Hudson Valley Community Seminar on Parkinson's disease and other Movement Disorders

Medical treatment of moderate to advanced PD

Patient and Caregiver Symposium

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WMC Health
MidHudson Regional Hospital
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NEW YORK MEDICAL COLLEGE
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All Roads Lead to Rome

Of the many themes for discussion in our office is the small world we live in. Although the Hudson Valley is large, we always seem to be running into people who are connected.

A story linked to this year’s Top Doctors feature is my new favorite small-world anecdote. Every year, we receive the list of Top Doctors from Castle Connolly, Medical Ltd., a healthcare research and information company. Our team then selects a handful of doctors to interview for profiles in the article. We choose these doctors based on a variety of factors including specialty, hospital, medical group, location, and gender.

This year, out of 410 doctors on our list, we managed to pick two doctors with a very strong connection—which was only discovered during the interviews.

Writer Melissa F. Perlman first spoke to Fabio Dumas, MD, who mentioned going to medical school in Italy. That same evening she spoke to Barbara Chai-Aryamonti, MD, who also mentioned studying in Italy. “I asked if she knew Dr. Dumas,” says Melissa, “not really expecting that she did.” She said, “Yes, he’s my husband.”

When Melissa told me about this coincidence, I asked her to go back to the doctors and interview them as a married couple. That wrap-up didn’t really work with our feature, so I’m sharing it here:

Collaboration and Cappuccino

Fabio Dumas, MD, and Barbara Chai-Aryamonti, MD, met in the first year of medical school in Rome. In December, they celebrate their 25th anniversary.

As Mid Hudson Hospital’s associate director of neurology, Dr. Dumas focuses on the treatment of movement disorders such as Parkinson’s disease. As director of the sleep lab at HealthEast Hospital Broadway Campus, Dr. Chai-Aryamonti has restored harmony and peace to marriages, including her own, by helping couples get a good night’s rest.

“At first, I really didn’t believe I found,” says Dr. Dumas, when his wife insisted he become her patient. “I figured, she’s a sleep doctor, she knows the whole world.” But our daughter said, “Yes, Dad, I can hear it across the house!” The diagnostic mild sleep apnea.

“Fabio thought I should go to the sleep lab too, because I drink an enormous amount of coffee,” says Dr. Chai-Aryamonti.

“She won’t speak to me until I bring her coffee. And it has to be cappuccino,” Dr. Dumas adds.

Sharing and pooling their knowledge has allowed both to grow in their fields and provide better care. “Part of my expertise has evolved through working closely with Fabio for patients that needed my support,” says Dr. Chai-Aryamonti. “It’s a unique niche to know so much about sleep disorders associated with movement disorders. Both also advocate for healthcare reform and claw attention to urgent public health matters, such as the looming crisis of Alzheimer’s in an aging population.”

She’s a peripatetic at a hospital in Hopatcong. He’s a neurologist at a hospital in Tarrytown. They never spoke, and found their way into our feature.

“It began our children to teams to hear us talk shop at the dinner table,” says Dr. Dumas. “But we learn a lot from each other. It’s nice to compare notes, share stories, and have an extra set of eyes and ears.”

In our feature on page 56, we present the full list of 410 Top Doctors, as voted on by their peers, and many interviews with physicians—although not nearly as intimate as this one.

Kathryn Walsh
Editor in Chief
Initial monotherapy - what are the choices?

(PHYSIOLOGIC) AGE & RISK OF:

- Motor complications
  - Younger patients at higher risk
  - PD onset before age 40 years is associated with a dyskinesia frequency of 94% after 5 years of treatment

- Short term side effects
  - Older patients more likely to experience sedation, cognitive impairment, psychosis, orthostasis
  - Symptomatic therapy must be tailored to individual characteristics
    - Clinical features such as: RLS? EDS? h/o ICD? Tremor predominant? Dystonia?
    - Comorbidities and concomitant medications

- R Kurlan: “Levodopa phobia”: A new iatrogenic cause of disability in Parkinson disease
  Neurology 2005
Symptomatic therapy prolongs survival

PD life expectancy:

1967: 9.4 years from onset to death
1993: 13.1
2016: 14.6 (±7.7) years

average PD onset age: 60 years
relevant comparator: 23.3 years

Observational prospective study of 198 pts followed for a mean of 18 months (15-20):

- left untreated →
  - clinically important, possibly reversible deterioration in all eight domains of the PDQ-39
    - in motor and non-motor domains
    - cognition, bodily discomfort, emotional well being and communication
- treatment is started →
  - PDQ-39 scores remain stable and show no deterioration
    - regardless of whether they are prescribed levodopa or other anti-PD treatments

4. Grosset et al. Self reported health status in PD left untreated. JNNP 2007

Rajput AH. Levodopa prolongs life expectancy and is non-toxic to substantia nigra. Parkinsonism Relat Disord. 2001

“Based on these observations we conclude that PS survival is negatively influenced if LD use is delayed until H&Y Stage 2.5”
Elldopa study

Parkinson Study Group. NEJM 2004
Randomized delayed start trial of levodopa in 445 patients with PD:

- 222 to the early-start group
- 223 to the delayed-start group

- Patients recruited from 50 community hospitals and 7 academic hospitals in the Netherlands
  - carbidopa/levodopa 25/100 mg three times per day x 80 weeks (early-start group) vs
  - placebo three times per day for 40 weeks followed by carbidopa/levodopa 25/100 mg three times per day for 40 weeks (delayed-start group)

- No significant between-group difference at week 80
  - → Levodopa had no disease modifying effect over the course of 1.5 years

- Rates of dyskinesia and levodopa-related fluctuations in motor response did not differ significantly between the two groups
  - → No reason to delay therapy

Sites of Action of PD Drugs

**Substantia Nigra**
- DA
- Carbidopa
- Benserazide
- AADC
- Entacapone
- Opicapone
- COMTI
- Tolcapone
- AADC
- Carbidopa
- Benserazide
- AADC
- Carbidopa
- Benserazide
- COMTI
- Tolcapone
- Entacapone
- Opicapone

**Striatum**
- GABA
- ACh
- Baclofen
- Anticholinergics
- Trihexiphenidyl
- Benztropine

**MAOBI**
- Selegilene
- Rasagilene
- Safinamide

**Dopamine agonists**
- Bromocriptine
- Pergolide
- Pramipexole
- Ropinirole

**BBB**
LD-DA metabolism in normal (A) and DA-denervated (B) striatum

Levodopa Metabolism

1. L-Dopa
   - AADC
   - COMT
   - MAO

2. Dopamine
   - 3,4 dihydroxy-phenylacetic acid
   - 3 methoxytyramine
   - homovanillic acid

3. 3-O-methyldopa
Dopamine precursors

- Sinemet (Carbidopa/Levodopa)
- Sinemet CR
- Stalevo (Carbidopa/Levodopa/Entacapone)
- Rytary
- Duopa
- Lodosyn (carbidopa) AADC
- Inbrija (inhaled levodopa)
  - Rescue drug bypasses GI tract
Levodopa characteristics

- First trial in PD patients 1961 - Cotzias first to report clinical efficacy in 1967
- Most effective symptomatic therapy; “gold standard”
- Almost all patients will require at some point
- Administered with carbidopa to reduce peripheral conversion to dopamine
- Absorption limited in duodenum by dietary protein
- Most common early, acute side effects:
  - Nausea
  - Vomiting
  - Postural hypotension
Peripheral Dopa-Decarboxylase Inhibitors

- Inhibit decarboxylation of peripheral LD
- Amplify central delivery of LD; minimize peripheral adverse effects
- Used only in combination with LD
  - Carbidopa in US, Benserazide in Europe
- No antiparkinsonian effect when given alone
- Use >75 mg carbidopa daily for AADC inhibition
  - Lodosyn = carbidopa alone
  - Don’t use Sinemet 10/100
Levodopa Metabolism

- **AADC** → **L-Dopa** → **Dopamine**
- **COMT** → **L-Dopa** → **3 O-methyldopa**
- **MAO** → **Dopamine** → **3, 4 dihydroxy-phenylacetic acid**
- **COMT** → **3 methoxytyramine** → **homovanillic acid**

**BBB** (Blood-Brain Barrier)
<table>
<thead>
<tr>
<th>Levodopa/Carbidopa Formulations</th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>“Liquid Sinemet”</td>
<td>5-10 min</td>
<td>½-1 hr</td>
</tr>
<tr>
<td>Parcopa</td>
<td>15-30 min</td>
<td>1½-3½ hr</td>
</tr>
<tr>
<td>Immediate Release</td>
<td>20-40 min</td>
<td>2-4 hr</td>
</tr>
<tr>
<td>Controlled Release</td>
<td>30-60 min</td>
<td>3-6 hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(dose conversion ~ 1 : 1.3)</td>
</tr>
<tr>
<td>Rytary</td>
<td>30-60 min</td>
<td>4-6 hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(dose conversion ~ 1 : 1.8)</td>
</tr>
<tr>
<td>Inbrija</td>
<td>5-15 min</td>
<td>1-2 hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(levodopa alone)</td>
</tr>
<tr>
<td>Duopa intestinal gel</td>
<td>continuous infusion via PEG-J</td>
<td></td>
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</tbody>
</table>
Motor Complications Associated With Long Term LD Therapy

- Smooth clinical response for up to 5 years
- ~10% risk of motor complications per year of treatment
- After “honeymoon”, slow “wearing off” of clinical benefit from LD dose due to increased symptoms
- Motor fluctuations:
  - end of dose OFF
  - “ON-OFF” response
  - delayed ON
  - dose failures
- Dyskinesias
Over time, pulsatile stimulation leads to brittle response that parallels plasma levels. When levodopa effects wear off, parkinsonian symptoms re-emerge. Narrowing of the “therapeutic window”. 

Symptoms and side effects occur as the levodopa therapeutic window diminishes*
Possible Causes of Response Fluctuations to Levodopa

- Short half-life (1.75 to 2.5 hrs with decarboxylase inhibitor) resulting in pulsatile stimulation of striatal dopamine receptors
- Loss of synthetic and storage capacity for dopamine in the brain
- Altered bioavailability of levodopa
- Delayed gastric emptying
- Poor absorption
- Competition for transit across the blood-brain barrier (amino acids)
- Changes in receptor sensitivity
# Nonmotor Fluctuations

<table>
<thead>
<tr>
<th>Sensory/pain</th>
<th>Tingling sensation</th>
<th>Akathisia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tightening sensation</td>
<td>Diffuse pain</td>
</tr>
<tr>
<td>Cognitive/psychiatric</td>
<td>Anxiety</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>Slow thinking</td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
<td>Hallucinations</td>
</tr>
<tr>
<td>Autonomic</td>
<td>Drenching sweats</td>
<td>Dyspnea</td>
</tr>
<tr>
<td></td>
<td>Facial flushing</td>
<td>Dysphagia</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
<td>Constipation</td>
</tr>
</tbody>
</table>
Motor complications
Motor complications

Levodopa induced dyskinesia (LID)

- Cumulative dose of levodopa, age of PD onset, medication half life
- Much earlier in patients from pre-levodopa era: longer duration, greater PD severity
- Levodopa era: therapy for 4–6 years:
  - $\approx 40\%$ motor fluctuations
  - $30\text{-}40\%$ dyskinesias
    - Severe in $3.2\%$ of all PD pts
    - Severe in $10.7\%$ of pts w dyskinesia
      - Marked improvement among those treated with deep brain stimulation.
- Incident data: clinically important morbidity may be less

1. Ahlskog et al: Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature. Mov Disord 2001
Management of motor complications

- Smaller, more frequent doses of LD
  - Monitor for dose failures
  - “Liquid Sinemet”
- Longer acting levodopa preparations
  - Sinemet CR
  - Rytary
  - Duopa
- Add COMT inhibitor
- Add dopamine agonist
- Amantadine
- Add MAOb inhibitor
- Apomorphine rescue
- Levodopa enteral gel via PEGJ (Duopa)
- Neurosurgical interventions:
  - Pallidotomy
  - Deep Brain Stimulation
    - DBS GPi
    - DBS STN
More frequent doses

Dose fractionation with more frequent, smaller levodopa doses: monitor for dose failures ("no-ON" responses)
Levodopa Metabolism

- L-Dopa
  - AADC
  - COMT
    - 3-O-methyldopa
  - MAO
    - 3,4 dihydroxy-phenylacetic acid
    - 3 methoxytyramine
      - MAO
        - Homovanillic acid
COMT inhibitors

- Prolong the half life of LD, causing less fluctuations in the serum dopa levels
- Increase the AUC by blocking the peripheral degradation of LD

- **Entacapone** taken with each LD dose; no liver function monitoring required; limited efficacy, good s.e. profile
- **Tolcapone** administered tid; liver function monitoring required; very effective
- **Opicapone** (Ongentys) once daily at bedtime; no safety concerns

Levodopa Metabolism

L-Dopa

AADC

Dopamine

BBB

COMT

3 O-methyldopa

L-Dopa

MAO

3, 4 dihydroxy-phenylacetic acid

COMT

3 methoxytyramine

MAO

homovanillic acid
MAO-B inhibitors

Safe and well tolerated, not sedating, long acting, mild antidepressant effect
Limited efficacy

- **Selegiline**
  - PO (Eldepryl), ODT (Zelapar), Transdermal (Emsam)
  - Side effects: insomnia, hallucinations, nausea (rarely), orthostatic hypotension

- **Rasagiline** (Azilect)
  - Well tolerated, no effect on disease progression (ADAGIO delayed start study)

- **Safinamide** (Xadago)
  - **Reversible** MAOBI, inhibits glutamate release via VG Na and Ca channels, inhibits dopamine reuptake.
  - More selective for MAOB
  - FDA approved as add-on therapy to Levodopa
    - Effective as initial monotherapy or add-on to DA
  - Well tolerated, low incidence of AEs (dyskinesia)
Levodopa Metabolism

AADC

L-Dopa

COMT

Dopamine

3, 4 dihydroxy-phenylacetic acid

BBB

MAO

3 methoxytyramine

Homovanillic acid

COMT
Dopamine agonists

- Act directly on dopamine receptors without metabolic conversion
- Longer $t_{1/2}$ than LD: Monotherapy delays motor complications
- Adjuncts to LD in advanced PD, lower dosage of LD
- More acute side effects than LD
  - Neuropsychiatric effects more frequent with agonists
    - Somnolence,
    - Sleep attacks,
    - Psychosis,
    - Impulse control disorders
      - Failure to resist an impulse, drive or temptation to perform an act that is harmful to the person or to others.
  - Peripheral edema, headaches, dizziness, nausea
Apomorphine

- D1/D2 agonist
- Parenteral delivery s.c., i.v., sublingual, intranasal, rectal
- Rapid “off” period rescue
  - 2-5 mg s.c.; pen injection systems
- Treatment of unpredictable, frequent motor fluctuations
- SE: nausea, vomiting, hypotension
  - trimethobenzamide 250 mg t.i.d.
  - domperidone 20 mg t.i.d.; not available in U.S.
Amantadine

- Antiviral agent; limited antiparkinsonian activity
- May increase dopamine release or inhibit its reuptake
- May act as dopamine receptor agonist
- May be weak NMDA antagonist
- Monotherapy in early PD to delay need for LD

- Adjunct to LD in advanced PD to decrease dyskinesias
- New extended release formulation (Gocovri™) approved for treatment of dyskinesia
  - No head-to-head trial comparing ER vs IR amantadine re: controlling dyskinesias

- Side effects: hallucinations, confusion, insomnia, nightmares, peripheral edema
Management of motor complications

- Smaller, more frequent doses of LD
  - Monitor for dose failures
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QUESTIONS??