Parkinson's Disease

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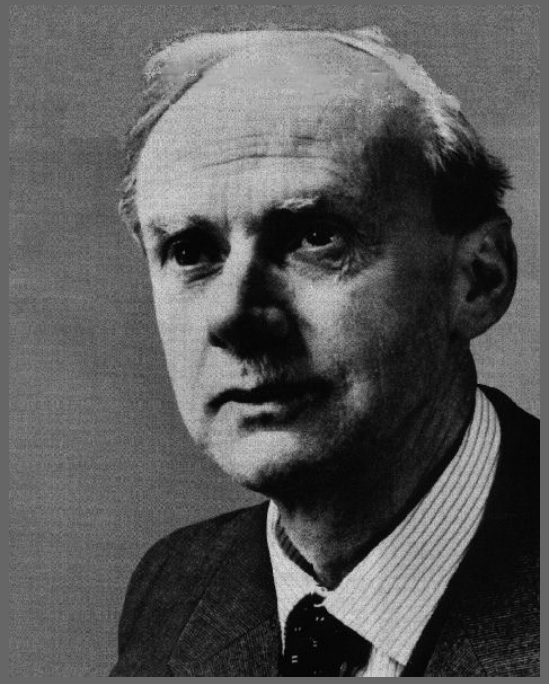
Objectives

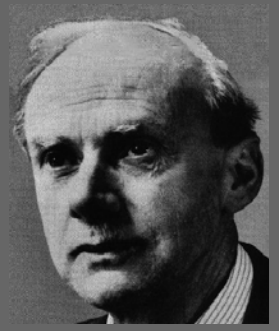
- Explain mechanism of action of carbidopa/levodopa, dopamine agonists, MAO-B inhibitors, and COMT inhibitors
- Outline a management strategy for a newly diagnosed PD patient using carbidopa/levodopa, including how to titrate doses
- Explain a medication management strategy for the patient experiencing "wearing off" while being treated with carbidopa/levodopa

Let's start with a mini-case



- Paul Dirac is a 65-year old gentleman who presents with a new complaint of tremor in his right hand which makes it difficult for him to cook and write.
- Upon examination, the clinician notes a marked pill-rolling tremor along with very mild cogwheel rigidity, and slowed movements. PD's physical exam is otherwise normal, as are his CBC, chemistry panel and electrolytes.
- He has no other complaints or medical conditions
- What does Mr. Dirac likely have? Should it be treated?

Mr. Dirac is not alone…



- Higher incidence in males – 2:1 M:F ratio
- Affects 1-2% of the population over 60 yrs old
- Ages 50-80 most commonly affected
- Mean age at onset 57 years
- One million people in the US with PD
- 20 new cases per 100,000 persons per year
- $6 billion per year by the US govt

Olanow CW. Neurology. 2009;72 (21 Suppl4):S1-136
Lewitt PA. N Engl J Med. 2008 Dec 4;359:2468-76.

Pathophysiology

- Neurodegenerative disease
  - Progressive loss of dopaminergic neurons
  - Symptoms caused by decreased stimulation of the motor cortex by the basal ganglia. This occurs as a result of insufficient dopamine production in the dopaminergic neurons of the substantia nigra
  - This changes the normal relationship between inhibitory and excitatory pathways impacting the motor cortex
  - Posture, muscle tone, and regulation of voluntary muscle activity affected

Olanow CW. Neurology. 2009;72 (21 Suppl4):S1-136

http://mda06im.webnode.com/parkinsons-spectrum-diseases/

Pathophysiology

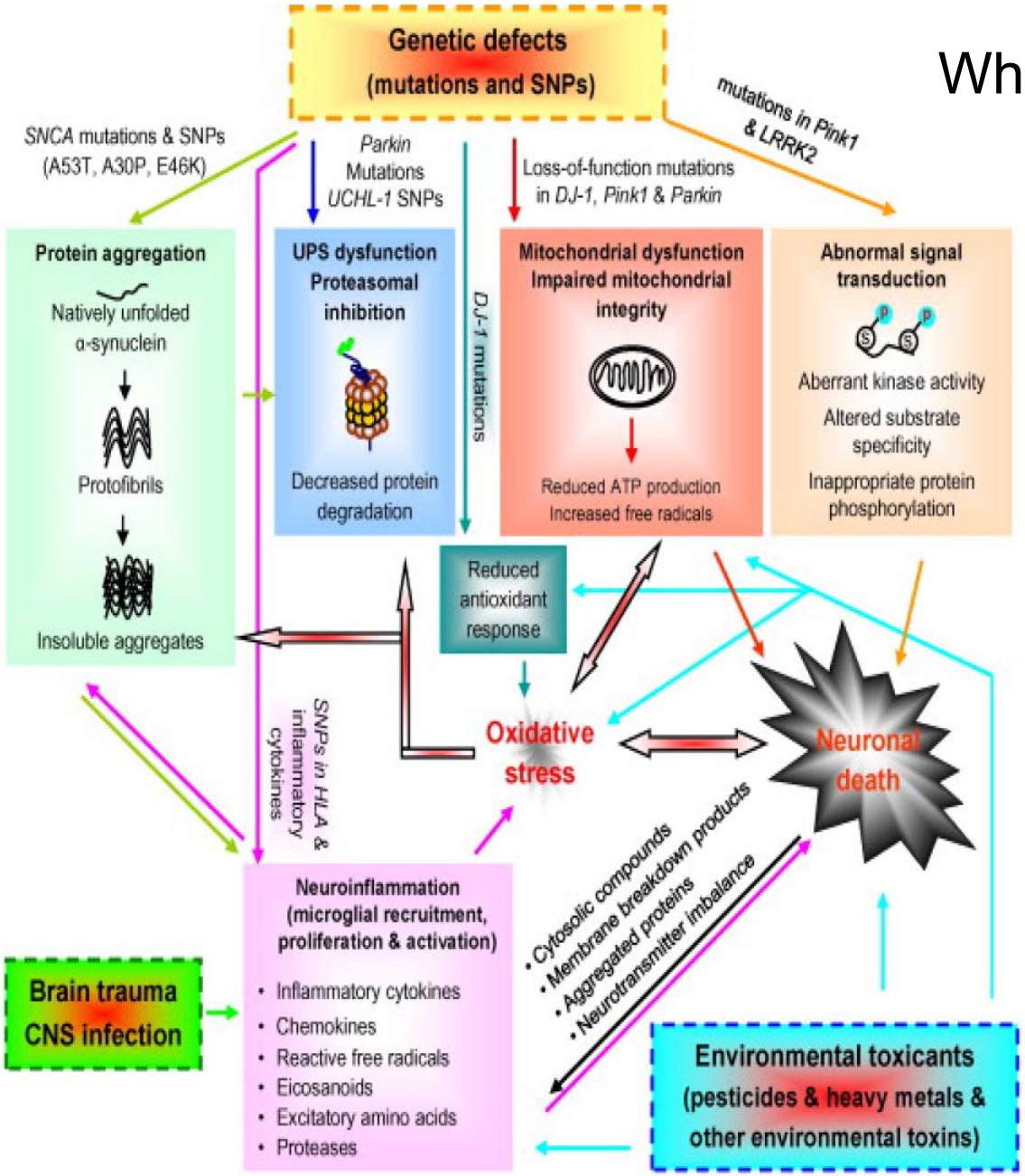
- Two hallmarks of PD:
  - Depigmentation of DA-producing neurons
  - Presence of Lewy Bodies

Stage	Lewy Body Location	Symptoms
Pre-motor (Early)	Medulla Oblongata Locus Coeruleus Raphe Nuclei Olfactory bulb	Anxiety Depression Depression Smell changes
Motor stage	Midbrain (Substantia Nigra pars compacta) -	Motor features
Advanced stage	Cortex	Cognitive changes Behavior changes

Etiology of PD

- Idiopathic: most common
- Oxidative insult
- Trauma
- Infections
- Genetics: 10-15% with suggestive family history
- Environmental toxins
- Medications that can exacerbate or mimic Parkinsons: dopamine antagonists, some antiepileptics, calcium channel blockers, and more….

Lewitt PA. N Engl J Med. 2008 Dec 4;359:2468-76



What goes wrong in PD?

Three types of insults shown here

1. Trauma or infection
2. Environmental toxins
3. Genetic defects

Harm done in five ways

1. Protein aggregation
2. Dysfunctional protein degradation
3. Abnormal signal transmission
4. Mitochondrial dysfunction
5. Oxidative stress

Ali SF.. Int J Environ Res Public Health. 2011 8(12):4702-13.

Examples of drugs implicated in drug-induced parkinsonism:

Drugs commonly implicated

- Typical antipsychotic agents (eg chlorpromazine, promazine, haloperidol, trifluoperazine, sulpiride, flupentixol, pimozide, fluphenazine, benperidol
- Calcium channel agents (eg flunarizine, cinnarizine)
- Antiemetic agents (eg prochlorperazine, metoclopramide)
- Atypical antipsychotic agents, particularly at higher doses (eg risperidone, olanzapine)
- Antihypertensive agents (eg reserpine, α-methyldopa)
- Tetrabenazine

Thanvi B Drug induced parkinsonism. Postgrad Med J. 2009;85(1004):322-6.

Examples of drugs implicated in drug induced parkinsonism:

- Atypical antipsychotic agents (eg quetiapine, clozapine)
- Calcium channel agents (eg diltiazem, verapamil)
- Antiarrhythmic agents (eg amiodarone)
- Antidepressants (MAOI, SSRI, TCA)
- Anticonvulsants (eg sodium valproate)
- Lithium
- Miscellaneous: anticancer drugs (tamoxifen, thalidomide), hormones (levothyroxine, medroxyprogesterone), some of the antibiotics, antiviral and antifungal agents

Drugs less commonly or rarely implicated

Thanvi B Drug induced parkinsonism. Postgrad Med J. 2009;85(1004):322-6.

Diagnosis

- Step 1: Presence of bradykinesia and at least one of the following:
  - Resting tremor
  - Rigidity
  - Postural instability
- Step 2: Exclude other types of disorders
- Step 3: Presence of at least 2 supportive criteria
  - Asymmetry of symptoms or motor signs
  - Clear benefit from dopaminergic medications
    - Marked improvement/worsening with dose increases/decreases
    - Clear on-off fluctuations including end-of dose wearing off
  - Presence of levodopa dyskinesias
  - Rest tremor (unilateral at onset)
  - Olfactory loss or positive cardiac scintigraphy

Diagnosis of PD

- Laboratory or imaging tests not clinically useful yet
- Diagnosis is based on clinical features.
- Cardinal features of PD
  - Bradykinesia
    - Seen in just about all Parkinson patients
  - Resting tremor
    - May be subtle, only involving a thumb or a few fingers
  - Rigidity
    - Noted on clinical exam rather than seen by the observer
  - Gait and balance
    - the patients may walk with small steps, occasional freezing, as if the foot were stuck

Fernandez HH. Updates in the medical management of Parkinson disease. Cleve Clin J Med. 2012 Jan;79(1):28-35

Features not characteristic of typical PD (Other etiologies should be sought)

- Falls at presentation and early in disease
- Poor response to levodopa
- Symmetry at onset
- Rapid progression
- Lack of tremor

Uptodate, Diagnosis of Parkinson disease
Bloem BR. *Lancet*. 2011;377:125-126

Unified Parkinson's Disease Rating Scale

- UPDRS has more than 100 elements, used in nearly all PD treatment studies
- Part I: Mentation, behavior, and mood
- Part II: Activities of Daily Living (ADL) e.g.,
- Part III: Motor exam e.g.,

Uptodate, Diagnosis of Parkinson disease

Hoehn and Yahr Scale

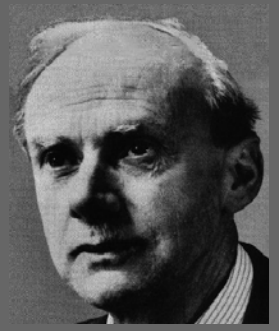
- Used in clinical staging for individual patients
- Stage 0: No clinical signs evident.
- Stage 1: Unilateral involvement only. Functional impairment usually minimal or absent.
- Stage 2: Bilateral involvement. No impairment of balance.
- Stage 3: Bilateral involvement. Symptoms worse. First sign of impaired righting reflexes.
- Stage 4: Fully developed, severely disabling disease. Unassisted standing and walking but markedly incapacitated.
- Stage 5: Confined to bed or chair unless aided.

Principles of Management

- Goals of therapy
  - Relieve symptoms
  - Preserve functional capacity
  - Preserve and improve quality of life
  - Minimize adverse effects of therapy

THERE IS NO CURE

For our patient, consider the elements in management of Parkinsons Disease, now and later



- Patient and family education
- PT and OT
  - Slow movement is an important aspect of PD, so exercise is often recommended in the treatment plan, but with little evidence
  - Small trials have been promising but inconclusive…but see next page
- Attention to proper diet, fluid intake, swallowing
- Watch for and manage depression, other neuropsychiatric issues
- Social support
- Medication

Treadmill training vs no treadmill training, evaluation of data from 203 patients (mean age 65) from 8 randomized controlled and randomized controlled crossover trials (Cochrane review)

Measure	Differences (95% CI)	*P* Value
Walking speed (SMD)	0.50 (0.17 to 0.84)	.003
Stride length (SMD)	0.42 (0.00 to 0.84)	.05
Walking distance (MD), m	358 (289 to 426)	<.0001
Cadence (MD)	1.06 (−4.32 to 6.44)	.70
Patient dropout rate (RD)	−0.07 (−0.18 to 0.05)	.26

Exercise also found useful in a 2011 study

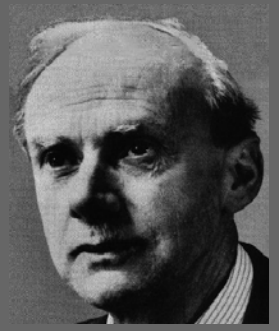
Mehrholz J. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD007830
http://www.medscape.com/viewarticle/716069
American Academy of Neurology (AAN) 63rd Annual Meeting: Abstract P05.288. 4/13/11

Exercise Summary

- Treadmill work
- Tai Chi

- Exercises should attempt to improve:
  - Balance
  - Flexibility
  - Strength

- Exercise can reduce 2ndary effects of rigidity and flexed posture.



Mr. Dirac is encouraged and is going to start a walking program……

What are his pharmacologic treatment options for his early Parkinson's disease

Review some options: Anticholinergic agents Advantages

Benztropine and Trihexyphenidyl

- Some antiparkinsonian efficacy (tremor)
  - Dopamine provides negative feedback to acetylcholine neurons in striatum
  - Loss of dopamine neurons results in relative increase in cholinergic activity
- Inexpensive
- Peripherally acting agents may be useful in treating sialorrhea

Anticholinergic agents: Disadvantages

- Not very effective for the more disabling features of PD
- Troublesome central and peripheral cholinergic side effects
- Anti-SLUD effects
  - Salivation, lacrimation, urination, defecation
- Cognitive side effects – especially in older patients!

MAO-B Inhibitors selegiline, safinamide, and rasagiline

Advantages

- Irreversibly inhibits MAO type B to spare levodopa
- Can be used as monotherapy
- Reduced motor fluctuations and increased “on” time with levodopa
- Once-daily dosing (rasagiline and safinamide)
- Selegiline ODT available (Zelapar): absorbed into buccal mucosa
- Well-tolerated

MAO-B Inhibitors: Disadvantages

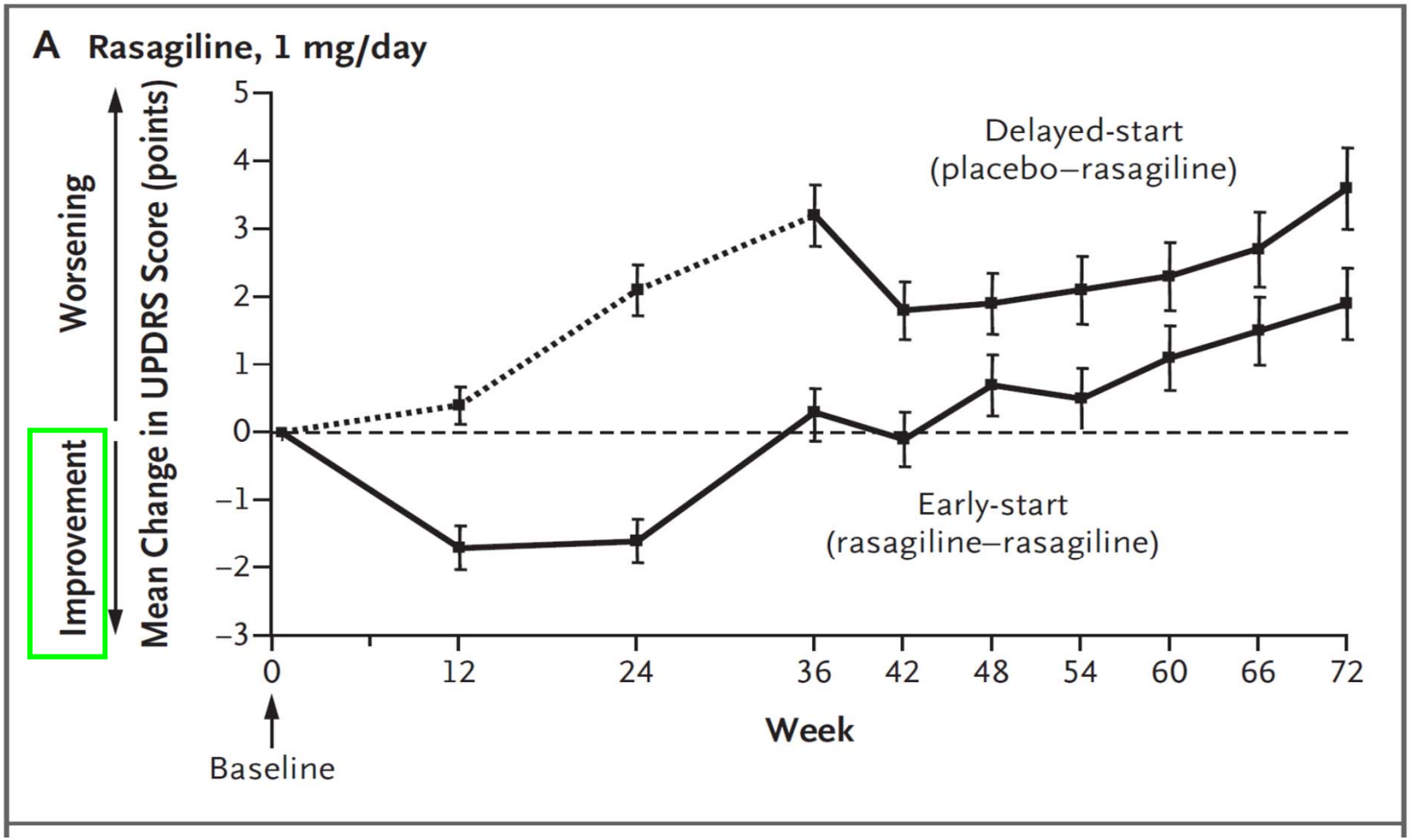
- Modest antiparkinsonian effect
- Amphetamine and methamphetamine metabolites may cause insomnia (take early in the day)
- Possibility of provoking hypertensive reactions due to mechanism of action
  - In practice, unlikely to cause hypertensive reactions
- SE – nausea, headache, hallucinations, confusion
- Don't use safinamide with:
  - Dextromethorphan
  - Opioids
  - St. John's Worst
  - Antidepressants
  - Cyclobenzaprine

Beyond symptom treatment, is rasagaline neuroprotective?

- 1176 subjects with untreated Parkinson's randomly assigned to receive either
  - Rasagiline (1 mg or 2 mg/d) for 72 weeks (the early-start group)
  - OR placebo for 36 weeks, followed by rasagiline (1 mg or 2 mg/d)) for 36 weeks (delayed-start group).
- Measure UPDRS at intervals
- If rasagaline IS neuroprotective, the group who received drug for 72 weeks would be BETTER than the other group

Olanow CW. Neurology. 2009;72 (21 Suppl4):S1-136

Changes in UPDRS scores over 72 weeks



BUT, 2mg/d dose did not give this positive result, thus caution needed in interpreting the study as a whole
Other flaws in study are concerning and it is not definitive

C. Warren Olanow and O. Rascol Neurology April 6, 2010 74:1149-1150

Olanow CW. N Engl J Med 2009;361:1268-78.

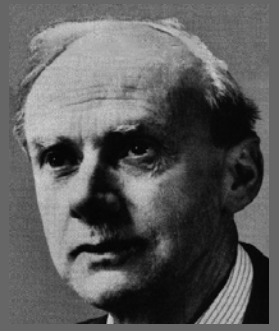
Another option: Amantadine (Gocovri, Symmetrel)

- Relief with mild S/Sx, especially tremor
  - 100 mg BID-TID (IR)
- Mechanism of action unclear
- Adjust for renal impairment
- Side effects
  - CNS--caution in elderly or confused patients
  - Convulsions with very high doses or with renal impairment
  - GI complaints - take with food
  - Livedo reticularis

Amantadine ER (Gocovri)

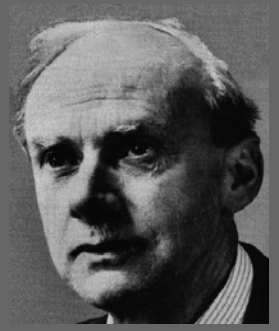
- Approved for levodopa dyskinesias
- Also may reduce “off” time in levodopa-treated patients
- Dose: 137-274mg once daily
- Taken at bedtime
  - Plasma concentration peaks in AM and is sustained throughout day
- Side Effects: hallucinations, dizziness, dry mouth, edema, orthostatic hypotension

Mini-case



- PD was excited about the news on rasagiline
- He was started on rasagiline 1 mg/d and benztropine 1 mg bid.
- Why did the physician prescribe an anticholinergic?
- PD returns three weeks later with his wife. They both note that the tremor is somewhat better, but not to his satisfaction.
- He has a new complaint of constipation. He also finds difficulty in urination (difficulty in starting the stream). He also has dry mouth. He has no complaints regarding confusion or memory, with which his wife concurs.

Mini-case



- What change in medications could be tried for PD?

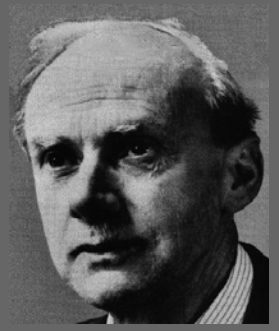
  Increase dose of benztropine

  Add metamucil and tamsulosin, and lozenges for dry mouth

  Stop the benztropine, continue rasagiline, consider starting carbidopa/levodopa

ANSWER:

Mini-case continued



- For PD, benztropine was discontinued
- Rasagiline was continued
- PD was started on Carbidopa / levodopa, He did well, with improvement in tremor, gait, and mobility
- No bothersome side effects (no n/v, confusion, dizziness)

Carbidopa/Levodopa

L-dopa converted into dopamine within dopaminergic neurons

But L-dopa largely metabolized in the periphery

- Levodopa alone: ~1% of Levodopa crosses blood brain barrier (BBB)
- Levodopa with carbidopa: ~5-10% of Levodopa crosses blood brain barrier (BBB)

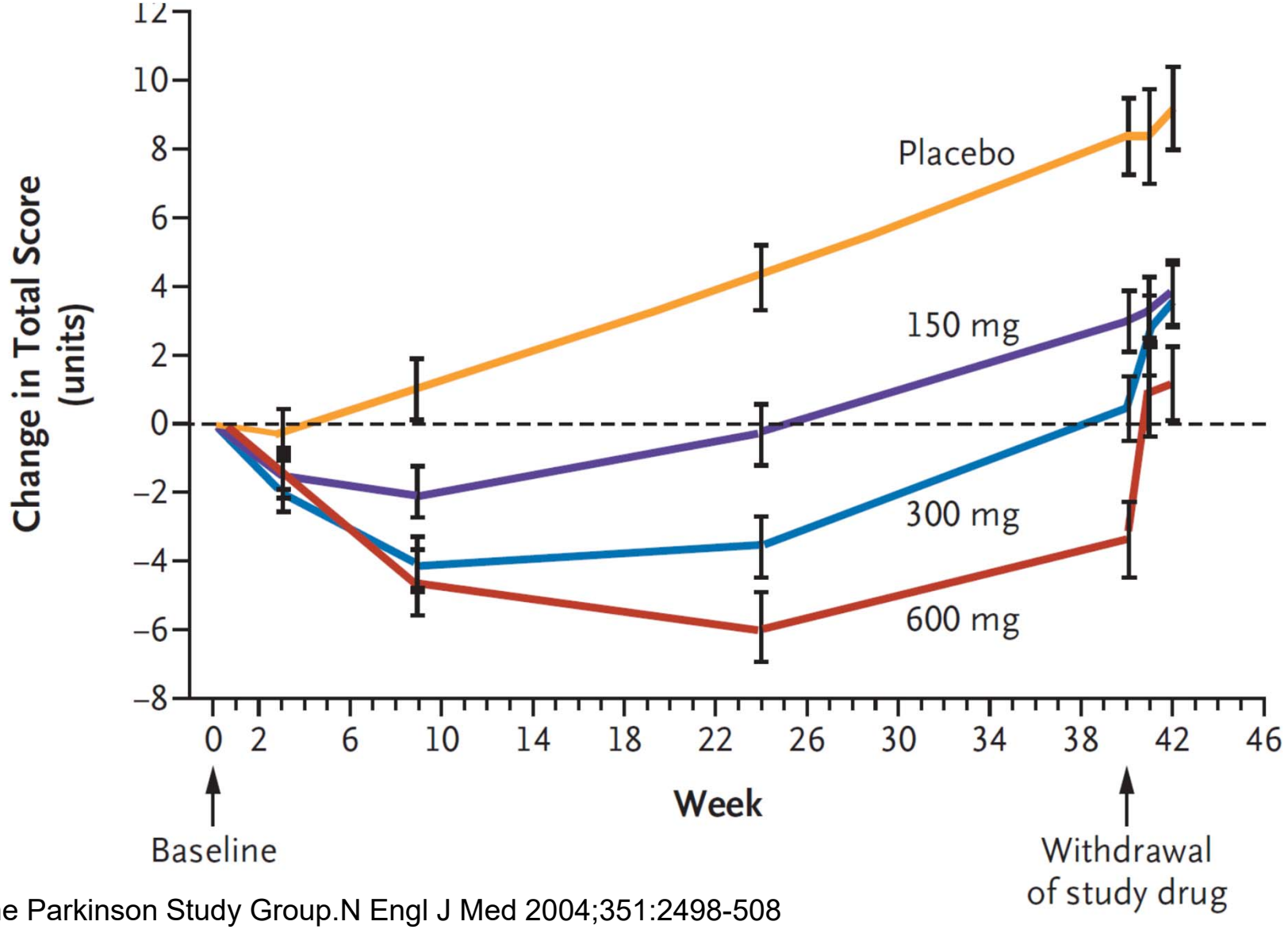
Koller WC. Neurology. 62(1 Suppl 1):S1-8, 2004

Levodopa: Advantages

- Most efficacious antiparkinsonian drug
- Virtually all PD patients respond
- Improves disability, and prolongs capacity to maintain employment and independent activities of daily living
- Reduces mortality

Olanow CW. Neurology. 2009;72 (21 Suppl4):S1-136

A classic study of levodopa: changes in UPDRS with change in dose



The Parkinson Study Group.N Engl J Med 2004;351:2498-508
Lewitt PA.N Engl J Med. 2008 Dec 4;359:2468-76

Levodopa: Disadvantages

- Motor complications
  - Dyskinesias: choreiform movements, dystonia
  - Motor fluctuations
- Neuropsychiatric problems: confusion, psychosis, hallucinations
- Sedation
- Does not treat the nondopaminergic features of PD (e.g., freezing, postural instability, autonomic dysfunction, dementia)
- Need to taper off to avoid hyperpyrexia syndrome
- There are still concerns levodopa may be neurotoxic, although recent study is reassuring*

*Lees AJ. *Neurology* Published online September 14, 2011.
Poewe W. Neurology. 2009 Feb 17;72(7 Suppl):S65-73.
Olanow CW. Neurology. 2009;72 (21 Suppl4):S1-136

Administration and titration of carbidopa/levodopa

- Daily dosage is approximately 300-1500 mg in 3 to 6 divided doses, although some patients will need more frequent or higher dosing.
- Titrate doses slowly to achieve desired symptom relief while minimizing adverse effects
  - For example, start with IR carbidopa/levodopa 25/100 tid, increase by one tablet every other day as needed and tolerated
    - With IR carbidopa/levodopa 25/250, increase by ½ -1 tab every 1-2 days
    - maximum of 8 tablets of any strength per day or no more than 200mg carbidopa/day or 2000mg levodopa/day
  - Tablets with other ratios of carbidopa/levodopa available to aid in dosing

Lexicomp Drug information handbook, 19th ed. 2011

Administration and titration of carbidopa/levodopa

- Carbidopa/levodopa also available as controlled release (CR)
- CR carbidopa/levodopa 50/200 bid to start, can increase by one tablet every 3 days, at least 6 hrs apart; maximum of 8 tablets/day
- Elderly carbidopa/levodopa 25/100 bid to start.
- Maximum 200mg carbidopa/d and 2000mg levodopa

Lexicomp Drug information handbook, 19th ed. 2011

Administration and titration of carbidopa/levodopa

- 75-100mg/d carbidopa/d is usually sufficient, but the occasional patient may need up to 200 mg/day to completely suppress nausea.
  - Carbidopa *(Lodosyn)* is available alone in doses of 25 mg and can be added in with other doses of carbidopa/levodopa.

- Best absorption is without food. Dietary protein competes with levodopa during intestinal absorption and in crossing the blood-brain barrier. Taking protein late in the day can aid absorption.

Lexicomp Drug information handbook, 19th ed. 2011

Administration and titration of carbidopa/levodopa

- Carbidopa/levodopa tablets are sometimes crushed and mixed with a beverage for quicker effect. An ODT form is also available (Parcopa); this must be allowed to dissolve in the mouth so is absorbed

- Carbidopa/levodopa CR can be helpful in the "wearing off" phenomenon, but it is unevenly absorbed, is slower to take effect and patients may need to take an IR preparation at the same time.

Lexicomp Drug information handbook, 19th ed. 2011

Complications in Levodopa Treatment

- "Wearing off" or end of dose fluctuations
- "On-Off" phenomena
- Peak dose dyskinesias
- Start hesitation ("freezing")
- Slow onset of response

Strategies include dose adjustment and use of other medications (see LATER in talk)

Half of patients show decreased efficacy after 2 years

Instead of levodopa/carbidopa, what about dopamine agonists?

- Directly activate dopamine receptors
  - D2 agonist role best understood in PD treatment
  - Role of D3 not well understood
- Can be used initially as monotherapy
- Often eventually requires combination with levodopa

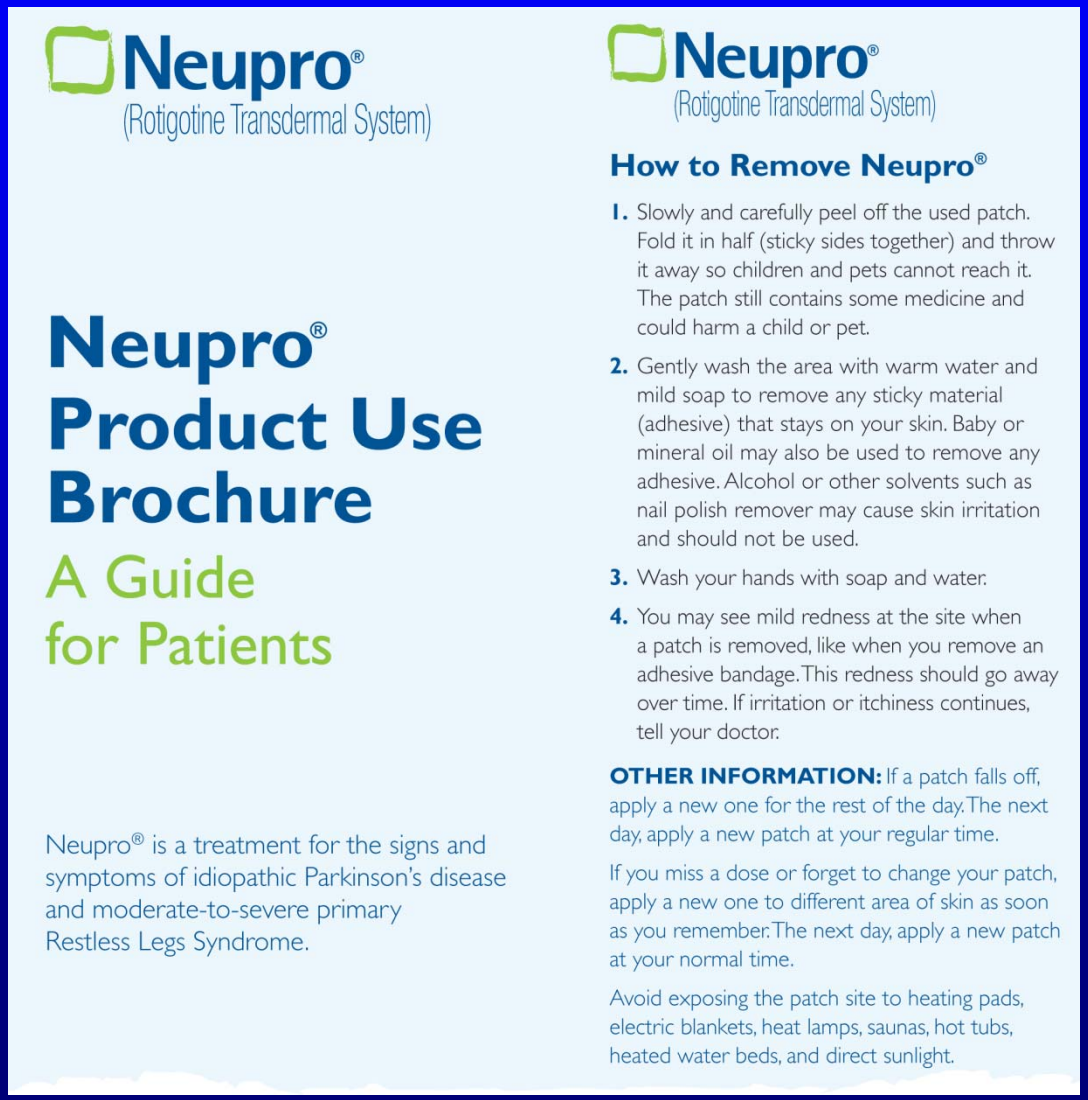
Antonini A. Neurol Sci (2008) 29:S371–S374

Dopamine Agonists

- Bromocriptine (Parlodel^{R})
- Ropinirole (Requip^{R})*
- Pramipexole (Mirapex^{R})**
- Rotigotine patch…on the market, then OFF the market due to crystals forming in the patch, BACK on the market 2012, and now approved for early stage as well as advanced PD

*Generic since 2008
**Generic since 2010

Neupro instructions are extensive..this is just how to *remove* the patch



Neupro®
(Rotigotine Transdermal System)

Neupro® Product Use Brochure

A Guide for Patients

Neupro® is a treatment for the signs and symptoms of idiopathic Parkinson's disease and moderate-to-severe primary Restless Legs Syndrome.

Neupro®
(Rotigotine Transdermal System)

How to Remove Neupro®

1. Slowly and carefully peel off the used patch. Fold it in half (sticky sides together) and throw it away so children and pets cannot reach it. The patch still contains some medicine and could harm a child or pet.
2. Gently wash the area with warm water and mild soap to remove any sticky material (adhesive) that stays on your skin. Baby or mineral oil may also be used to remove any adhesive. Alcohol or other solvents such as nail polish remover may cause skin irritation and should not be used.
3. Wash your hands with soap and water.
4. You may see mild redness at the site when a patch is removed, like when you remove an adhesive bandage. This redness should go away over time. If irritation or itchiness continues, tell your doctor.

OTHER INFORMATION: If a patch falls off, apply a new one for the rest of the day. The next day, apply a new patch at your regular time.

If you miss a dose or forget to change your patch, apply a new one to different area of skin as soon as you remember. The next day, apply a new patch at your normal time.

Avoid exposing the patch site to heating pads, electric blankets, heat lamps, saunas, hot tubs, heated water beds, and direct sunlight.

Dopamine Agonists: Advantages

- Antiparkinsonian effects when used as monotherapy or as an adjunct to levodopa
- Reduced risk of developing levodopa-related motor complications
- Do not generate oxidative metabolites
- Levodopa sparing effect
- Potential neuroprotective benefits (controversial)

Antonini A. Neurol Sci (2008) 29:S371–S374

Dopamine Agonists

- Side effects
  - Orthostatic hypotension
  - Nausea and vomiting
  - Nasal stuffiness, constipation (bromocriptine)
  - Mental changes
  - Dyskinesias
  - Pleuropulmonary fibrosis (bromocriptine)

Serious concerns with Dopamine Agonists

- Impulse control disorders
- Psychosis – see Table 43-5
- Sleep attacks
- 9/19/12: FDA warning about possible increased risk of heart failure with pramipexole

http://www.fda.gov/Drugs/DrugSafety/ucm319779.htm#safety

Dosing for pramipexole

Pramipexole

- start at 0.125 mg tid, increase to 0.75 mg tid over 4-6 weeks.
- Further increases should be slower, up to the maximum daily dosage of 4.5 mg
- There may be little efficacy and increased adverse effects when more than 1-1.5mg/d is taken.

Extended-release pramipexole *(Mirapex ER)*

- start at 0.375 mg daily, titrate at one week or longer, to 0.75mgday, then by 0.75 mg increments up to a maximum of 4.5 mg per day.

Lexicomp Drug information handbook, 19th ed. 2011

Dosing for ropinirole

- Start at 0.25 mg tid, titrate up by 0.25 mg or 0.5 mg per dose each week, up to 3 mg or 4 mg tid.
- Many patients may need to slowly increase the dose, up to the maximum of 8 mg tid.

Extended-release ropinirole *(Requip XL)*

- start at 2mg once daily for 1-2 weeks; can increase after 1 week by 2mg/day. Maximum dose 26mg.

- When discontinuing, taper slowly over the course of a week.

Lexicomp Drug information handbook, 19th ed. 2011

Place in Therapy for Ropinirole, Pramipexole

- Modestly less effective than levodopa
- Reasonably well-tolerated
- May allowing for delay in levodopa initiation or decreased levodopa dose
- Caution in elderly or those with CNS deficits, as these agents can lead to hallucinations, confusion
- Do NOT DISCONTINUE SUDDENLY – neuroleptic malignant syndrome or akinetic crisis

Antonini A. Neurol Sci (2008) 29:S371–S374

Management of dopaminergic side effects

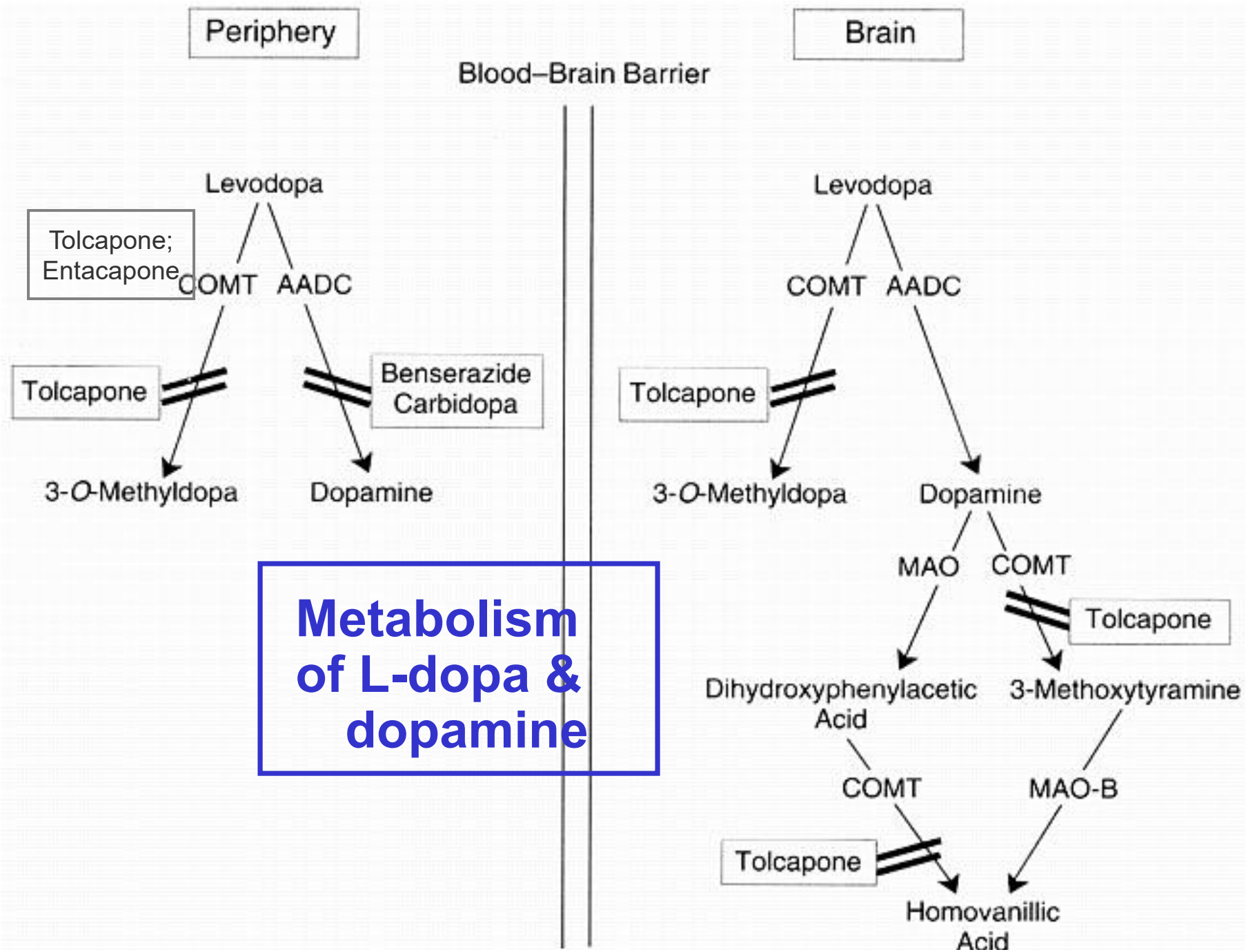
Dopaminergic Side Effect	Management
Nausea	- Give extra carbidopa or domperidone
Orthostasis	- Taper and D/C amantadine, MAO-I, and DA; - lower doses of BP medications (if applicable) - Droxidopa
Confusion or Hallucinations	- Taper and D/C amantadine, MAO-I, and DA; - Reduce levodopa dose
ICD	- Reduce dose of DA
Dopamine dysregulation syndrome	- Limit doses increases of DA - Cutaneous apomorphine infusion for off-period dysphoria - Low-dose clozapine or quetiapine

COMT Inhibitors : Levodopa-sparing agents

- Tolcapone (Tasmar^{R})
- Entacapone (Comtan^{R})

- Catechol-O-methyl transferase (COMT) inhibitors block the degradation of dopamine and levodopa by COMT

- Tolcapone spares central and peripheral levodopa
- Entacapone works peripherally


Periphery
Brain
Blood–Brain Barrier
Levodopa
Tolcapone; Entacapone
COMT
AADC
Tolcapone
Benserazide Carbidopa
3-O-Methyldopa
Dopamine
Levodopa
COMT
AADC
Tolcapone
3-O-Methyldopa
Dopamine
MAO
COMT
Tolcapone
Dihydroxyphenylacetic Acid
3-Methoxytyramine
COMT
MAO-B
Tolcapone
Homovanillic Acid
Metabolism of L-dopa & dopamine

Tolcapone

- Dosing: 100-200 mg TID
- Most problematic adverse effect
  - Rare but potentially catastrophic hepatotoxicity
  - Now discontinued in UK as a result
  - Written consent required for use

Monitor LFT's

- Discontinue if LFT's >2x upper limit of normal
- Benefit should be seen ≤ 3 weeks of therapy
  - discontinue if not

Tolcapone Adverse Effects cont'd

- Most side effects dopaminergic
  - decrease levodopa dose can be used
- Diarrhea
- Potential for interactions with warfarin

Entacapone (Comtan^{R})

- Newer COMT inhibitor
- Dosing: 200 mg with each dose of Sinemet
- Increases 'on' time and decreases 'off' time.
- Diarrhea as AE
- Dyskinesias reported in about 25% of patients
- Not shown to produce hepatotoxicity as for tolcapone
  - LFT monitoring not required

COMT inhibitor Place in Therapy

- Unique mechanism of action allows for levodopa-sparing effect
- May provide a way to help manage motor fluctuations in advanced PD
- Stalevo
  - combination of carbidopa/entacapone/levodopa
  - Fewer tablets for patient to take
  - STALEVO 50 12.5 200 50
  - STALEVO 100 25 200 100
  - STALEVO 150 37.5 200 150.
  - …other dose combinations also available

Seeberger LC Neurother (ISSN: 1473-7175, 1744-8360) 8/31/09

Why the problem of motor fluctuations in advanced PD?

- Wearing off, sudden on-off
  - With advanced PD, there are fewer dopaminergic neurons to buffer fluctuations in dopamine within striatum
  - Pulsatile stimulation with intermittent dosing of dopaminergic drugs is not ideal
  - Continuous dopamine stimulation likely preferable, but difficult to achieve
  - Even CR may not provide smooth delivery
    - Erratic gastric emptying a problem as absorption is intestinal
  - Further research needed on formulation/administration of L-DOPA to stabilize plasma levels

Espay AJ. Neurol Clin. 2010 Nov;28(4):913-25
Olanow CW. Neurology. 2009;72 (21 Suppl4):S1-136

Treatment strategies for advanced PD

- "Wearing off" phenomena
  - Change to CR Sinemet
  - Consider liquid formulation of L-Dopa/carbidopa
  - Dose more frequently
  - Add dopamine agonist
  - Add COMT inhibitor
  - Add selegiline, rasagiline, amantadine, or anticholinergic agent

Olanow CW. Neurology. 2009;72 (21 Suppl4):S1-136

Poewe W. Neurology. 2009 Feb 17;72(7 Suppl):S65-73.

Treatment strategies for advanced PD

- Slow onset of response
  - give on empty stomach
  - give protein late in the day
  - give standard Sinemet in the morning

- Inadequate response at peak dose
  - Increase levodopa dose
  - Add dopamine agonist
  - Add other anti PD drugs (selegiline or rasagiline, amantadine, or anticholinergic agent)

More treatment strategies for advanced PD

- Unpredictable “On-off”
  - Add entacapone for the patient on levodopa/carbidopa
  - Try rasagiline
  - Add dopamine agonist
  - Apomorphine
  - selegiline
  - Consider surgery

Treatment strategies for advanced PD

- Dyskinesias
  - Decrease individual doses of levodopa
  - Increase frequency of levodopa dosing
  - Add dopamine agonist
  - Early morning levodopa (for morning dystonia)
  - CR Sinemet at bedtime (sleep through dyskinesia)
  - Consider surgery

Espay AJ. Neurol Clin. 2010 Nov;28(4):913-25 Olanow CW. Neurology. 2009;72 (21 Suppl4):S1-136
Swope DM. Neurology. 62(6 Suppl 4):S27-31 Pahwa R. Neurol Clin 22 S35–S52, 2004

Treatment strategies for advanced PD

- Apomorphine (Apokyn)…for sudden “off” periods
  - D1 and D2 agonist
  - given via subcutaneous injection
  - use for severe motor fluctuations (acute, intermittent treatment of hypomobility or "off" episodes)
  - Adverse effects include nausea, vomiting, low blood pressure, fainting, hallucinations, and excessive sleepiness
  - Caution in pt taking drugs that prolong the QT/QTc interval

Espay AJ. Neurol Clin. 2010 Nov;28(4):913-25
FDA Consumer, 0362-1332, Vol. 38, Issue 4

Treatment strategies for advanced PD

- Apomorphine administration
  - initial dose determination with BP standing and supine pre & post-dose
  - if significant orthostatic hypotension experienced, do not prescribe
  - Not >5 times or over 2 mL (20 mg) per day;
  - must pretreat with antinausea medication
    - Trimethobenzamide (TIGAN) 300 mg tid po started 3 days before the initial dose of apomorphine, continued at least during the first two months of therapy.
    - Do NOT give with 5HT3 antagonist (ondansetron, other) because the combination can lead to very low BP and fainting

Espay AJ. Neurol Clin. 2010 Nov;28(4):913-25

FDA Consumer, 0362-1332, 7/1/2004,Vol. 38, Issue 4

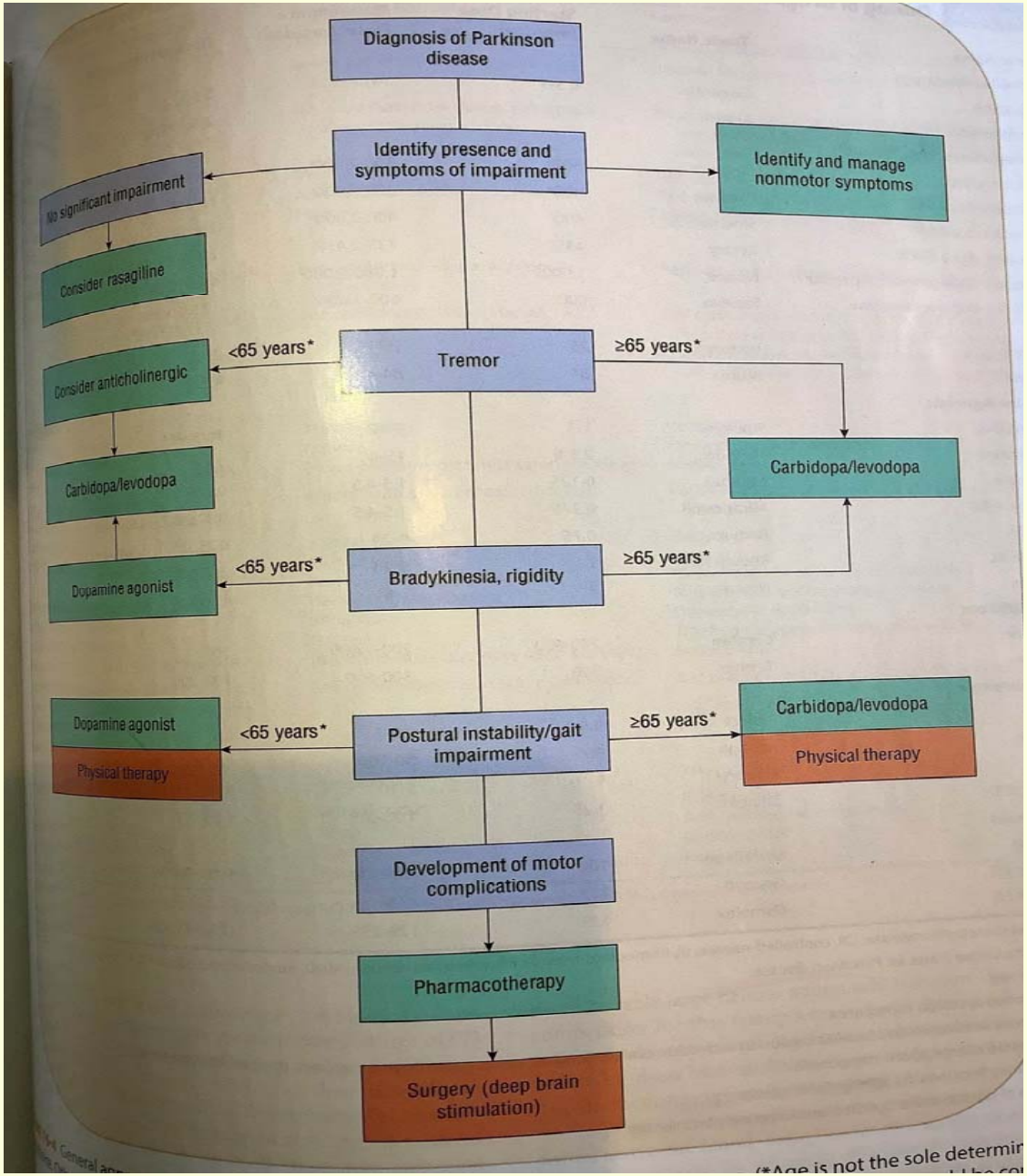
Treatment strategies for advanced PD

- Istradefylline (Nourianz)
  - Adenosine A_{2A} receptor antagonist
  - Blocking these receptors
  - Used to treat sudden "off" episodes
  - Adverse effects:
    - Dyskinesia, dizziness, constipation, nausea, hallucinations, insomnia
    - If hallucinations/dyskinesias, or impulse control disorders occur, reduce dose or D/C
  - Dose: 20-40 mg once daily (20 mg with moderate hepatic impairment)

Treatment strategies for advanced PD

- Istradefylline is CYP3A4 substrate:
  - Avoid combination with strong CYP3A4 inducers
  - Limit dose to 20 mg with strong CYP3A4 inhibitors
  - Other drug interactions:
    - Digoxin (↑ digoxin conc)
    - Dofetilide (↑ dofetilide conc)
    - St. John's worst (↓ istradefylline conc)

Treatment Algorithm – Figure 76-4



Mini-case

- EM is a 63 year old lady who has had Parkinsons disease for four years. She has been taking Sinemet CR 50/200 tid for the last year.

- Lately she has noticed that she will all of a sudden find herself unable to get out of her chair and will even find that she hesitates when she is walking from one room to another. She is very distressed at this.

- Although she also has bilateral tremor and rigidity, she finds the inability to move the most troublesome. EM is extremely sharp, still wins at cards twice a week, and has no problem remembering everything the doctor tells her.

Mini-cases

- What might EM be experiencing?
  - On-Off phenomenon
- What alternatives could be considered for EM?
- What is the best choice for change of therapy among the following?
  - Switch to immediate release sinemet
  - Increase the amount of carbidopa she is taking
  - Add entacapone

Mini-cases

- EM was given entacapone 200 mg tid in addition to her Sinemet CR, and has returned to clinic the next month.
- She states that she is doing much better and not “stopping in my tracks”, but now finds herself sometimes “doing weird squirmy movements, and I don’t know why” .
- She states that she feels good mentally and is having no problems with memory.
- What is EM probably experiencing?
- What would you recommend?

Dyskinesias due to over stimulation of dopamine receptors; decrease Sinemet CR dosing…this worked very well

Non motor features of Parkinson's Disease … minimal response to dopaminergic therapy

Fernandez HH. Updates in the medical management of Parkinson disease. Cleve Clin J Med. 2012 Jan;79(1):28-35

Craniofacial features

Masked facies (reduced facial expression)
Sialorrhea (drooling; may appear decades before the onset of tremor)
Anosmia (loss of sense of smell)
Hypophonia (soft speech)
Dysarthria (difficulty pronouncing words)
Dysphagia (trouble swallowing)

Sensory features

Paresthesia (sensations of tingling, prickling, or numbness)
Pain

Autonomic features

Urinary disturbance—urgency, nocturia
Constipation
Sexual dysfunction

Non motor features of Parkinson's Disease… minimal response to dopaminergic therapy

Neuropsychiatric features

Depression
Anxiety
Apathy
Dementia
Psychosis

Other

Fatigue
Sleep disturbance
Seborrheic dermatitis
Eye abnormalities

Fernandez HH. Updates in the medical management of Parkinson disease. Cleve Clin J Med. 2012 Jan;79(1):28-35

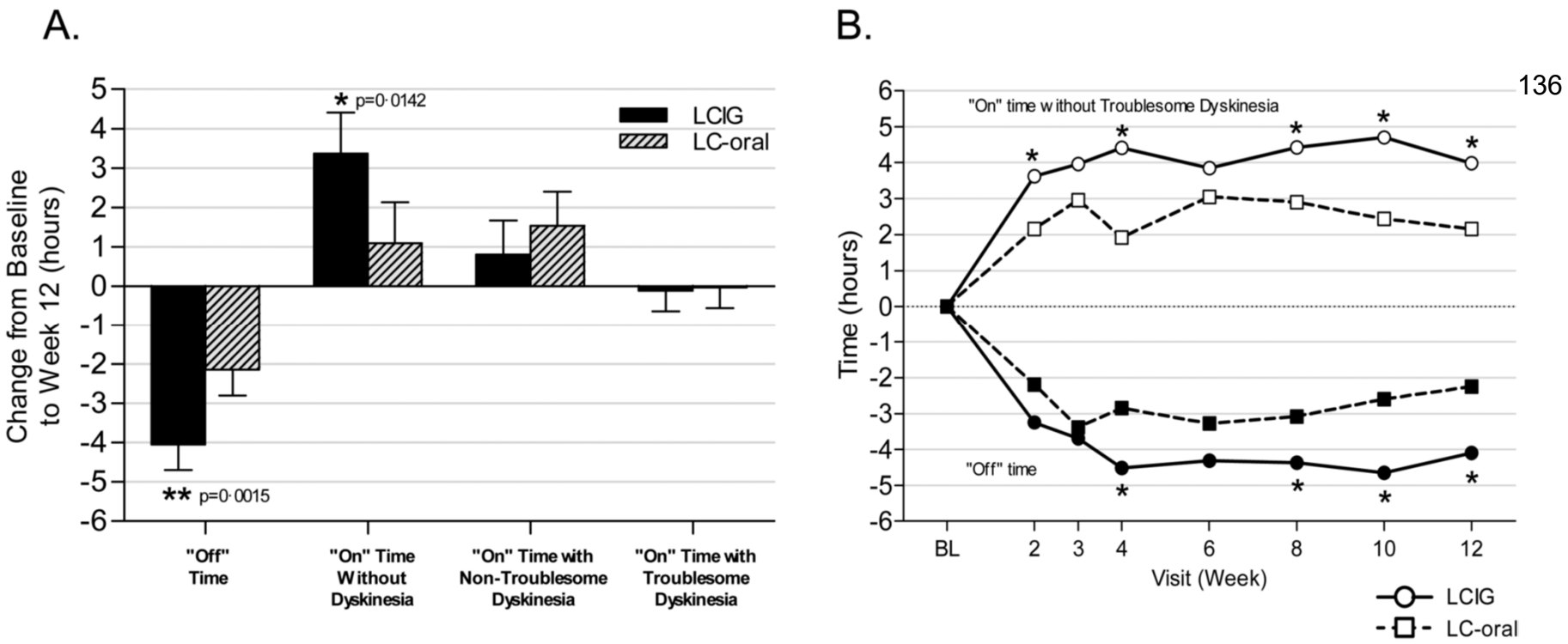
Disabling Motor Complications – Device-assisted therapies

- Reducing “off” and increasing “on” time:
  - Deep-Brain stimulation **
  - Continuous levodopa intestinal gel infusion **
  - Continuous SQ apomorphine infusion

- Investigational Therapies
  - Gene therapy
  - Neural transplantation (stem cells)
  - Levodopa prodrug

** also improves dyskinesias

A comparison of levodopa administered by standard oral dosing and by continuous intraintestinal infusion: promising but is it practical?



Mean number of “off ” hours and dyskinesia scores at baseline when patients were treated with regular levodopa and after 6 months of treatment with a continuous levodopa infusion.

Lancet Neurol 2014;13:141-149

Duopa (levodopa/carbidopa) - enteral suspension -

- 4.63 mg carbidopa and 20 mg levodopa per mL
- One cassette contains 2000 mg administered over 16 hours
- Prior to initiating Duopa, patients should be on IR levodopa/carbidopa
- Infused through a jejunal tube (PEG-J) with the CADD-Legacy 1400 Infusion pump
- Once pump is turned off, patients should take nighttime dose of IR carbidopa/levodopa

Duopa

Conclusions

- Adjustment of levodopa dose, formulation, and regimen, addition of levodopa-sparing agents such as dopamine agonists and COMT inhibitors may improve management of these late complications
- Selegiline and rasagiline are useful as monotherapy or adjunct therapy with carbidopa/levodopa
- Subcutaneous apomorphine can be used for sudden off episodes
- Patient education and individualization of therapy is crucial

Take home messages about pharmacotherapy

- Patient education essential
  - diary keeping can be a helpful strategy
- For mild symptoms early in disease, amantadine or selegiline or rasagiline can be useful
- Anticholinergic agents can be useful for tremor
- Some patients are started off right away with dopaminergic therapy
- Carbidopa/Levodopa provides best symptom control
  - But, eventually will need more frequent dosing and will have motor fluctuations
- When dopaminergic therapy needed, either dopamine agonists or carbidopa/levodopa are reasonable choices