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Diagnosis and Treatment of Parkinson's Disease

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Parkinson's Disease

- 2nd most common neurodegenerative disorder
  - lifetime risk: 1 in 40-100
- Age of onset
  - Common after 60 y/o
  - Young onset (20-50 y/o) 10-15%
- Men get it more often than women
- 5% Inherited
- 95% likely caused by genetic predisposition and environmental influences

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Parkinsonism

- Tremor (rest)
- Rigidity
- Bradykinesia/akinesia
- Decreased facial expression
- Stooped posture
- Micrographia/hypophonia
- Postural instability

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Not all Parkinsonians have Parkinson's Disease

Neurodegenerative Disorders

- Idiopathic Parkinson's Disease
- Multiple System Atrophy
- Progressive Supranuclear Palsy/CBGD
- Diffuse Lewy Body Disease

Secondary Parkinsonism

- Vascular
- Neuroleptics
- Normal Pressure Hydrocephalus

Differential Diagnosis

Parkinsonism	Plus
• Multiple System Atrophy	postural instability
• Shy-Drager	dysautonomia
• Striatal nigral degeneration	non dopa-responsive
• OPCA	cerebellar dysfunction
• Progressive Supranuclear Palsy	gaze paresis
• Diffuse Lewy Body Disease	dementia
• Corticobasal Degeneration	dystonia, apraxia

Most do not respond to L-dopa and have early loss of postural reflexes

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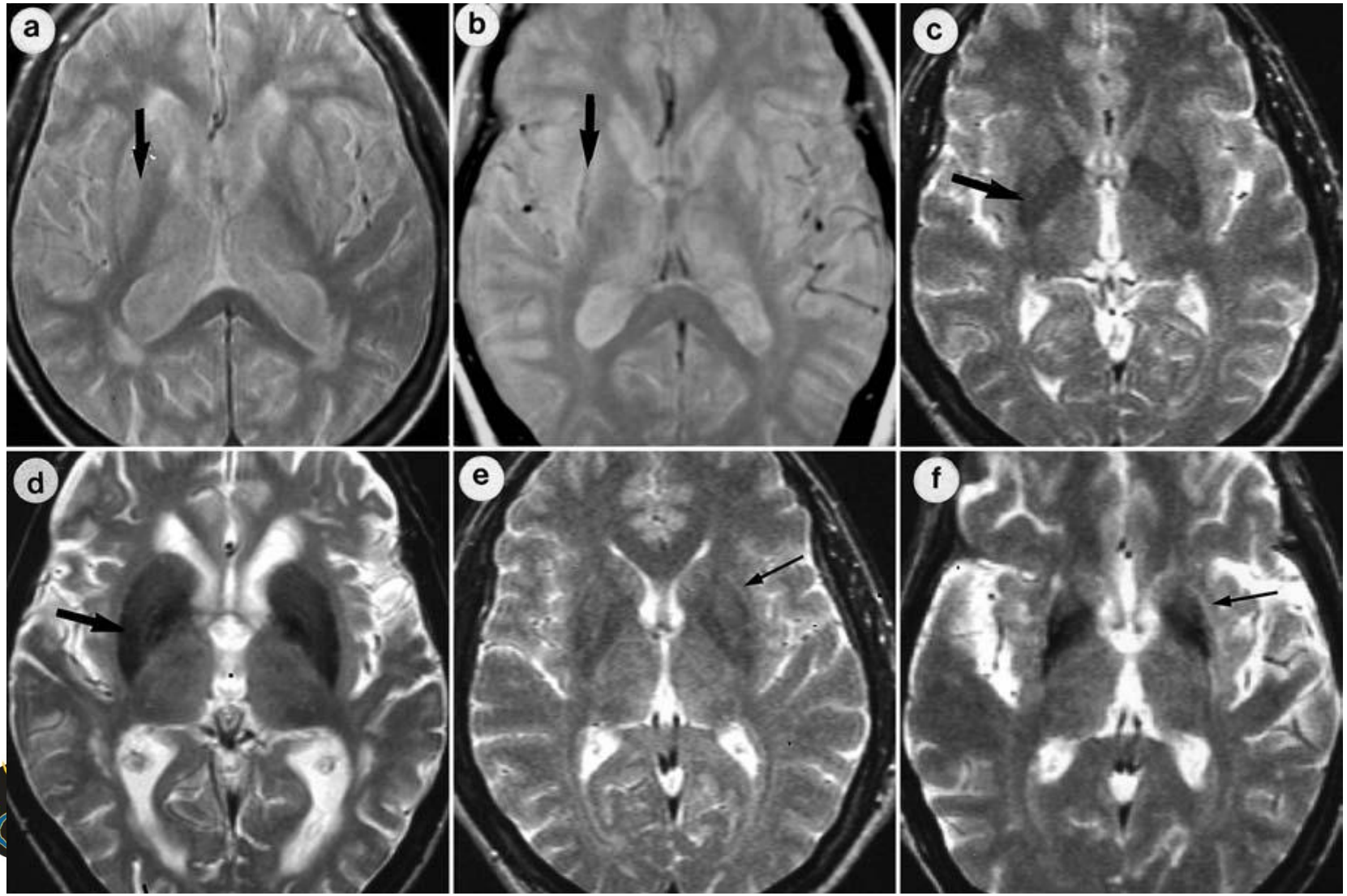
MRI and MSA



^{18}F-Dopa PET

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

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Pavese and Brooks, 2008

Think Parkinson's Disease

With:

- Asymmetric onset
- L-dopa responsive
- Rest tremor

Without:

- Cerebellar signs
- Long-tract signs
- Early dementia
- Early dysautonomia
- Early falls

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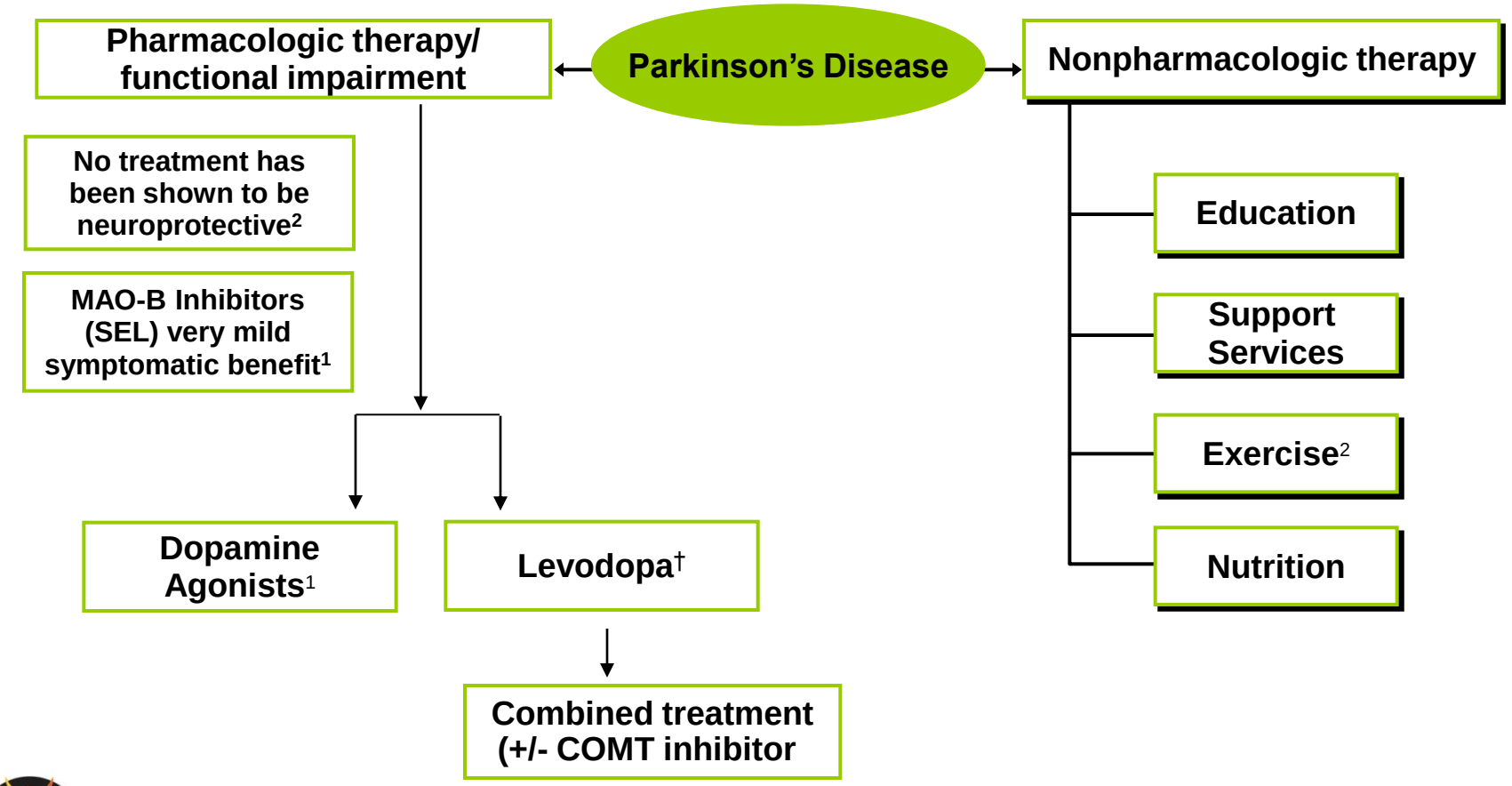
Initiation of Treatment

- General Considerations
  - Age
    - Young onset
      - neuroprotection
      - motor fluctuations
    - Older patients
      - cognitive issues
      - comorbidities
  - Disability
  - Cost

Early Parkinson's Disease Treatment Guidelines*



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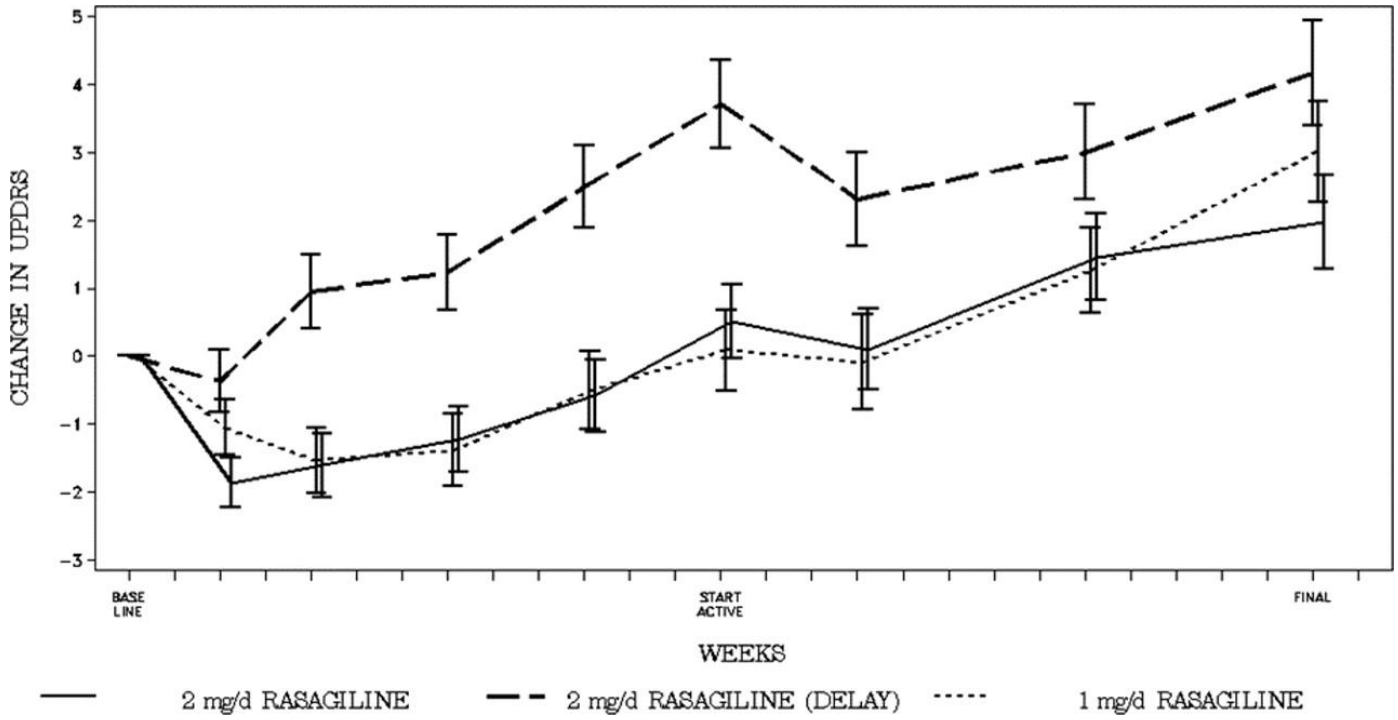
* AAN guidelines last updated in 2006 (2)

MAO-B Inhibition

Selegiline and Rasagiline

- Both have small symptomatic effect.
- Both might slow disease down a little.
- Rasagiline and SL selegiline have been shown to help wearing off (PO selegiline not well studied).

Rasagiline: The TEMPO Trial



Siderowf, A. et al. Neurology 2006;66:S80-S88

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NEUROLOGY

Levodopa

- Efficacy
  - Most efficacious medication for control of PD symptoms.
  - Improves UPDRS motor scores by approx 50% in advanced patients.
  - Short half-life
  - Significant protein effect
- Side-effects
  - Long-term risk of motor fluctuations

Clinically, Levodopa Slows Ds Progression

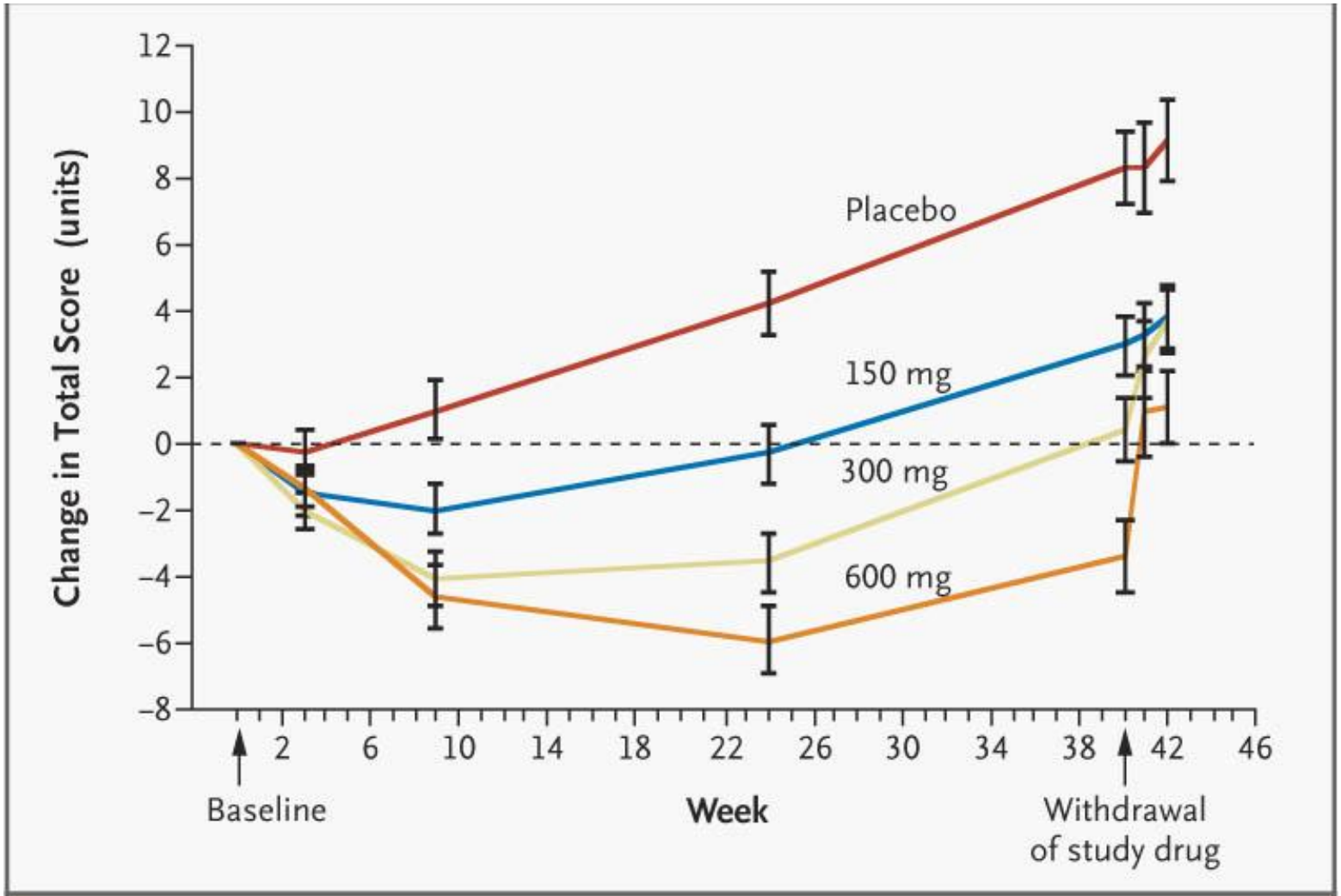


Figure 2. Changes in Total Scores on the Unified Parkinson's Disease Rating Scale (UPDRS) from Baseline through Evaluation at Week 42.

Protein Effect

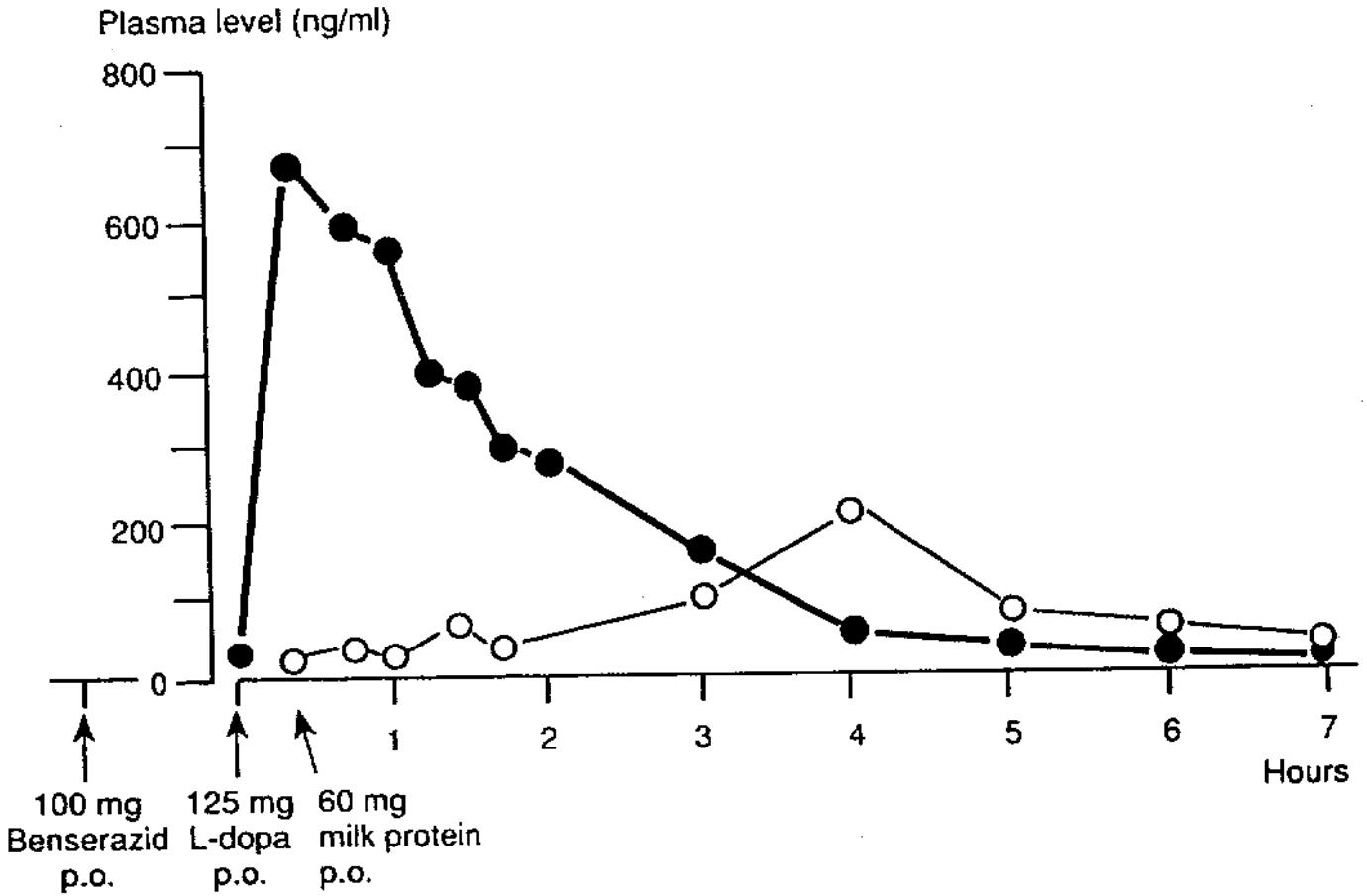
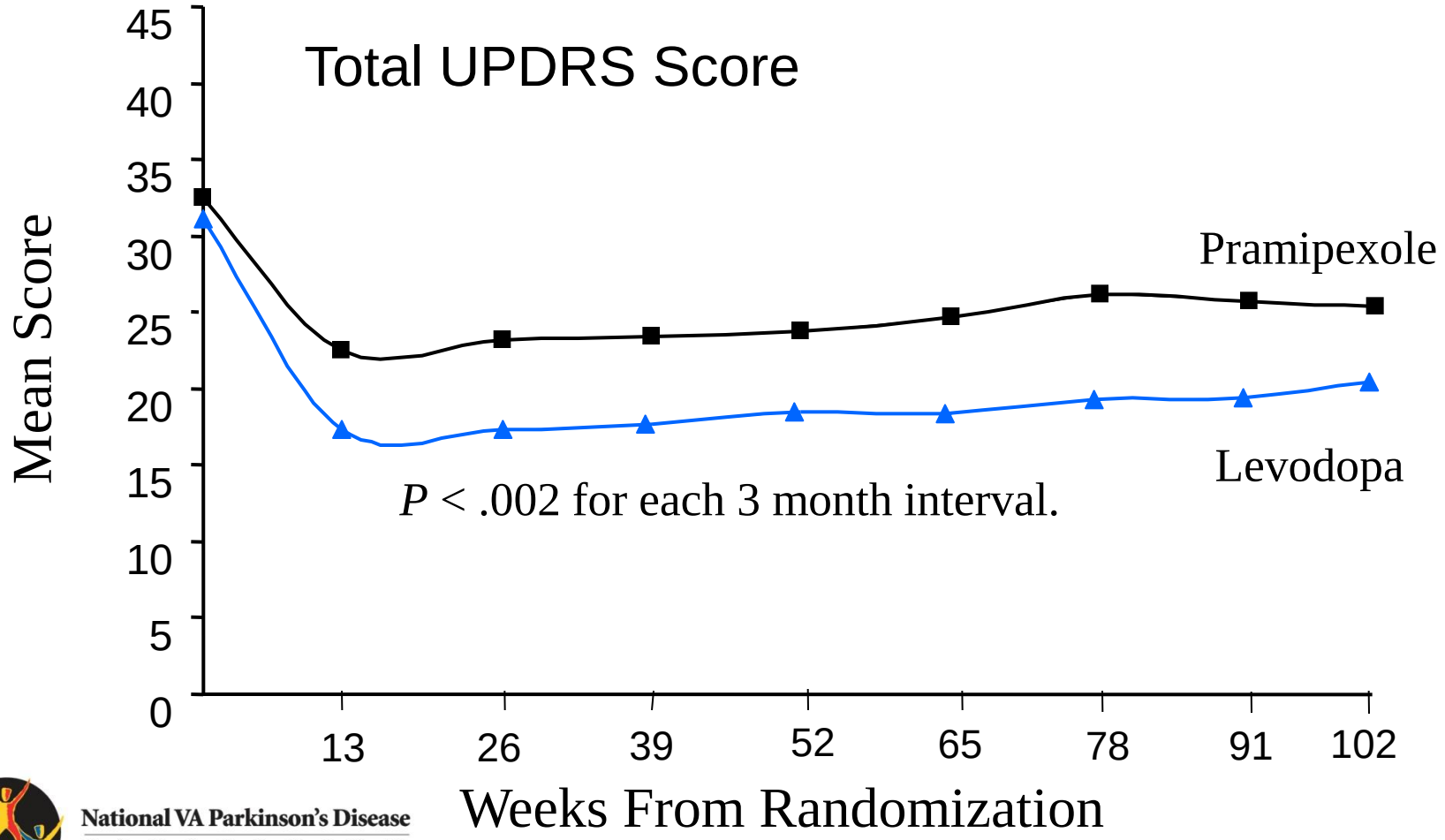


FIG. 8.2. Levodopa plasma levels following a standard oral dose of 125 mg given on an empty stomach *(dark symbols)* or with a 60-mg milk protein drink *(open symbols).* Note delayed plasma peak and reduced area under the curve when the drug was taken with protein.

Dopamine Agonists

- Efficacy
  - Less efficacious than levodopa
  - Have long half-lives
  - Less likely to cause motor fluctuations
  - Absorption without transporter (no protein effect)
  - Potential alternate routes of administration (e.g. patch, injection)
- Side-effects
  - Relatively more common than for levodopa especially in the elderly
  - Include sedation, hallucinations, impulse control, nausea

CALM-PD: Pramipexole vs Levodopa



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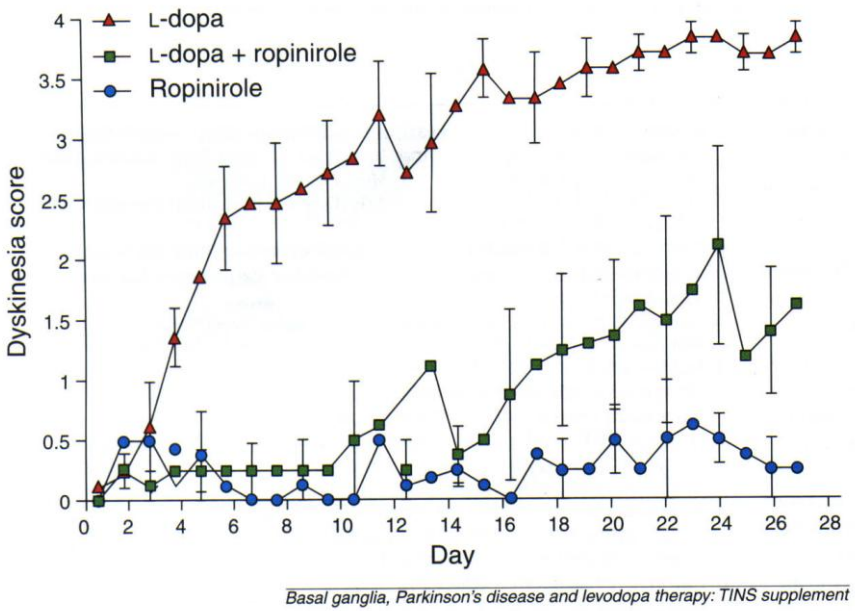
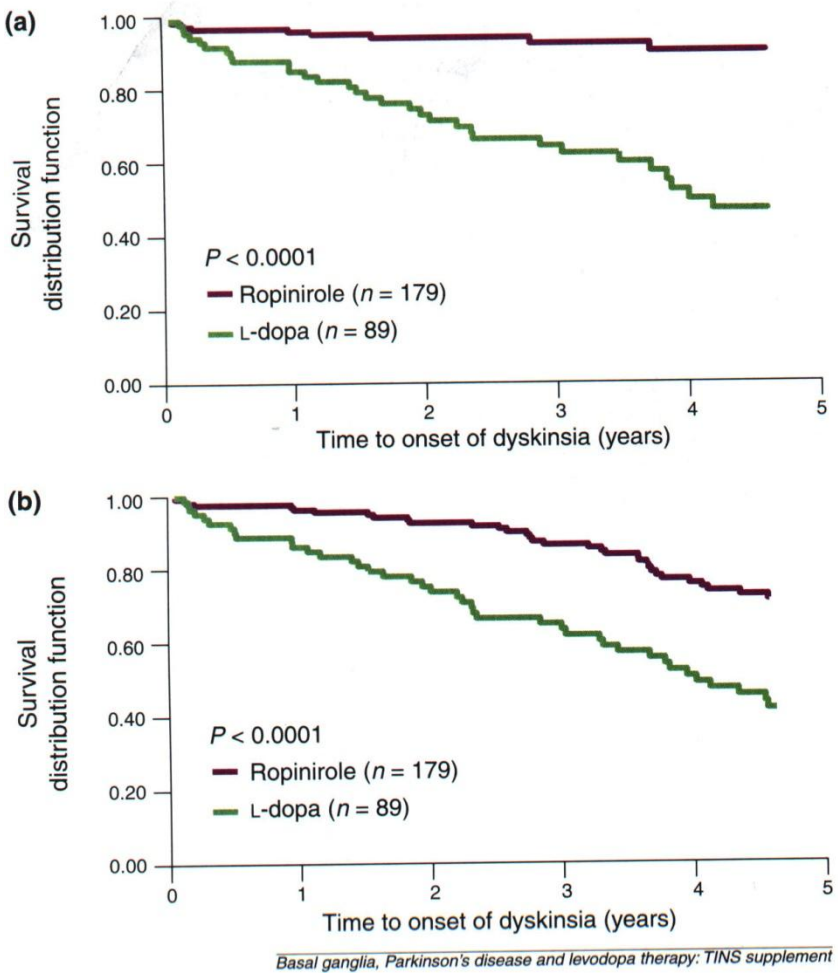
5 Yr Ropinirole vs. Levodopa



Basal ganglia, Parkinson's disease and levodopa therapy: TINS supplement

Fig. 1. Dyskinesias in MPTP monkeys. Frequency of dyskinesia in 1-methyl-4-phenyl-1,2,3,6-



Basal ganglia, Parkinson's disease and levodopa therapy: TINS supplement

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Rascol 2000

Initiating Therapy

Disabled

Yes

-MAO-B I
-agonist (young)
-Sinemet CR

inadequate response

-reg sinemet
-question Dx
-COMT-I
-antichloinergic

No

-educate
-exercise
-MAO-B I?

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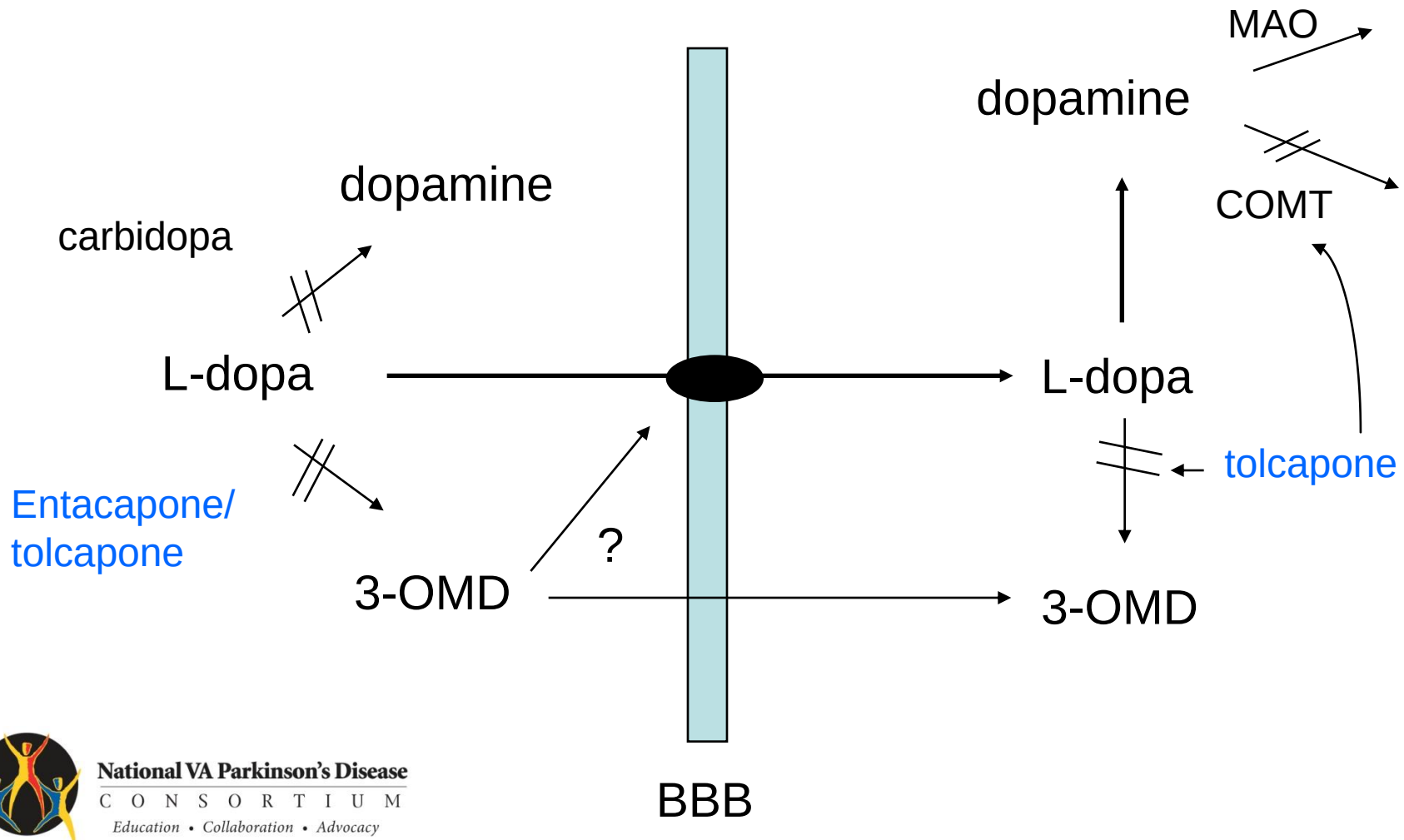
Advancing Parkinson's Disease

- Motor fluctuations (young)
  - Wearing off
  - Dyskinesias
  - On-off phenomenon
- Non-Motor Problems
  - Medication-induced psychosis
  - Cognitive decline
  - Postural instability
  - Urinary problems
  - Sleep problems

Principles of Managing Fluctuations

- Decrease fluctuations of L-dopa blood levels
  - Use smaller more frequent dosing.
  - Use combination of regular and CR Sinemet.
  - Add COMT inhibitor
  - Add MAO-B inhibitor
- Add DA agonist and reduce L-dopa
- Add amantadine for dyskinesias
- Surgery

Levodopa Biochemistry



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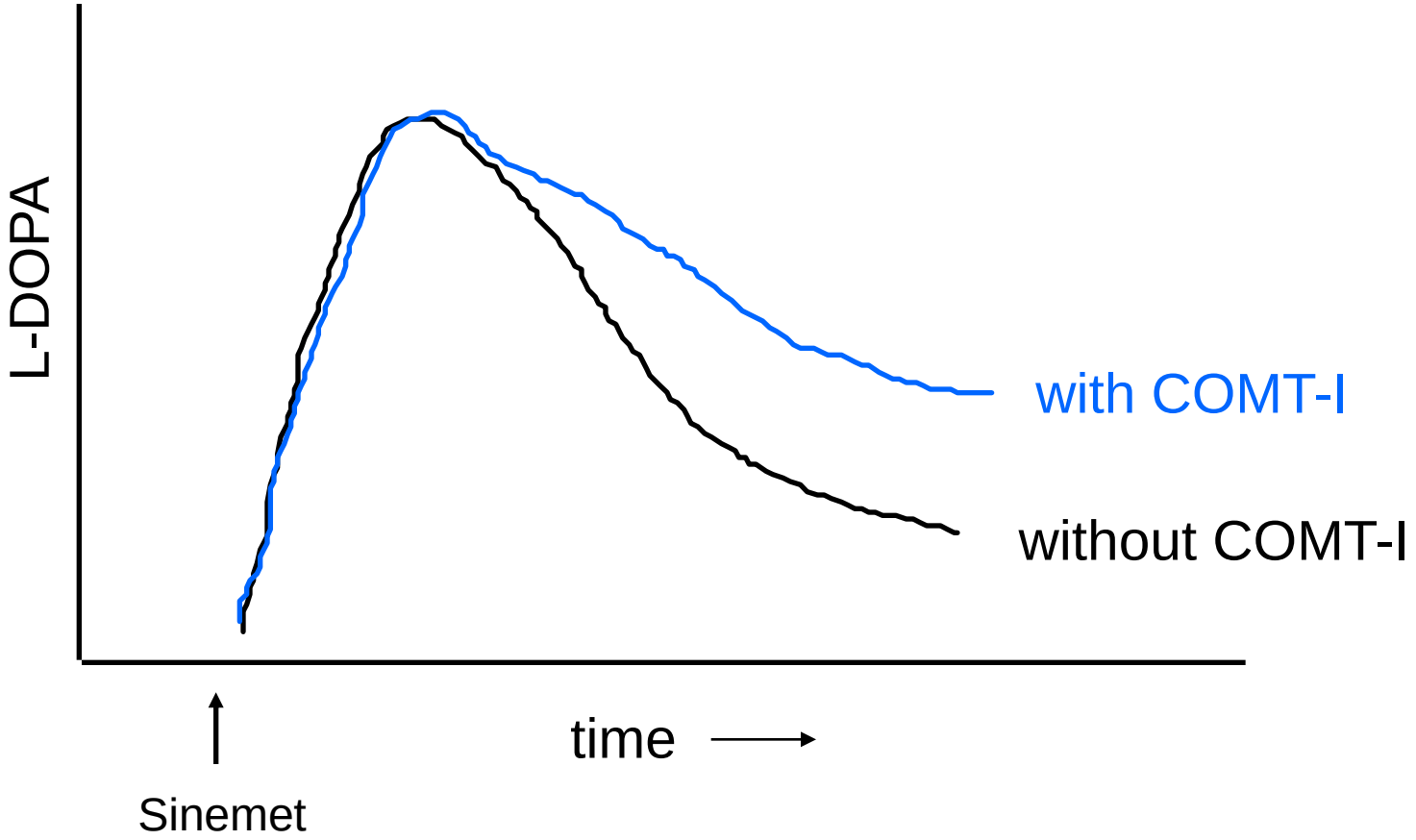
Effect of COMT-I on Plasma Levels



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Advancing Parkinson's Ds

- Hallucinations
  - D/C selegiline, anticholinergics, amantadine
  - lower dopaminergic medications (agonist 1st)
  - clozapine, quetiapine, cholinesterase-I
- Falls
  - optimize therapy
  - R/O orthostatic hypotension
  - physical therapy for training and assistive devices.

Advancing Parkinson's Ds (cont.)

- Depression
  - serotonin uptake inhibitor (e.g.Paxil, Celexa), nortriptyline, NA/Serotinergic uptake inhibitors, Wellbutrin
- Dementia
  - R/o other causes (metabolic, structural etc.)
  - Reduce medications as much as possible
  - Consider cholinesterase-I, memenatine

Advancing Parkinson's Ds (cont.)

- Sleep Problems
  - sleep hygiene
  - optimize DA therapy
  - treat depression
  - Consider sleep study (apnea, RSB)
  - Sleep initiation: short acting benzo (Ambien, Sonata), Rozerem.
  - Sleep maintenance: Lunesta, Ambien CR, tricyclic antidepressant (nortriptyline, trazadone), Remeron, Benadryl

Summary

- Motor fluctuations are treatable but can require time and persistence
- Identify and treat non-motor problems, they can be very disabling
- When in doubt, call or refer to the National VA Parkinson's Disease Consortium

http://www.vapdconsortium.org

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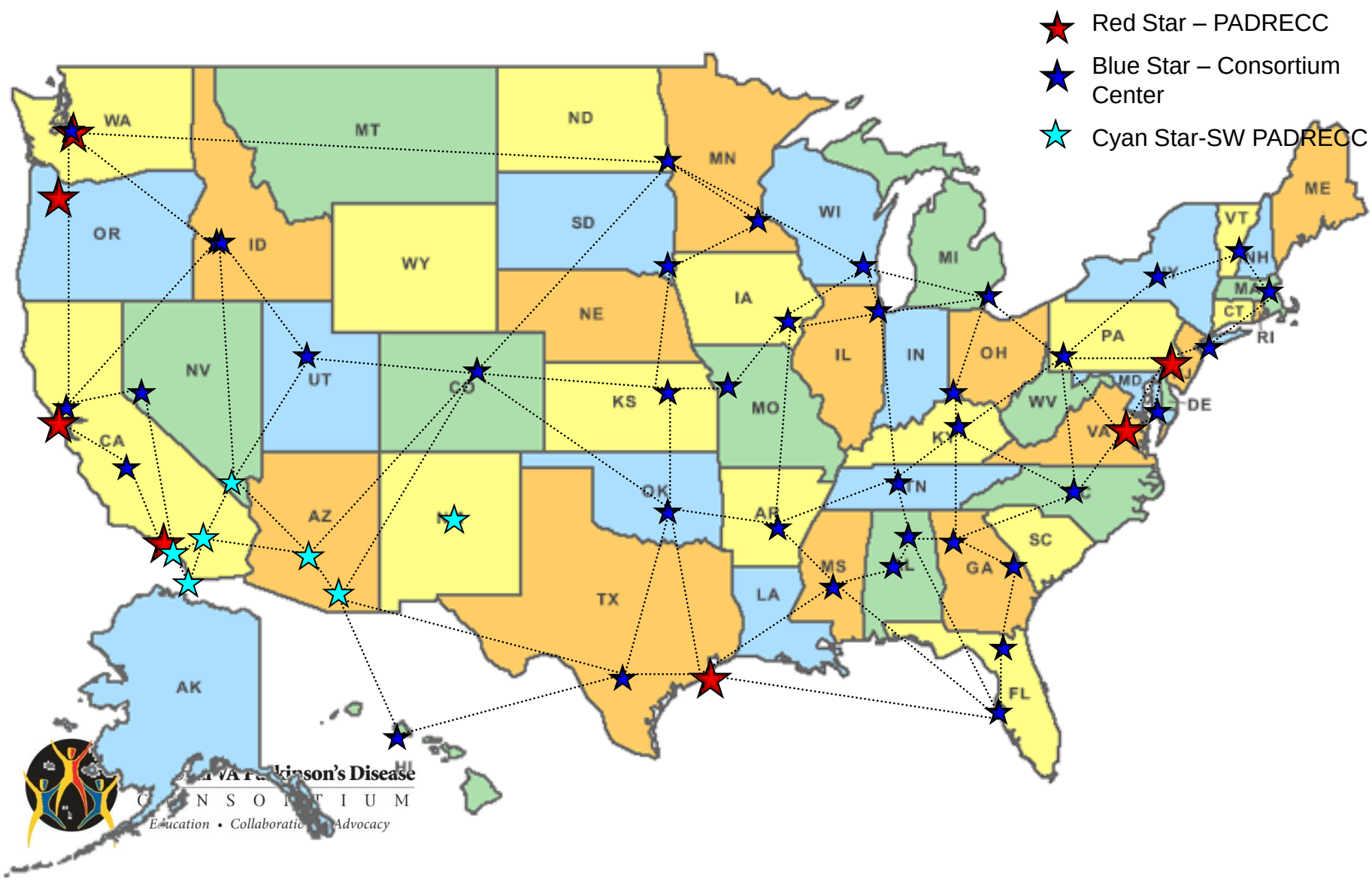
Consortium Center Network



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