AN

ESSAY

ON THE

SHAKING PALSY.

BY

JAMES PARKINSON,
MEMBER OF THE ROYAL COLLEGE OF SURGEONS.

LONDON:
PRINTED BY WHITTINGHAM AND ROWLAND,
Goswell Street,
FOR SHERWOOD, NEELY, AND JONES,
PATERNOSTER ROW.
1817.
“Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forward, and to pass from a walking to a running pace: the senses and intellects being uninjured.”

Dr. James Parkinson
"AN ESSAY ON THE SHAKING PALSY"
1817
PD: A Chronic Neurodegenerative Ds. Epidemiology

- 1 Million in USA
- 50,000 New Cases per Year
- Majority Over Age 65
  - Incidence: 1.6 / 100 over age 60
    2/100 >80 Years
    4% with onset <50
- Males > Females
Natural History of PD

Hoehn and Yahr Scale 1949-1964*

Progression to Stage III, IV, or V

- <5 years: 37%
- 5-9 years: 63%
- 10-14 years: 67%

- Up to one third of patients may never be totally disabled.

- Many plateau at Stage III

This series includes some patients with postencephalitic parkinsonism.

*Summary data from 183 patients followed from 1949-1964.
Cause of PD

- Progressive Loss of Dopamine Neurons in the Substantia Nigra
  - Cholinergic, adrenergic and serotonergic neurons also affected
- Symptoms Appear After 80% Loss
- Cause of Cell Death Unknown
- Not an Inherited Illness As a Rule
Parkinson’s Disease

Onset of Symptoms

Survivors

80% loss

Substantial Nigra Cells

Depigmentation of Substantia Nigra

Brain of Normal Patient

Brain of Patient with Parkinson's Disease
Major Symptoms

- Rigidity
- Bradykinesia
  - difficulty initiating movement
  - slowness of movement
  - staring, masked facies
- Postural Imbalance
- Tremor-70% of patients affected
  - “Not everything that shakes is PD”
Associated Symptoms

- Constipation
- Small writing
- Soft, hoarse speech
- Swallowing difficulties
- Oily, scaly skin
- Breathing irregularities
- Urinary problems
- Low blood pressure
Psychiatric Symptoms

- Hallucinations
- Depression
- Dementia
- Paranoia
- Sleep disorders
- Nocturnal Wandering
- Sundowning Syndrome
- Psychosis
Neurodegenerative Diseases With Parkinsonism Features

- Progressive supranuclear palsy
- Multiple system atrophy
  - Shy-Drager syndrome
  - Olivopontocerebellar degeneration
  - Striatonigral degeneration
- Corticobasal ganglionic degeneration

Clinical Management

- Early Drug Therapies
- MAO-B Inhibitors
- Anticholinergics, Amantadine
- Dopamine Agonists
- Levodopa/Carbidopa - most effective
- COMT Inhibitors
- Non-pharmacologic Therapy
- Surgery – Deep Brain Stimulation
Early Therapies

- **Amantadine**
  - Effective primarily for bradykinesia
  - Mild clinical improvement
  - Therapeutic effect: usually less than 6 months, some longer

- **Anticholinergics**
  - Effective primarily for tremor and rigidity
  - Effective in 30-50% of patients
  - Artane, Cogentin
Azilect - Rasagiline

- Newest MAO-B inhibitor – long acting
- Data shows benefit over selegiline.
- Use alone or in combination with Sinemet
- Side effect profile similar to selegiline
- Standard dose 1 mg daily
Selegiline

- MAO-B inhibitor
- Delays need for levodopa therapy
- Prolongs initial benefit of levodopa
- Extends time before increasing levodopa
- Prolongs time before response fluctuations occur
- Dosing: 5 mg QAM, 5 mg QNoon
Dopamine Agonists

- Directly activates dopamine receptors
- Bypass degenerating dopamine neurons
- No enzymatic conversion
- No toxic metabolites
- No transport competition with amino acids
Dopamine Agonists

Dopamine agonist molecule

Dopamine molecule

Dopamine receptor
Benefits of Early Use of Dopamine Agonists

- Reduced risk of dyskinesia compared with levodopa therapy
- Antiparkinsonian effects comparable with levodopa in early stages of disease
- Levodopa can be added later as needed

Dopamine Receptor Agonists

- Mirapex - pramipexole
- Requip - ropinirole
- Neupro Patch - rotigotine

- Apokyn – apomorphine
  - Only injectable dopamine agonist
  - Limited usage of injection
  - Implantable pump being studied
Neupro - Rotigigitine

- Available only in patch form
- Continuous 24 hour delivery
  - Acts like a long acting DA
- Not any more effective than other Das
- Use to smooth out motor fluctuations
- Approved for RLS treatment
Dopamine Agonists - Adverse Reactions

- Nausea
- Hallucinations
- Confusion/psychosis
- Hypotension
- Dry mouth
- Constipation
- Foot swelling
- Compulsive Behaviors
Dopamine Agonists and Sleep Disturbances

- Unintended sleep episodes
- Sedation

- Patients should be cautioned about potential sedative effects
  - Other sedating drugs, including alcohol, should be avoided
  - Caution is advised regarding operation motor vehicles for all patients on dopamine agonists
Levodopa/Carbidopa
The Gold Standard

- **Dopa decarboxylase** converts L-dopa into dopamine
- **Carbidopa** inhibits dopa decarboxylase, does not cross blood-brain barrier
- **Levodopa** crosses blood-brain barrier
- **Dopamine** does not cross blood-brain barrier
Response of Parkinson’s Disease Patients to Levodopa

Marsden CD, Parkes JD. Lancet. 1977;1:345–349
Levodopa Therapy Complications

- Freezing
- On-off attacks
- Dyskinesias
- Dystonias
- Complications related to long term, high dose therapy
Reducing Long-term Levodopa Complications

- Delay levodopa therapy until functional problems develop
  - Don’t play your Ace card first
- Start with alternative drug therapy
- Combine levodopa with complimentary drugs (e.g. MAO-B inhibitors, COMT inhibitors)
Sinemet CR

- Controlled Release preparation
- Slower onset of action: 60-90 minutes
- Sustained, moderate levodopa levels
- Decreased dosing frequency
- Higher incidence of dyskinesias
  - Not used much any longer
Rytary

- New Extended Release Carbidopa-Levodopa
- Capsule with granules
- Patients Function Better
- Longer “On-time”
- Less Dyskinesia and Motor Fluctuations
Rytary Capsules

NEW

Rytary™ (Carbidopa and Levodopa) Extended-Release Capsules

23.75 mg / 95 mg • 36.25 mg / 145 mg
48.75 mg / 195 mg • 61.25 mg / 245 mg

Every Moment Counts
Plasma Levodopa Levels

Plasma levodopa levels ng/ml

Sinemet® given

Sinemet® CR given

Statistically significant

Parcopia

- Rapidly dissolving L-dopa/carbidopa
- Available in same strength as Sinemet.
- Good for early morning dosing and in patients with swallowing difficulty.
COMT Inhibitors

- Comtan - entacapone
- Tasmar - tolcapone
  - Potential Liver Toxicity Problems
  - Increased brain levodopa levels by blocking peripheral metabolism
  - Sustained brain dopamine levels by blocking metabolic pathway
Stalevo – Now Generic

- Combined: Comtan + Sinemet
- Smaller size tablet
  - Easier to swallow
- Fewer daily tablets
- Reduced cost
Stalevo™ Tablets Are Available in Three Strengths

- 12.5/50/200 mg tablets
- 25/100/200 mg tablets
- 37.5/150/200 mg tablets
Autonomic Dysfunction

- Many systems affected
- Orthostatic Hypotension - Common
  - Dehydration - essentially 100% of all PD patients
  - **Fluids** - 1 liter or more daily (no soda)
  - **Florinef** - mineralocorticoid agent
  - **Midodrine** - Alpha-adrenergic agonist
  - **Droxydopa** – New synthetic amino acid precursor prodrug to the neurotransmitters norepinephrine and epinephrine. Crosses blood-brain barrier.
Parkinson Dementia

- May begin subtly
- Mild forgetfulness
- Slowly worsens – Affects 65% of PD patients

Treatment

- Aricept, Exelon Patch
  - Only Exelon Patch FDA Approved for PD dementia
- Namenda XR
  - Some anti-Parkinson effect
Depression in Parkinson Ds

- Depression is a common clinical disorder
- Occurs in 50% of all Parkinson patients
- Can be subtle. Need to ask patient and caregiver
- Early treatment improves quality of life
- Can occur anytime in course of PD
Non-pharmacologic Therapy

- **Diet:** low protein, high fiber, more fluids
- **Exercise:** physical & mental
  - What ever it takes, do this
- **Physical Therapy:** gait rehab
- **Speech Therapy:** swallowing tx
- **Caregiver Support**
- **Patient/Caregiver Education**
- **Psychosocial Consultation**
Daytime Sleepiness

- A significant problem due to PD and meds
- Reversal of sleep-wake cycle
- Limit daytime naps
- Get more exercise
  - Get out and move
- Nuvigil – a non-amphetamine stimulant

- Drink coffee-caffeinated
- 2-3 cups in A.M.
Conclusions

- Not everything that shakes is Parkinson’s
- Avoid starting Sinemet as 1st line therapy
- Non-pharmacological treatment
  - Get out and get moving
  - Drink more fluids
- Aggressively manage constipation
- Avoid falls and injuries
- Family/Caregiver support
  - Support Groups
Sarasota Neurology, PA

- Sarasota Neurology, P.A.
  - 3501 Cattlemen Rd, Ste B
  - Sarasota, FL  34232
  - (941)-955-5858

- ParkinsonDoctor.com
- Deep Brain Stimulator Management