and disease duration less than 7 years.

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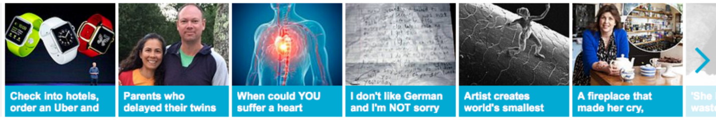

Drugs for Parkinson's disease can turn patients into gamblers, sex addicts and compulsive shoppers

- Impulsive and compulsive behaviour is common with dopamine agonists
- Dopamine agonist drugs were 277 times more likely to result in a report of specific impulse control symptoms than other drugs, report found
- Up to 14% of patients develop changes in behaviour when taking them

By ANNA HODGEKISS FOR MAILONLINE

PUBLISHED: 11:57, 22 October 2014 | UPDATED: 13:52, 22 October 2014

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ORIGINAL CONTRIBUTION

Impulse Control Disorders in Parkinson Disease

A Cross-Sectional Study of 3090 Patients

Arch Neurol. 2010 May;67(5):589-95.

Daniel Weintraub, MD; Juergen Koester, PhD; Marc N. Potenza, MD, PhD; Andrew D. Siderowf, MD, MSCE; Mark Stacy, MD; Valerie Voon, MD; Jacqueline Whetteckey, MD; Glen R. Wunderlich, PhD; Anthony E. Lang, MD, FRCPC

TALK TO BOTH THE PATIENT AND THE SPOUSE/ PARTNER BEFORE STARTING Rx AND AT EVERY SUBSEQUENT VISIT

- 3090 patients with PD receiving Rx in 46 MovDisord centers in U.S. and Canada
- An ICD was identified in 13.6% of patients
  - Gambling in 5.0%
  - compulsive sexual behavior in 3.5%
  - Compulsive buying in 5.7%
  - binge-eating disorder in 4.3%
  - 3.9% had 2 or more ICDs.
- Impulse control disorders were more common in patients treated with a dopamine agonist than in patients not taking a dopamine agonist (17.1% vs 6.9%; odds ratio [OR], 2.72; 95% confidence interval [CI], 2.08-3.54; *P*.001).

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ORIGINAL CONTRIBUTION

Dopamine Agonist Withdrawal Syndrome in Parkinson Disease

Arch Neurol. 2010;67(1):58-63

Christina A. Rabinak, BSE; Melissa J. Nirenberg, MD, PhD

Definition: a cluster of physical and psychological symptoms that correlate with dopamine agonist withdrawal in a tapered manner, causing clinical distress or social/occupational dysfunction, are refractory to levodopa and other PD medications, and cannot be accounted for by other clinical factors. Not a behavioral "off."

Symptoms of DAWS resemble those of other drug withdrawal syndromes: anxiety, panic attacks, agoraphobia, depression, dysphoria, diaphoresis, fatigue, pain, orthostatic hypotension, and drug cravings.

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Research

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

At baseline the following antidepressants (daily dose) were allowed: amitriptyline, 50 mg or less; trazodone hydrochloride, 100 mg or less; citalopram hydrobromide, 20 mg or less; sertraline hydrochloride, 100 mg or less; paroxetine hydrochloride, 30 mg or less; and escitalopram oxalate, 10 mg or less. There was no restriction in tyramine dietary intake.

There were no serious adverse events in the combined rasagiline-antidepressant group suggestive of serotonin syndrome.

JAMA Neurol. 2015

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Serotonin Toxicity Association with Concomitant Antidepressants and Rasagiline Treatment: Retrospective Study (STACCATO)

Michel Panisset,[1] Jack J. Chen,[2,*] Sean H. Rhyee,[3] Jill Conner,[4] Julie Mathena,[4] and the STACCATO study investigators

[1]Hôpital Notre-Dame du CHUM, Montréal, Québec, Canada; [2]Loma Linda University, Loma Linda, California; [3]University of Massachusetts Medical School, Worcester, Massachusetts; [4]Teva Neuroscience, Inc., Kansas City, Missouri

	No. (%)[a]			
	Group R+ATD (n=471)	Group R (n=508)	Group ATD (n=525)	Total (N=1504)
Hospitalizations, ED visits				
Patients with one or more hospitalizations and/or ED visits	55 (11.7)	41 (8.1)	99 (18.9)	195 (13.0)
Total number of hospitalizations and ED visits	80	64	222	366
Medical records obtained and reviewed[b]	60 (75.0)	50 (78.1)	184 (82.9)	294 (80.3)
Occurrence of STS				
Patients with incomplete, ineligible, or missing records[c]	25 (5.3)	21 (4.1)	39 (7.4)	85 (5.7)
Patients with known outcome	446 (94.7)	487 (95.9)	486 (92.6)	1419 (94.3)
Patients with STS, no. (95% CI)[d]	0 (0, 0.8)	0 (0, 0.8)	0 (0, 0.8)	0 (0, 0.3)

Panisset, Pharmacotherapy 2014

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Initial symptomatic therapy of PD: Summary

- No long term advantage to levodopa sparing strategies.
- Long term outcomes are similar, regardless of which medication is started first.
- Young patients at greater risk of motor complications are also at greater risk of ICD and DAWS.

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	Treatment of motor symptoms		Treatment of motor complications	
	Monotherapy	Adjunct to levodopa	Fluctuations	Dyskinesia*
Levodopa				
Levodopa-carbidopa	+	··	+	–
Levodopa-benserazide	+	··	+	–
Dopamine agonists (non-ergot)				
Apomorphine	–	+	+	–
Piribedil	+	+	–	–
Pramipexole	+	+	+	–
Ropinirole	+	+	+	–
Rotigotine	+	+	+	–
Dopamine agonists (ergot)				
Bromocriptine	+	+	+	–
Cabergoline	+	+	+	–
Monoamine oxidase type B inhibitors				
Rasagiline	+	+	+	–
Selegiline	+	–§	–§	–
Catechol-O-methyltransferase inhibitors				
Entacapone	··	+	+	–
Tolcapone	··	+	+	–
Others				
Amantadine	+	+	–	+
Anticholinergics†	+‡	+‡	–	–
Clozapine	+‡	+‡	–	+

+ indicates efficacious or likely efficacious. – indicates non-efficacious or insufficient evidence. ·· indicates not applicable. *Responses to peak dose dyskinesia (diphasic dyskinesia might respond to drugs used for motor fluctuations, particularly dopamine agonists). †Includes benztropine, ethopropazine, trihexyphenidyl, and others. ‡For treatment of tremor. §There is insufficient evidence but, in practice, selegiline is used and can be effective.

Table 2: **Pharmacological treatments for motor symptoms and complications** Lancet, 2015

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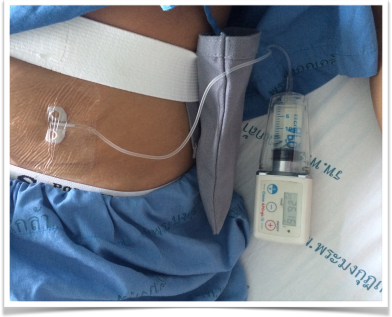
Chronic pump system for advance PD



continuous subcutaneous apomorphine infusion (CSAi)

Levodopa-Carbidopa Intestinal Gel (LCIG)

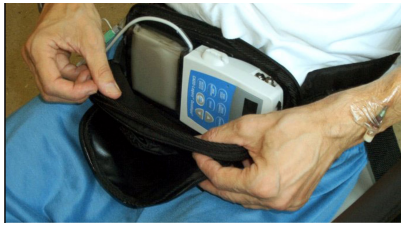


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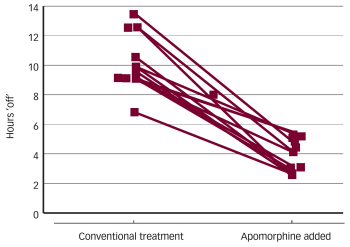
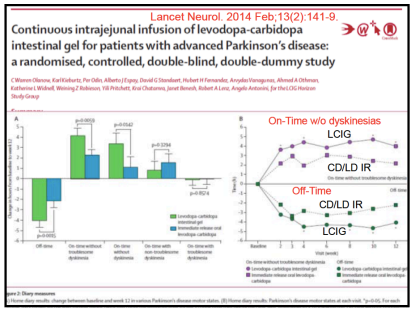
Figure 1: Effect of Apomorphine Given by Infusion Pump on Mean Hours of 'Off' Periods per Day Averaged Over One Week



Andrew Lees, Highlights of a Satellite Symposium Held at the XX World Congress on Parkinson's Disease and Related Disorders, 2013



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LCIG & CSAi: non-motor symptoms

TABLE 1. Descriptive and comparative statistics at baseline and follow-up for each group of treatment

	Intrajejunal Levodopa Infusion					Apomorphine Infusion				
	Baseline		Follow-up			Baseline		Follow-up		
	Mean	SD	Mean	SD	*P* Value	Mean	SD	Mean	SD	*P* Value
UPDRS part 3[a]	27.29	12.28	15.07	10.37	<0.0001	30.79	10.40	17.46	8.08	<0.0001
UPDRS part 4[a]	9.93	3.29	4.36	3.07	<0.0001	10.02	4.68	5.93	3.35	<0.0001
NMSS domains										
Cardiovascular	3.36	3.69	1.86	2.67	0.0076	3.19	4.57	2.07	2.49	0.23
Sleep/fatigue	16.68	10.97	8.64	8.26	<0.0001	16.98	10.12	12.98	10.13	0.024
Mood/apathy	15.79	12.85	11.89	13.04	0.021	18.81	18.00	9.98	10.17	0.0003
Perceptual/hallucinations	3.54	5.54	1.95	4.51	0.010	3.02	5.18	1.40	3.14	0.003
Attention/memory	10.20	9.35	7.60	8.68	0.011	8.77	8.24	5.79	6.35	0.003
Gastrointestinal	9.48	7.68	4.25	4.80	<0.0001	6.21	5.82	4.65	5.49	0.003
Urinary	11.5	10.42	5.48	5.78	0.0001	9.07	7.40	7.93	8.03	0.002
Sexual functioning	5.73	7.93	2.32	4.12	0.014	2.56	5.29	1.93	3.59	0.18
Miscellaneous	14.66	9.25	9.68	7.87	0.0008	13.77	10.94	9.49	8.15	0.50
NMSS total score	90.95	45.00	53.66	38.67	<0.0001	82.37	49.54	56.21	32.21	0.0007
PDQ-8 summary index[a]	48.58	14.62	31.96	14.89	<0.0001	49.85	16.59	35.03	18.00	<0.0001

Paired *t* test; the rest of comparisons, Wilcoxon's test. Significant if $P < 0.027$, after correction for multiple comparisons.

prospective, open-label, nonrandomized, multicenter

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Advantages of CSAi

Improves motor and non motor symptoms.

The least invasive device aided therapy.

Entirely reversible.

No upper age limit.

An option for patients with slight to moderate dementia.

Advantages of LCIG

Improves motor and non-motor symptoms.

The effects on motor symptoms have been varied in a randomized controlled trial.

No upper age limit.

An option for patients with slight to moderate dementia.

Possible monotherapy.

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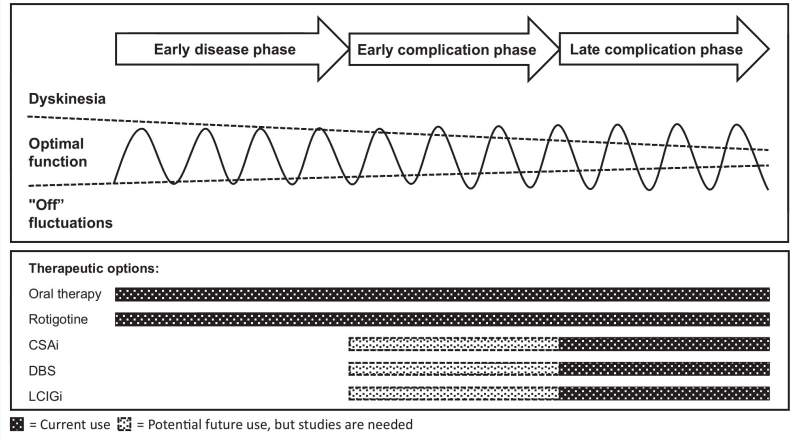

Jonathan Timpka, movement disorders clinical practice. 2016

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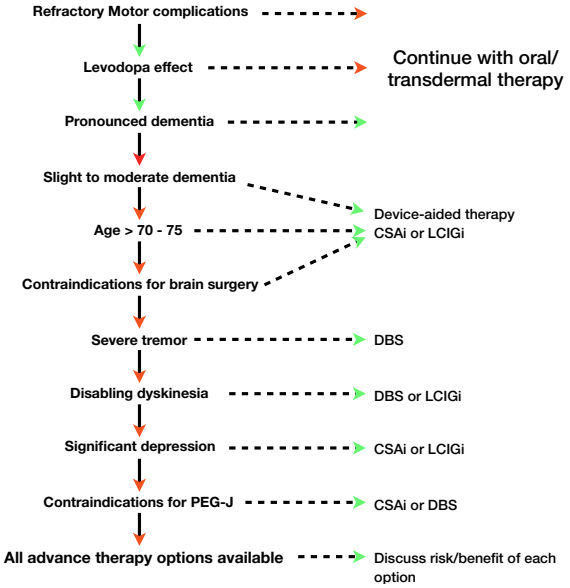

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