Update on Medical Treatment of Parkinson Disease

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Disclosures

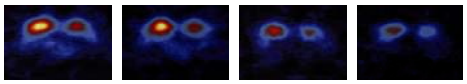
- Consultant and clinical investigator for Abbott/Abbvie – a product from Abbvie will be discussed.
- Consultant to Serina Therapeutics, Blue Rock Therapeutics and Voyager Therapeutics.
- No discussion of off-label use of approved medications is planned.

Etiology and Treatment: 1817

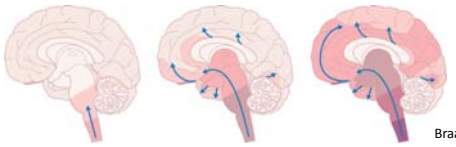
- Dr. Parkinson believed that the cause of the disease was in the medulla:
  we are led to seek for it in some slow morbid change in the structure of the medulla, or its investing membranes, or theca, occasioned by simple inflammation, or rheumatic or scrophulous affection
- Dr. Parkinson's Treatment
  blood should be first taken from the upper part of the neck, unless contra-indicated by any particular circumstance. After which vesicatories should be applied to the same part, and a purulent discharge obtained
- Dr. Parkinson's Prediction:
  there appears to be sufficient reason for hoping that some remedial process may ere long be discovered, by which, at least, the progress of the disease may be stopped.

A modern view: Features of Parkinson Disease

- Rest Tremor
- Bradykinesia
- Rigidity
- Postural Imbalance



Parkinson disease: Non-motor features, non-motor pathology

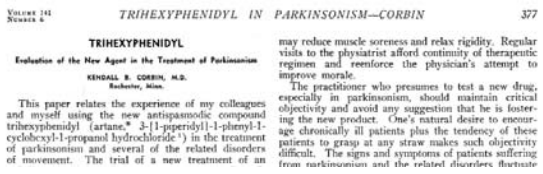


Braak, 2003

Early (premotor) features
- Hyposmia
- REM behavior disorder
- Autonomic disturbances

Late Features
- Excessive sleepiness
- Depression and anxiety
- Dementia

Treatment of Parkinson disease: 1949



VOLUME 141
NUMBER 6 TRIHEXYPHENIDYL IN PARKINSONISM—CORBIN 377

TRIHEXYPHENIDYL

Evaluation of the New Agent in the Treatment of Parkinsonism

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This paper relates the experience of my colleagues and myself using the new antispasmodic compound trihexyphenidyl (artane,* 3-[1-pperidyl]1-1-phenyl-1-cyclohexyl-1-propanol hydrochloride [1]) in the treatment of parkinsonism and several of the related disorders of movement. The trial of a new treatment of an

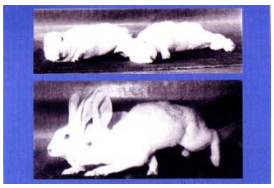
may reduce muscle soreness and relax rigidity. Regular visits to the physiatrist afford continuity of therapeutic regimen and reenforce the physician's attempt to improve morale.

The practitioner who presumes to test a new drug, especially in parkinsonism, should maintain critical objectivity and avoid any suggestion that he is fostering the new product. One's natural desire to encourage chronically ill patients plus the tendency of these patients to grasp at any straw makes such objectivity difficult. The signs and symptoms of patients suffering from parkinsonism and the related disorders fluctuate

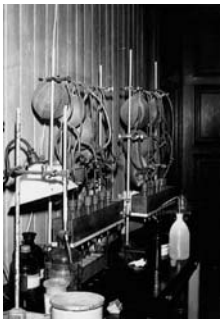
- Alternatives:
  - Diphenhydramine
  - Amphetamine
  - Belladona extracts, atropine alkyloids

JAMA. 1949;141(6):377-382

Dopamine and PD



1957: Arvid Carlsson discovers dopamine, and effects of DA depletion



1960: Oleh Hornykiewicz discovers loss of DA in PD

Levodopa Therapy for PD

tyrosine —(*TH*)→ L-DOPA —(*AADC*)→ DA

- **1961:** Efficacy of IV levodopa demonstrated by Birkmayer and Hornykiewicz

- **1969:** Long term treatment of PD with D,L dopa described by Cotzias
- **2000:** Carlsson, Kandel and Greengard awarded Nobel Prize in Physiology or Medicine

2017: Dopaminergic Treatments for PD

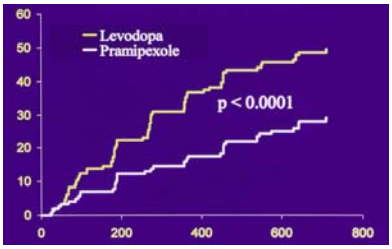
- Levodopa/carbidopa (Sinemet®, Rytary®, Duopa®)
- Pramipexole (Mirapex®)
- Ropinirole (Requip®)
- Rotigotine (Neupro®)
- Apomorphine (Apokyn®)
- Others that affect dopamine indirectly:
  - Rasagiline (Azilect)
  - Entacapone (Comtan®, Stalevo®)
  - Safinamide (Xadago®)

Treatment of Early PD

- Exercise and wellness
- Non-dopaminergic medications
  - MAO inhibitors – selegiline, rasagiline
  - Amantadine
- Dopaminergic medications
  - Levodopa
  - Dopamine agonists – pramipexole, ropinerol, rotigitine

CALM-PD: Wearing Off or Dyskinesias

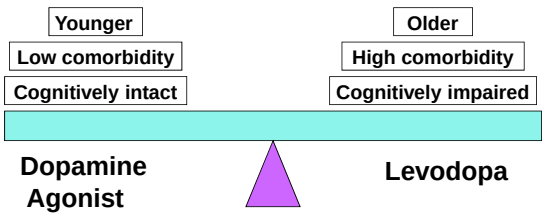
- Randomized trial comparing levodopa to pramipexole as initial treatment for PD
- 301 patients, followed for 2 years



- Initial treatment with pramipexole substantially reduced development of wearing off or dyskinesias.

Parkinson Study Group, JAMA18:1931-8 (2000)

Initial Dopaminergic Therapy in PD



Advanced PD: Motor Complications

- Complications are present in 50% of patients after 5 years of levodopa therapy
- Wearing off
  - Loss of efficacy at the end of the dosing interval
  - "On/Off" – sudden loss of efficacy
- Dyskinesia
  - Chorea, usually associated with peak dose effect
  - "Diphasic dyskinesias" – associate with rising or falling concentration of medication

Clinical Strategies for management of Wearing off and Dyskinesia

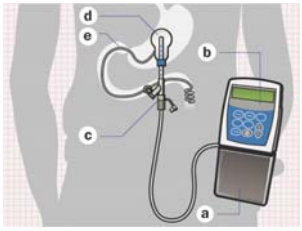
- Levodopa dose fractionation
- Long acting agents
  - Dopamine agonists – ropinerole, pramipexole
  - Slow release formulations – Requip XL®, Mirapex ER®
- Enzyme inhibitors
  - MAOb – selegiline, rasagiline, safinamide
  - COMT – entacapone
- Amantadine
  - Conventional or extended release (Gocovri®)

Management of wearing off : Enzyme inhibitor or dopamine agonist?

COMT (entacapone) MAO (rasagiline, safinamide)	Dopamine Agonists Pramipexole, ropinirole
✓ Convenience - "one size fits all" dosing	✓ Best approach for patients with both wearing off and dyskinesia, other complex patterns
✓ Low rate of adverse effects	X Titration is more labor intensive
✓ Often effective in simple wearing off	X Cognitive and cardiovascular adverse effects can be a problem
X Can make dyskinesias worse	

Duopa®: Carbidopa/Levodopa Gel

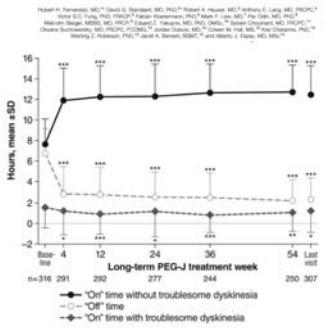
- Carbidopa/Levodopa in a gel form, infused in to the intestines using a pump.
- Intended for patients with wearing off and fluctuations



Richards, L. (2009) Intrajejunal duodopa improves nonmotor symptoms
Nat. Rev. Neurol. doi:10.1038/nrneurol.2009.84

RESEARCH ARTICLE

Levodopa-Carbidopa Intestinal Gel in Advanced Parkinson's Disease: Final 12-Month, Open-Label Results



Mov Disord. 2015 Apr;30(4):500-9

Duopa: Adverse Events

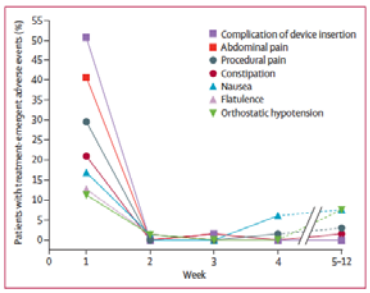


Figure 3: Timing of treatment-emergent adverse events reported by >10% of patients

Lancet Neurology, 2014: 13:141-49

New approaches to levodopa delivery

Approved

Rytary®

Each capsule contains both:
- Immediate-release beads
- Extended-release beads

Under Development

OBESO ET AL

TABLE 4. Novel formulations and deliveries of levodopa

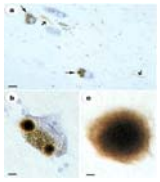
- IPX066 – Extended release carbidopa/levodopa containing immediate-release and extended-release levodopa
- XP21279 – actively transported levodopa prodrug that is actively absorbed by high-capacity nutrient transporters
- Accordion pill (AP09004) – extended release levodopa/carbidopa formulation with gastroretentive properties multilayer film, unfolds in the stomach
- DM1992 – gastroretentive, extended-release levodopa in bilayer tablet containing immediate-release and extended-release levodopa
- Carbidopa/Levodopa microtablet – dispersible carbidopa/levodopa 5/1.25 mg administered by means of electronic dispenser
- ODM-101 – levodopa/entacapone plus 65 or 105 mg of carbidopa
- Deuterated levodopa – deuterium–carbon bond is stronger than hydrogen–carbon bond, thus prolonging half-life of levodopa
- Levodopa methyl ester – transdermal delivery of levodopa
- Levodopa-carbidopa intestinal gel – carboxymethylcellulose aqueous gel delivered continuously to the proximal jejunum via a percutaneous gastrojejunostomy tube connected to a portable infusion pump
- CVT-301 – inhalable powder of levodopa without carbidopa
- ND0612 – liquid carbidopa/levodopa formulation delivered subcutaneously via patch-pump device

Future of Parkinson Therapy

- Disease Modifying
  - Synuclein based therapies
  - Immune therapies

Alpha-synuclein

- First linked to PD in the Contursi kindred, a family with early onset and rapid course - A30P mutation
- Several other families with additional mutations described
- Mutations are rare outside of families with clear AD inheritance
- Alpha-synuclein is a principal component of Lewy bodies and Lewy neurites in sporadic PD



Spillantini et al., Nature, 1997

Anti-synuclein Strategies

- Direct removal of alpha-synuclein

ClinicalTrials.gov

Row	Saved	Status	Study Title	Conditions	Interventions
1	☑	Recruiting	Single-Ascending Dose Study of BIIB054 in Healthy Participants and Early Parkinson's Disease	Parkinson's Disease; Healthy	Drug: BIIB054; Drug: Placebo
2	☑	Recruiting	A Study to Evaluate the Efficacy of RO7046015 in Participants With Early Parkinson's Disease	Parkinson's Disease	Drug: RO7046015; Drug: Placebo

- Improve protein clearance

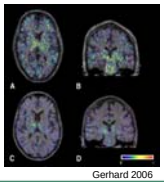
ClinicalTrials.gov

Row	Saved	Status	Study Title	Conditions	Interventions
1	☑	Recruiting	Impact of Nilotinib on Safety, Tolerability, Pharmacokinetics and Biomarkers in Parkinson's Disease	Parkinson Disease; Parkinsons Disease With Dementia	Drug: Placebo Oral Capsule; Drug: Nilotinib 150mg oral capsule [Tasigna]; Drug: Nilotinib 300mg oral capsule [Tasigna]
2	☐	Recruiting	Ambroxol as a Treatment for Parkinson's Disease Dementia	Parkinson's Disease Dementia	Drug: Ambroxol; Other: Placebo

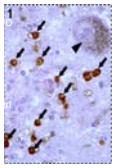
- Prevent prion-like propagation of alpha-syn
  - Anti-aggregants
  - Prevent release and reuptake of misfolded forms

Immune System Involvement in Parkinson disease

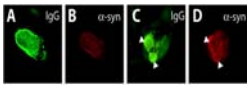
- Microgliosis around degenerating neurons of substantia nigra
- Genetic variation in HLA-DRA associated with increased risk
- Alterations in circulating T cells, and infiltration in to the brain
- Pro-inflammatory cytokines and IgG in midbrain and CSF



Gerhard 2006



Brochard 2009



Orr 2007

Concluding points

- 201 years have passed since James Parkinson's *Essay on the Shaking Palsy*
- Much of our current therapy is based on the discovery of the role of dopamine in PD
- Dopaminergic therapies are often limited by motor complications
- Many non-motor symptoms are difficult to treat
- The future is the disease-modifying treatments predicted by Dr. Parkinson