Medications in the treatment of Parkinson's disease

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Idiopathic Parkinson's Disease

- 2nd most common neurodegenerative disorder
  - lifetime risk: 1 in 40
- Age of onset
  - Common after 60 y/o
  - Young onset (20-50 y/o)
- Men get it more often than women

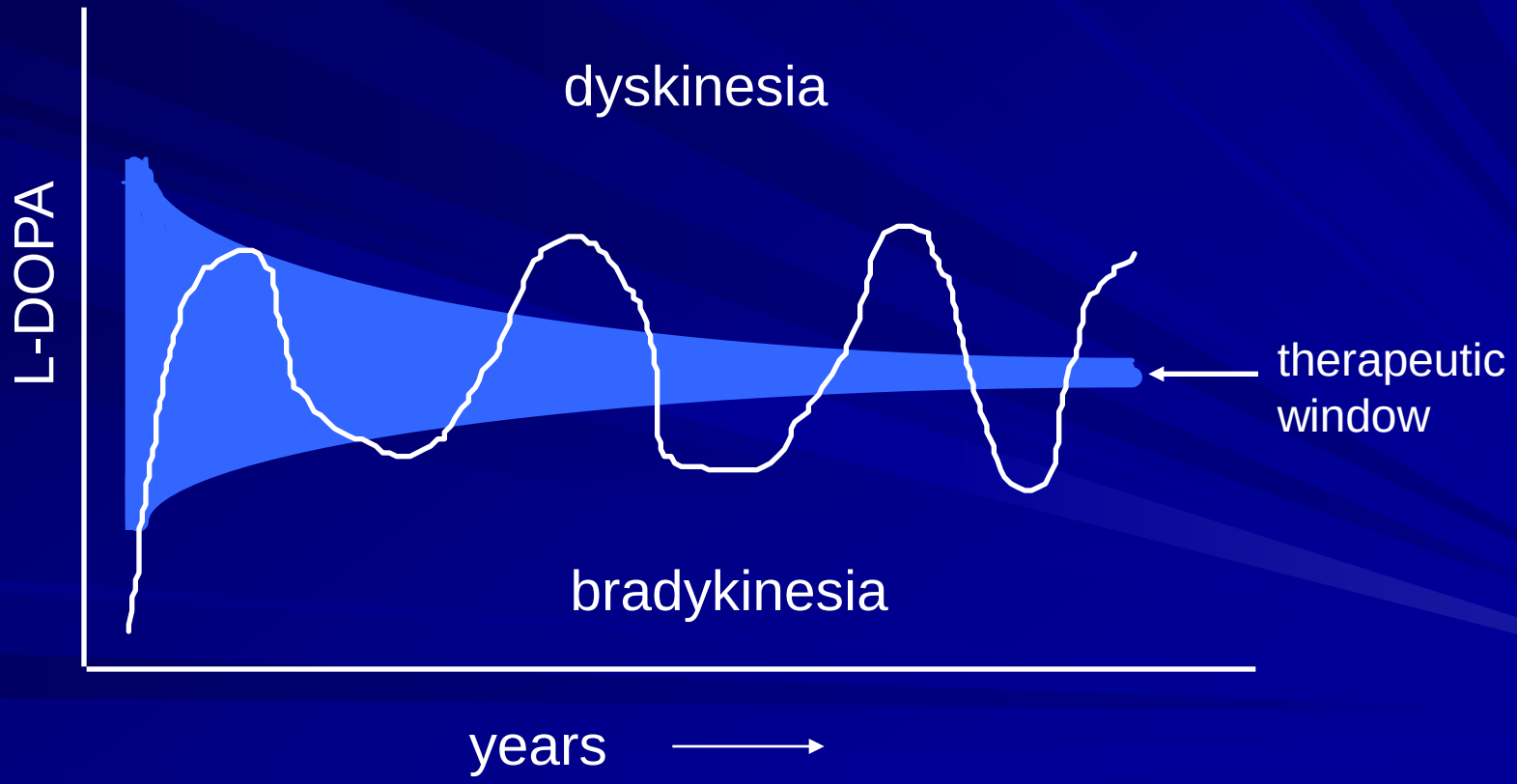
Parkinson's Disease Genes

Name and Locus	Gene	Mode of Inheritance;	Pathological Features	Protein Function
PARK1 4q21-q22	α-synuclein	AD	Lewy bodies	synaptic vesicle trafficking
PARK2 6q25.2-q27	Parkin	AR (AD?)	no Lewy bodies	Ubiquitin E3 ligase,
PARK3 2p13	Unknown	AD	Lewy bodies	
PARK4 4q21	triplication α -syn	AD	Lewy bodies	
PARK5 4p14	UCH L1	AD	?	Removes polyubiquitin
PARK6 1p35-p36	PINK1	AR	?	PTEN-induced kinase 1 (mito localized, protects UPS inhib)
PARK7 1p36	DJ-1	AR	?	Sumoylation pathway
PARK8 12q12	LRRK2	AD reduced penetrance	Lewy bodies	Kinase. GTPase
PARK9 1p36	ATP13A2	AR	?	Lysosomal ATPase
PARK10 1p32	Unknown	? Dominant		
PARK11 2q34	Unknown	AD reduced pen	?	
PARK12 Zq21	Unknown	X-linked	?	
PARK13 2p12	HTRA2	?Dominant	?	?Mitochondrial protein

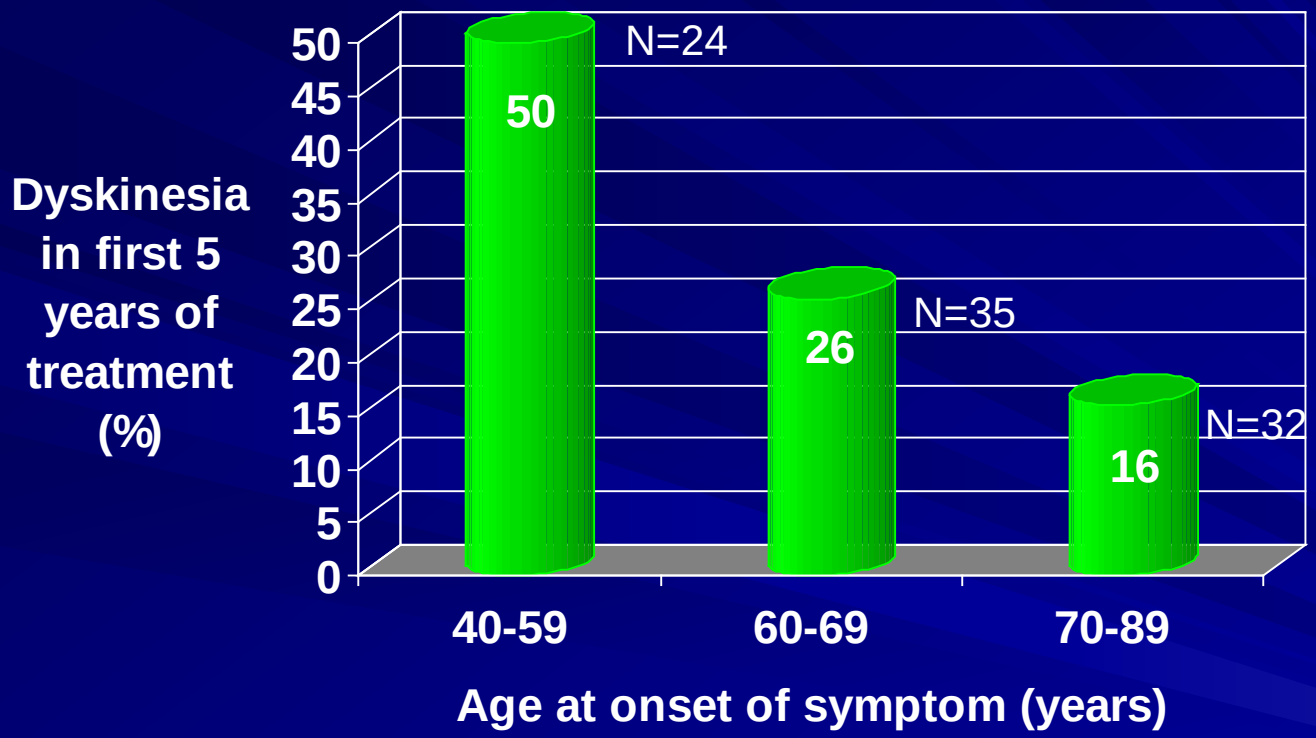
Treatment of Parkinson's Disease

- Nonpharmacologic
  - Education
  - Exercise
- Medications
  - Neuroprotective
  - Symptomatic
- Surgical
  - DBS, transplantation

NARROWING THERAPEUTIC WINDOW WITH TIME



Motor Fluctuations and Age



Adapted from: Kumar N et al. Movement Disorders 20(3); 2005, p342-344

Proposed Etiology of Motor Fluctuations

- Advanced disease (loss of DA neurons)
- Pulsatile stimulation of dopamine receptors is necessary for the development of motor fluctuations

  - Supported by experiments in rats and primates
  - Supported by short-term human experiments
  - No long-term human data

Initiation of Treatment

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

Considerations in Choosing a Medical Regimen

- Side-effects of all dopaminergic agents include:
  - Nausea
  - Dyskinesias
  - Psychosis (especially in elderly)
  - Orthostatic hypotension
  - Compulsions ?
- Relative benefits of agonists are often outweighed by SE in elderly

PD Medications

- Anticholinergic
  - Trihexyphenidyl
  - Benztropine
- Dopaminergic

  Precursor supplement
  - Levodopa

  COMT inhibiton
  - Entacapone

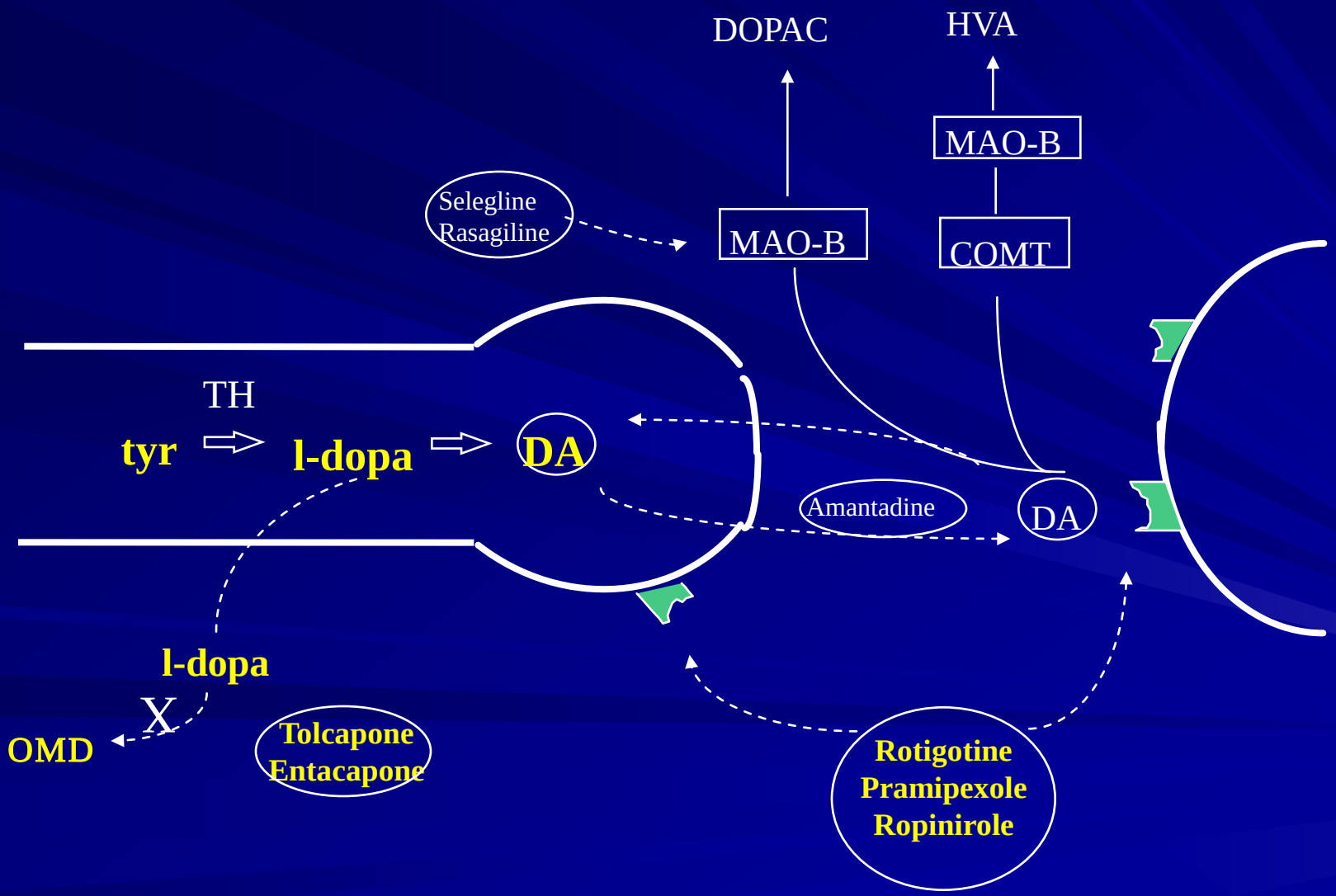
  MAOB inhibition
  - Selegiline
  - Rasagiline

  Receptor agonists
  - Pramipexole
  - Ropinirole
  - apomorphine

  Other

  Amantadine

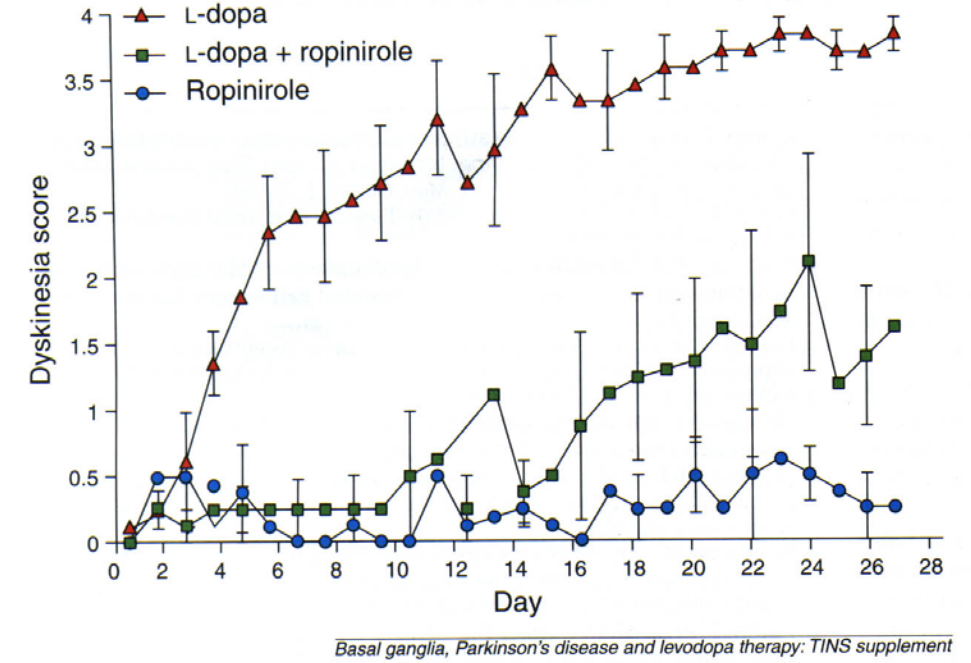
DRUGS FOR PARKINSON'S DISEASE



Dopamine Agonists

- In early PD
  - Delays need for L-dopa
  - Low incidence of dyskinesia as monotherapy
  - Not metabolized or effected by protein intake
  - Neuroprotection ?
  - Higher incidence of cognitive side-effects in the elderly and cognitively impaired

5 Yr Ropinirole vs. Levodopa

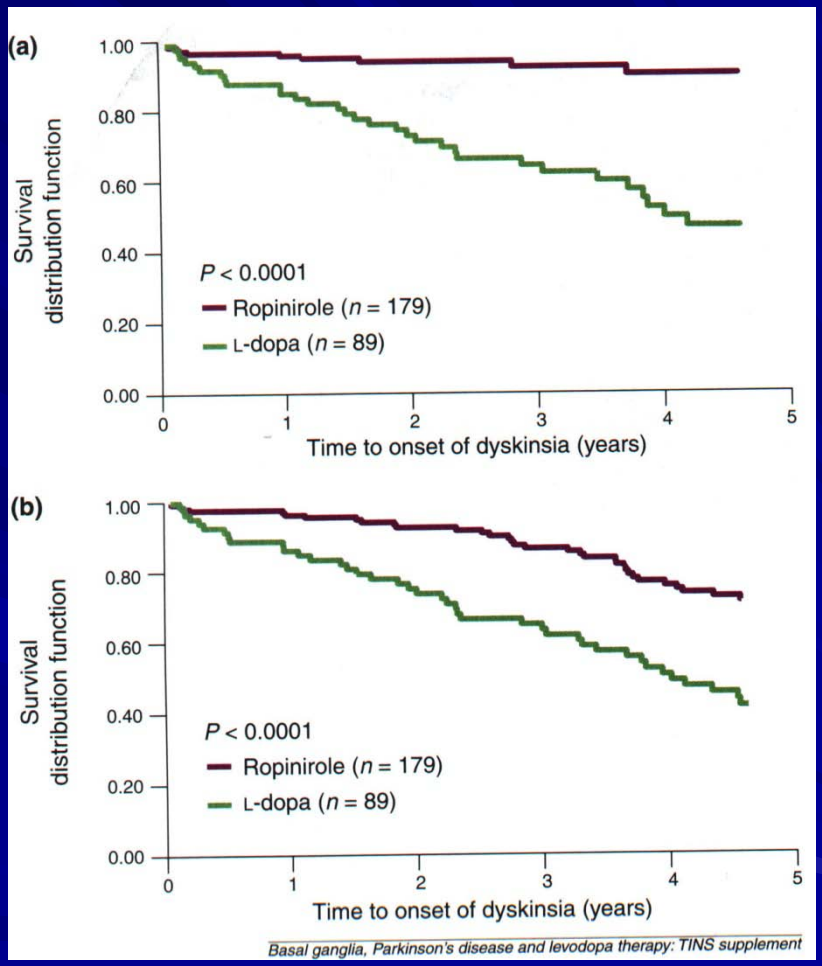


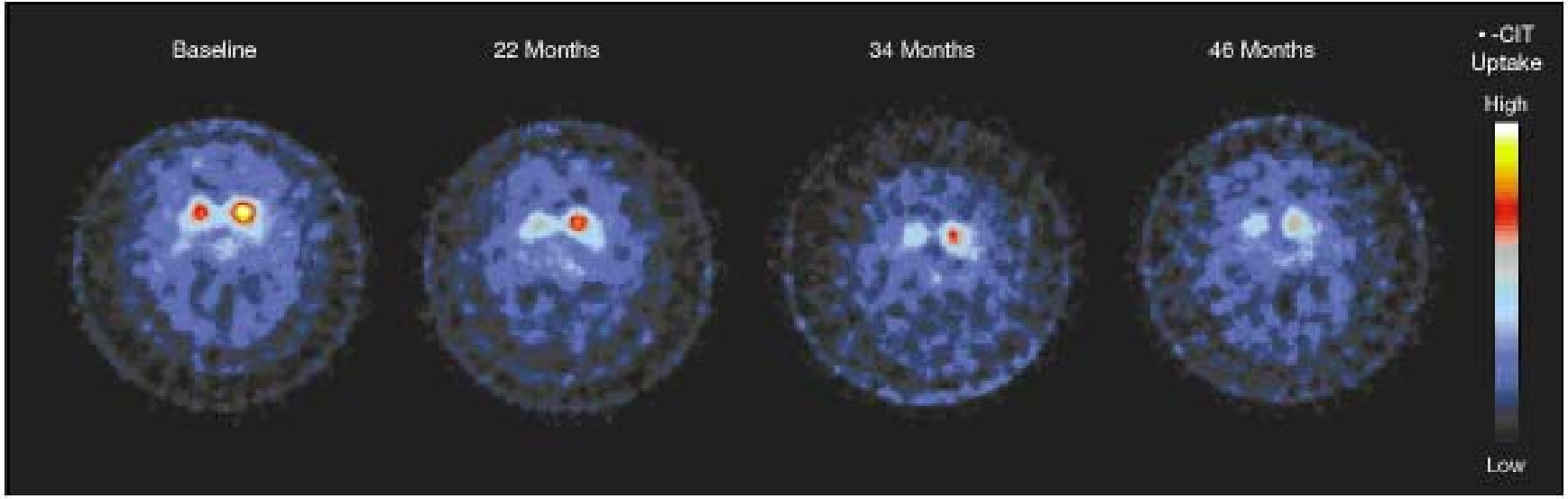
Basal ganglia, Parkinson's disease and levodopa therapy: TINS supplement

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

Rascol 2000

- 268 Subjects randomized to ropinirole or levodopa
- Open label supplementation allowed
- HR of remaining dyskinesia free 2.82
- 5 yr dyskinesia: levo-45%; agonist-20%

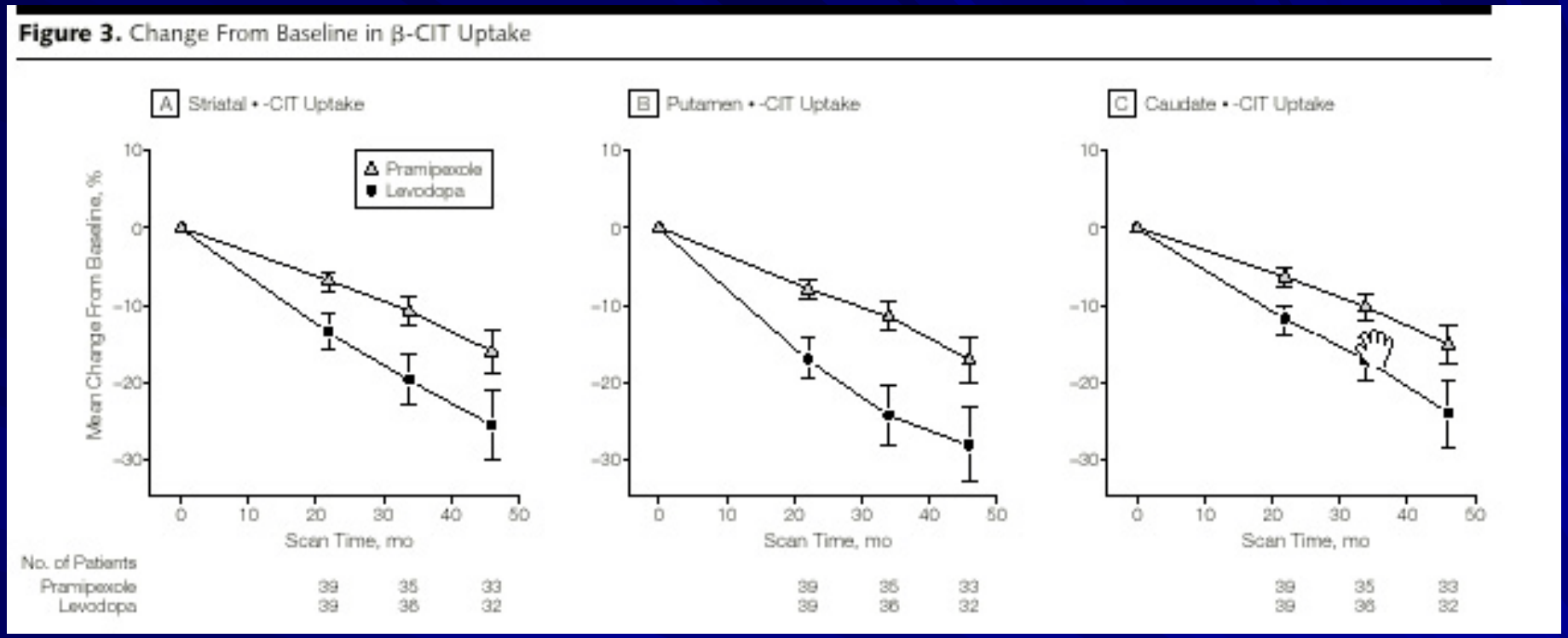




β-CIT indicates 2β-carboxymethoxy-3β(4-iodophenyl)tropane. Single-photon emission computed tomography (SPECT) [^{123}I]β-CIT images of progressive striatal dopamine transporter loss during the 46-month evaluation period for a representative patient. Loss of activity is more marked in the putamen than in the caudate. Levels of SPECT activity are color-encoded from low (black) to high (yellow/white).

- 82 PD patients at 17 sites in US and Canada enrolled between 1996 and 1997
- Randomized to pramipexole .5mg tid or levodopa 25/100 tid
- Open label levodopa could be added after 10 week escalation phase
- 46 month f/u

Parkinson Study Group. CALM-PD; JAMA, April 3, 2002 (287): 13



- Mean percent loss in striatal Beta Cit uptake was reduced in agonist group: 7.1% vs 13.5% at 22 mos; 16% vs 25.5% at 46 mos (P-.01)
- Beta Cit decline correlated with change in UPDRS (r=-.4; P=.001)

How do agonists fare after the first 4-5 years?

CALM-PD Long Term Data

- Mean 6 year follow-up
- 158 of the 183 who completed the CALM-PD trial and 64 of the 118 who had withdrawn prematurely from the CALM-PD trial were enrolled in the CALM cohort study.

Subject Outcomes at the Final Visit

Table 3. Subject Outcomes at the Final Visit[a]

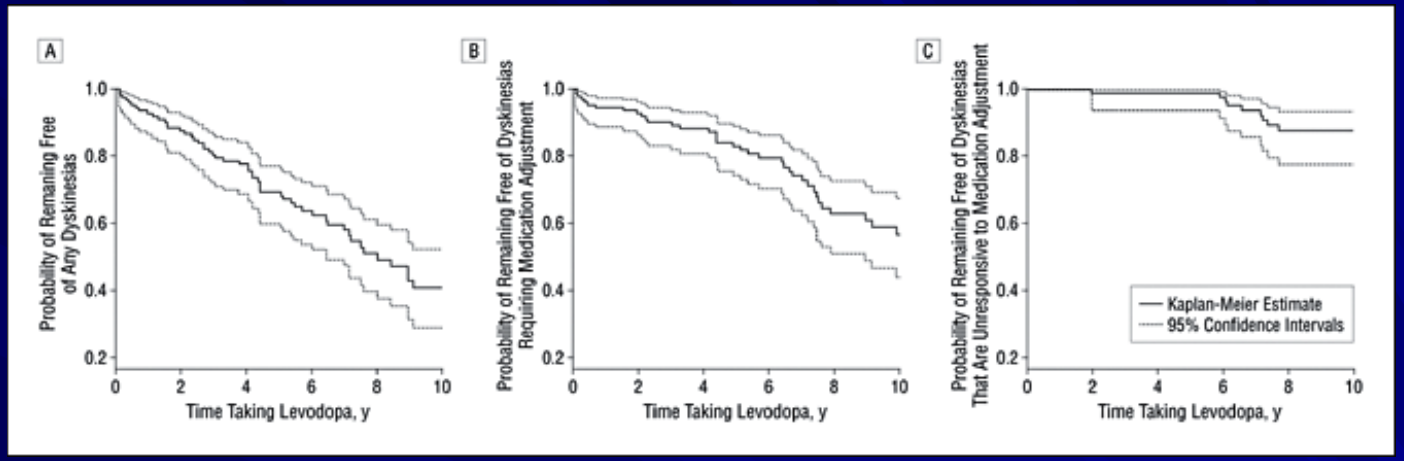
Outcome	Initial Pramipexole Treatment (n=108)	Initial Levodopa Treatment (n=114)	Treatment Effect (95% CI)	*P* Value
Self-reported disability by S/E ADL Scale score, mean (SD)				
Direct method	79.8 (15.4)	81.8 (14.9)	2.0 (−2.1 to 6.1)	.34
Indirect method	79.9 (16.2)	82.5 (14.6)	2.8 (−1.4 to 7.0)	.19
"On" state	82.8 (14.9)	84.8 (13.6)	2.4 (−1.5 to 6.2)	.23
"Off" state	65.8 (21.5)	72.0 (17.8)	5.7 (−1.0 to 12.4)	.09
Dopaminergic complications				
Any, No. (%)[b]	54 (50.0)	78 (68.4)	2.48 (1.39 to 4.44)	.002
Dyskinesias, No. (%)	22 (20.4)	42 (36.8)	2.56 (1.35 to 4.84)	.004
Wearing off, No. (%)	48 (44.4)	67 (58.8)	2.11 (1.19 to 3.71)	.01
Freezing, No. (%)	35 (34.7)	28 (26.2)	0.72 (0.39 to 1.35)	.30
Lang-Fahn ADL dyskinesia scale score, mean (SD)	1.1 (2.9)	1.3 (3.2)	0.7 (0.0 to 1.5)	.06
% of waking day in "on" state, mean (SD)	85.6 (21.2)	83.9 (17.8)	−3.2 (−8.4 to 2.1)	.24
UPDRS score change from baseline visit, mean (SD)				
Total	2.4 (17.4)	0.5 (17.1)	−3.8 (−8.3 to 0.8)	.11
Mental	0.9 (2.1)	1.1 (2.1)	0.0 (−0.6 to 0.6)	.95
ADL	1.0 (6.2)	0.9 (5.2)	−1.3 (−2.7 to 0.1)	.07
Motor	1.0 (12.2)	−1.2 (12.9)	−2.7 (−5.9 to 0.6)	.10
Nonmotor outcomes				
MMSE score change from baseline visit, mean (SD)	−1.1 (4.0)	−1.3 (3.9)	0.2 (−0.9 to 1.3)	.77
ESS score, mean (SD)	11.3 (5.8)	8.6 (4.7)	−2.5 (−4.0 to −1.1)	<.001
ESS score ≥10, No. (%)	58 (57.4)	38 (35.2)	0.39 (0.22 to 0.70)	.002
Geriatric Depression Scale score, mean (SD)	3.3 (3.2)	3.1 (3.4)	−0.1 (−1.0 to 0.9)	.89
Edema, No. (%)	29 (27.1)	16 (14.4)	0.48 (0.24 to 0.98)	.04
Edema that interferes with function, No. (%)	5 (4.6)	5 (4.4)	0.93 (0.25 to 3.47)	.92
Quality of life				
PDQUALIF total score change from baseline visit, mean (SD)	7.1 (12.0)	8.6 (10.5)	−0.2 (−3.3 to 2.9)	.90
EuroQol VAS score change from baseline visit, mean (SD)	−4.5 (17.7)	−5.6 (16.1)	−0.7 (−5.2 to 3.8)	.76
EQ-5D score change from baseline visit, mean (SD)	−0.08 (0.25)	−0.07 (0.22)	0.04 (−0.02 to 0.11)	.15
SF-12 physical component summary score, mean (SD)	37.4 (9.7)	38.7 (9.2)	−0.2 (−2.8 to 2.4)	.90
SF-12 mental component summary score, mean (SD)	43.2 (8.5)	42.2 (9.9)	−1.9 (−4.5 to 0.8)	.17

Abbreviations: ADL, activities of daily living; CI, confidence interval; ESS, Epworth Sleepiness Scale; MMSE, Mini-Mental State Examination; PDQUALIF, Parkinson Disease Quality-of-Life Scale; S/E, Schwab and England; SF-12, 12-Item Short Form Health Survey; UPDRS, Unified Parkinson's Disease Rating Scale; VAS, visual analog scale.

[a] For continuous outcomes, the treatment effect is expressed as the group difference in adjusted mean response (levodopa minus pramipexole) derived from an analysis of covariance model; for dichotomous outcomes, the treatment effect is expressed as the adjusted odds ratio (levodopa to pramipexole) derived from a logistic regression model. See text for details.

[b] Includes wearing off, on-off effects, or dyskinesias.

Parkinson Study Group CALM Cohort Investigators, Arch Neurol 2009;0:2009.32-8.



- Review of Rochester Epidemiology Project medical records linkage system
- All incident PD patients treated with levodopa in Olmstead county 1976-1990
- 126 patients
- Based on KM analysis, estimated dyskinesia rate: 30% at 5 treatment years, 59% by 10 years
- Bothersome dyskinesia: 17% at 5 yrs, 43% at 10 yrs
- Troublesome dyskinesia 12% at 10 yrs
- Univariate analysis: older age by 10 yrs decreased risk: HR .72

Van Gerpen, J. A. et al. Arch Neurol 2006;63:205-209.

Prevalence of motor complications at 10 years

Table 2 Prevalence of motor complications at final follow-up

Prevalence at final follow-up	L-dopa arm (n = 42)	Bromocriptine arm (n = 63)	Difference* (95% CI)	*p* Value
Any dyskinesia	58%	56%	−5.3% (−25%, 15%)	0.61
Moderate/severe dyskinesia	39%	35%	−6.0% (−25%, 13%)	0.51
Any fluctuations	50%	56%	5.1% (−15%, 25%)	0.61
Moderate/severe fluctuations	33%	35%	0.01% (−19%, 19%)	0.94

*Adjusted for baseline characteristics (age, duration of disease, baseline Hoehn & Yahr, Northwestern University Disability, and Webster ratings).

- PDRG-UK trial comparing levodopa, l-dopa + selegiline, and bromocriptine
- 782 subjects 1985-1990 randomized; 166 available at final assessment (21%)
- Mean duration follow-up at final assessment 14 yrs
- Disability scores were better in l-dopa arm after adjustment for baseline characteristics (p=.03)
- No difference in mortality rates, prevalence of dyskinesia, and dementia

Dopamine Agonists: Distinguishing Features

- Directly stimulate dopamine receptors
- No metabolic conversion; bypasses nigrostriatal neurons
- No absorption delay from competition with dietary amino acids
- Longer half-life than levodopa
- Monotherapy or adjunct therapy
- May delay or reduce motor fluctuations & dyskinesias associated with levodopa
- May be neuroprotective

DAs: Common Adverse Effects

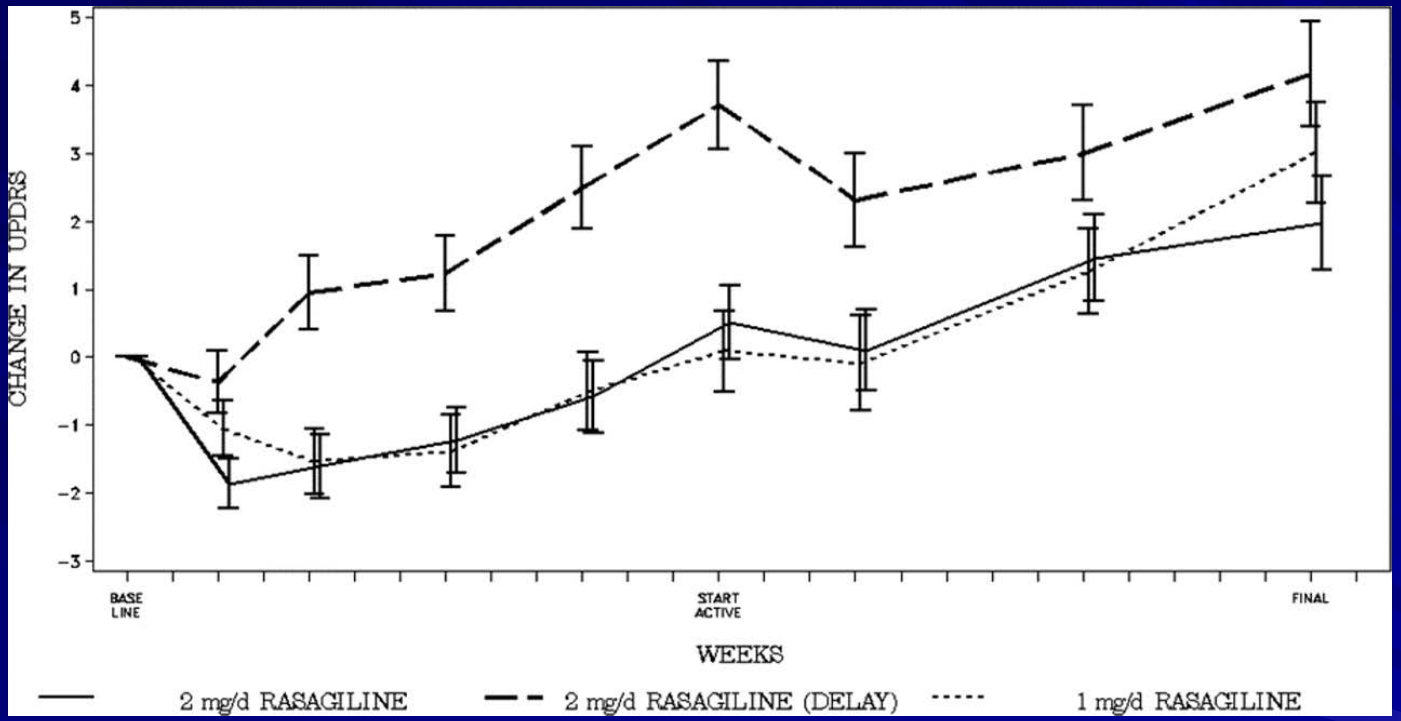
- Nausea, vomiting
- Dizziness, postural hypotension
- Headache
- Dizziness
- Drowsiness & somnolence
- Dyskinesias
- Confusion, hallucinations, paranoia

- ???ICDs

Selegiline

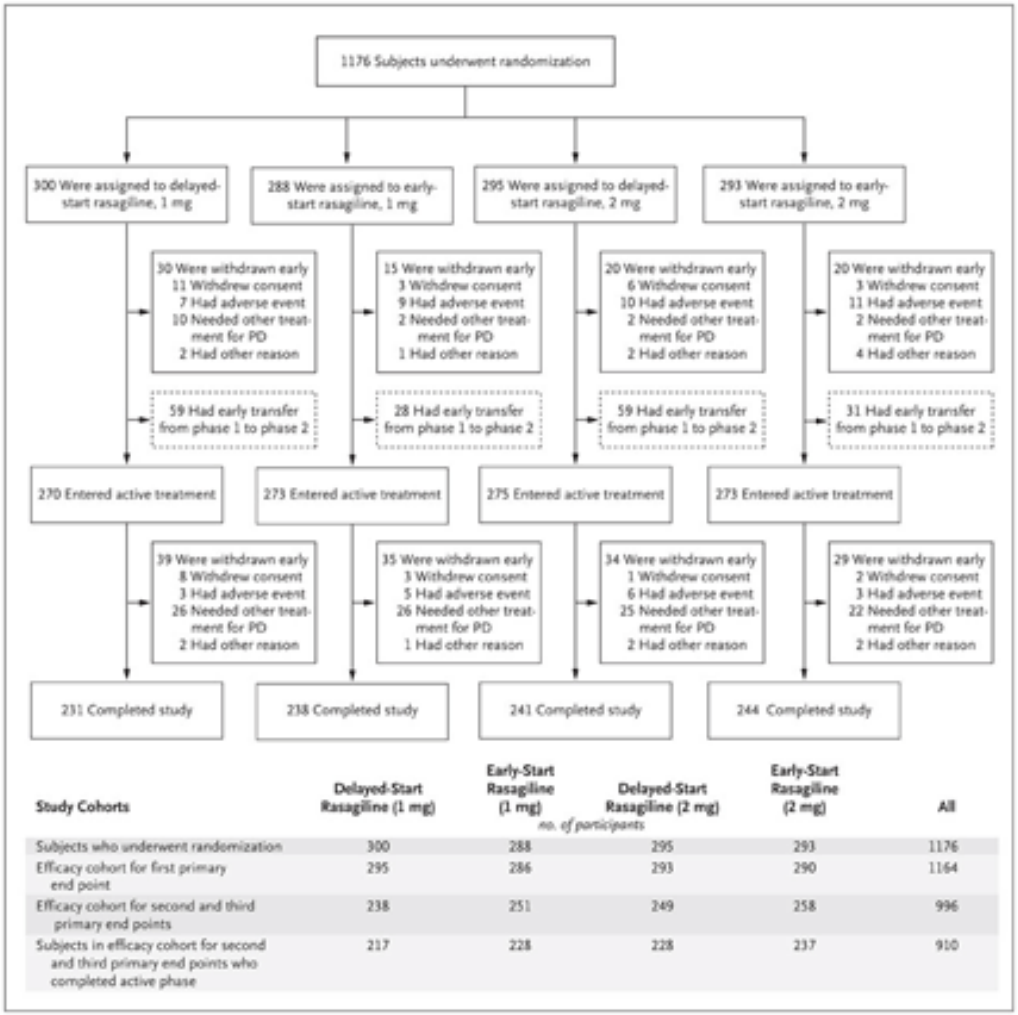
- Irreversible MAO-B inhibitor
- Clinically active by inhibiting dopamine metabolism in brain
- May be neuroprotective
- Dosage: 5 mg at breakfast and lunch
- Side effects: insomnia, hallucinations, nausea (rarely), OH
- Potential interactions with tricyclics and SSRI antidepressants

Rasagiline: The TEMPO Trial



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

Rasagiline- the ADAGIO trial



Study Cohorts	Delayed-Start Rasagiline (1 mg)	Early-Start Rasagiline (1 mg)	Delayed-Start Rasagiline (2 mg)	Early-Start Rasagiline (2 mg)	All
	no. of participants				
Subjects who underwent randomization	300	288	295	293	1176
Efficacy cohort for first primary end point	295	286	293	290	1164
Efficacy cohort for second and third primary end points	238	251	249	258	996
Subjects in efficacy cohort for second and third primary end points who completed active phase	217	228	228	237	910

Olanow CW, Rascol O, Hauser R, Feigin PD, Jankovic J, Lang A, Langston W, Melamed E, Poewe W, Stocchi F, Tolosa E; ADAGIO Study Investigators.
N Engl J Med. 2009 Sep 24;361(13):1268-78.

Rasagiline

Table 2. Results for the Primary and Secondary End Points.*

End Point	Estimated No. of Points	Confidence Interval†	P Value
First primary (estimated rate of change in UPDRS score/wk, wk 12–36)			
Placebo	0.14±0.01		
Rasagiline			
1 mg/day	0.09±0.02		
2 mg/day	0.07±0.02		
1 mg/day vs. placebo	−0.05±0.02	−0.08 to −0.01	0.01
2 mg/day vs. placebo	−0.07±0.02	−0.11 to −0.04	<0.001
Second primary (estimated change in total UPDRS score from baseline to wk 72)			
Rasagiline			
1 mg/day, early start	2.82±0.53		
1 mg/day, delayed start	4.50±0.56		
2 mg/day, early start	3.47±0.50		
2 mg/day, delayed start	3.11±0.50		
1 mg/day, early start vs. delayed start	−1.68±0.75	−3.15 to −0.21	0.02
2 mg/day, early start vs. delayed start	0.36±0.68	−0.99 to 1.70	0.60
Third primary (estimated rate of change in UPDRS score/wk, wk 48–72)			
Rasagiline			
1 mg/day, early start	0.085±0.02		
1 mg/day, delayed start	0.085±0.02		
2 mg/day, early start	0.094±0.01		
2 mg/day, delayed start	0.065±0.02		
1 mg/day, early start vs. delayed start	0.00±0.02	−0.04 to 0.04‡	<0.001
2 mg/day, early start vs. delayed start	0.03±0.02	−0.01 to 0.06‡	<0.001
Secondary (change in total UPDRS score from baseline to final visit in phase 1)			
Placebo	4.27±0.26		
Rasagiline			
1 mg/day	1.26±0.36		
2 mg/day	1.11±0.36		
1 mg/day vs. placebo	−3.01±0.43	−3.86 to −2.15	<0.001
2 mg/day vs. placebo	−3.15±0.43	−4.00 to −2.31	<0.001

Olanow CW, Rascol O, Hauser R, Feigin PD, Jankovic J, Lang A, Langston W, Melamed E, Poewe W, Stocchi F, Tolosa E; ADAGIO Study Investigators.
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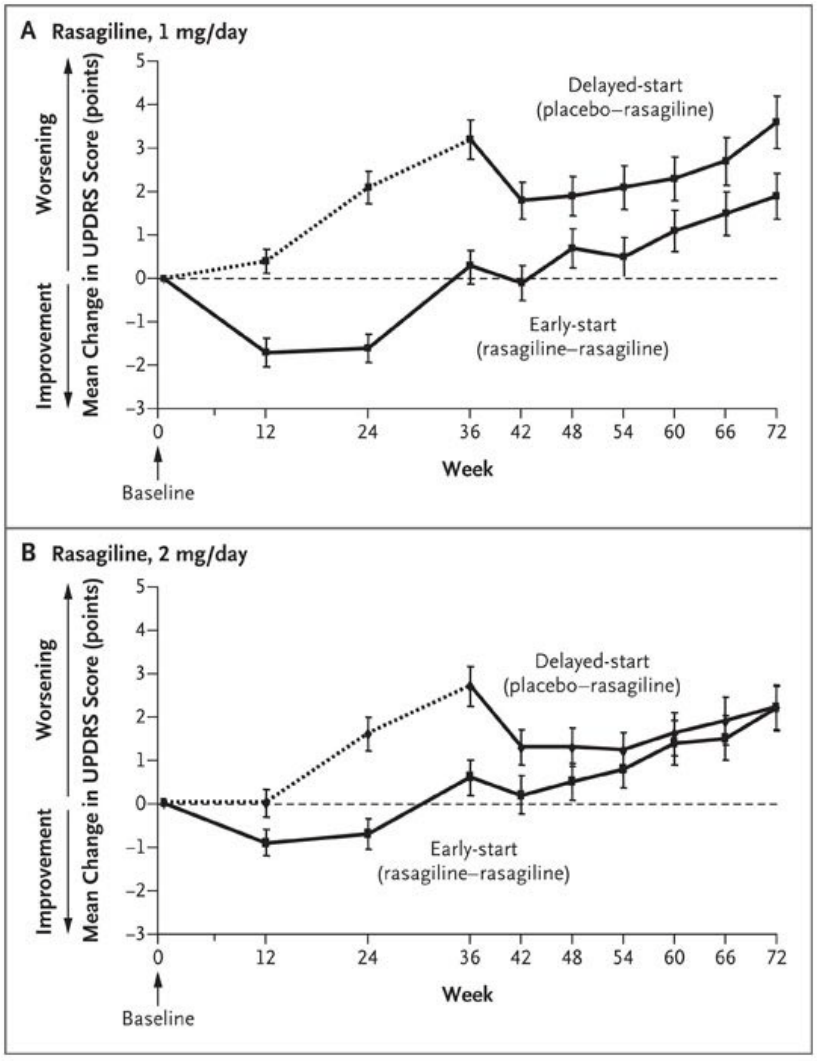
Rasagiline



The Adagio Trial

Olanow CW, Rascol O, Hauser R, Feigin PD, Jankovic J, Lang A, Langston W, Melamed E, Poewe W, Stocchi F, Tolosa E; ADAGIO Study Investigators.
N Engl J Med. 2009 Sep 24;361(13):1268-78.

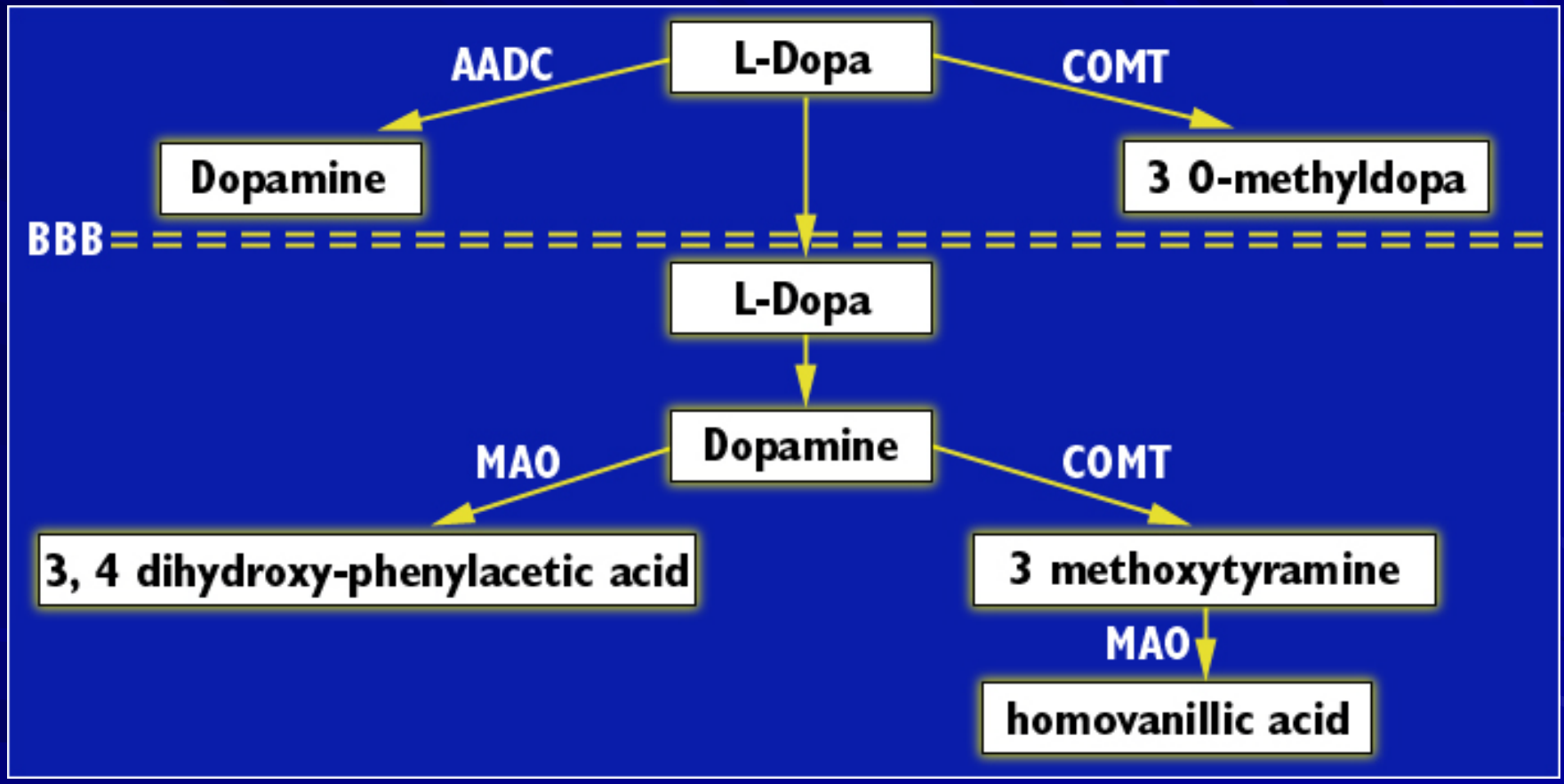
Levodopa

- Most effective drug for parkinsonian symptoms
- First developed in the late 1960s; rapidly became the drug of choice for PD
- Large neutral amino acid; requires active transport across the gut-blood and blood-brain barriers
- Rapid peripheral decarboxylation to dopamine without a decarboxylase inhibitor (DCIs: carbidopa, benserazide)
- Side effects: nausea, postural hypotension, dyskinesias, motor fluctuations

Sinemet

- L-dopa
  - Most effective Rx for majority of Sx
  - Pulsatile use likely leads to motor fluctuations
  - Carbidopa >75 mg/day

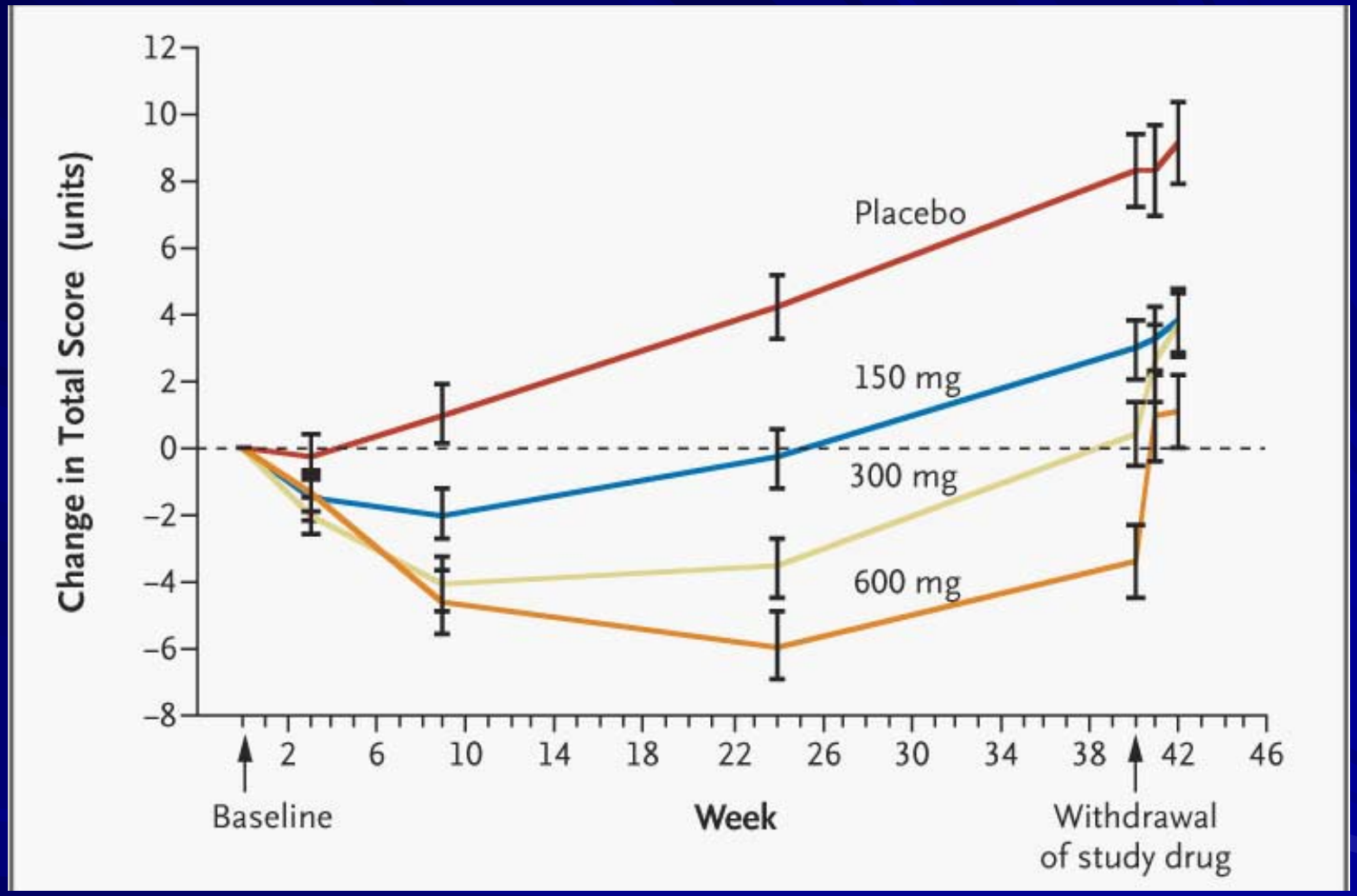
Diagram of LD Metabolism



Is Levodopa Toxic?

- Early patients develop motor fluctuations, but may be a function of neuronal cell loss
- Increased life expectancy with LD introduction
- LD-naive advanced PD patients develop fluctuations almost immediately with LD induction
- No LD neuronal dropout in laboratory animals
- Some believe continuous infusion may be safer than pulsatile therapy

Levodopa Toxicity: The ELLDOPA Trial



Fahn S and The Parkinson's Study Group N Engl J Med 351;24 December 9 2004

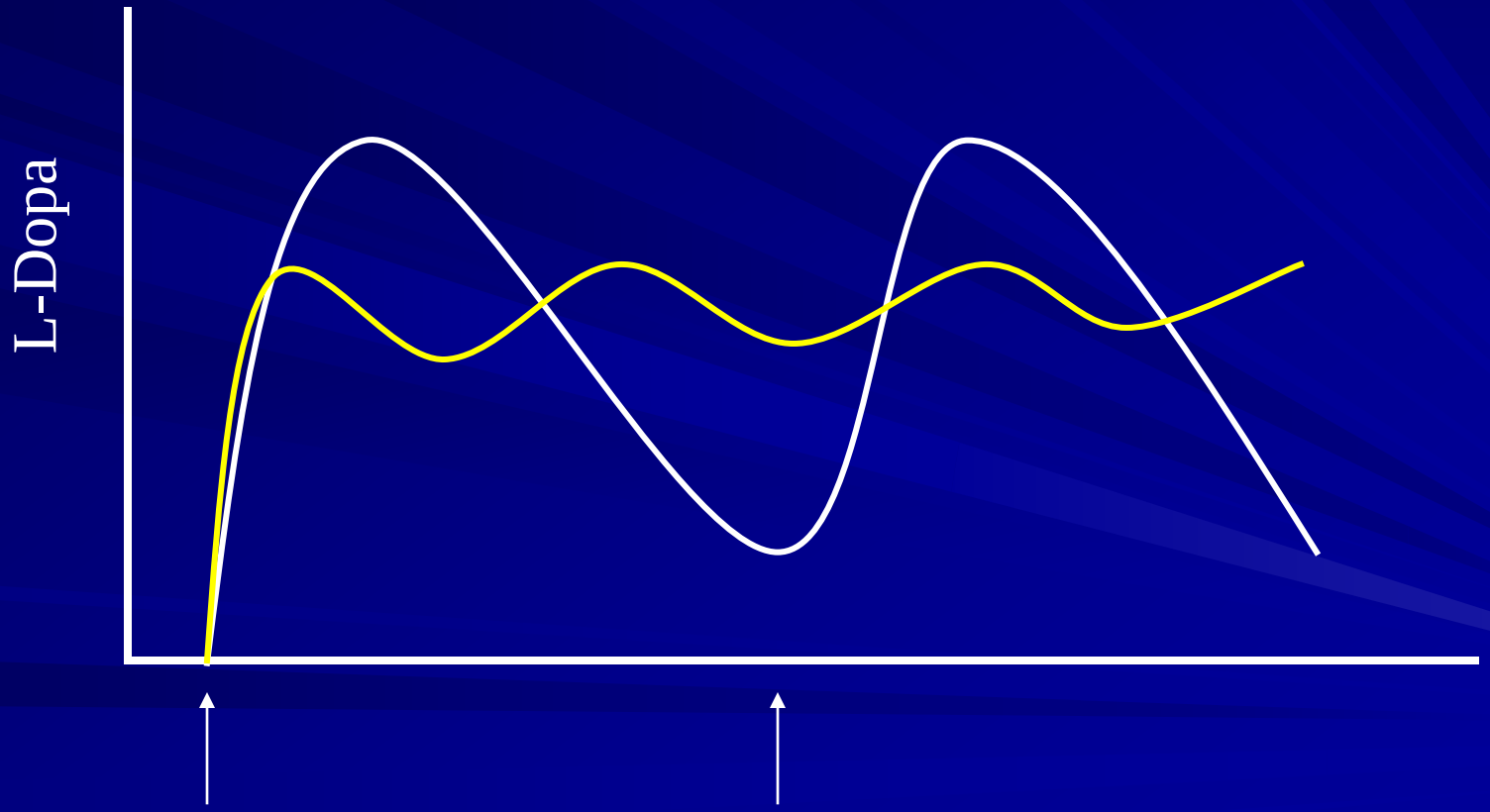
Levodopa-Induced Dyskinesias

- Manifestation of excessive dopaminergic stimulation
- Typically late effect, and with higher doses
- Narrowing of therapeutic window
- Rare in LD-naive patients on DA monotherapy
- Most common is “peak dose” dyskinesia
  - disappears with dose reduction
- Choreiform, ballistic and dystonic movements
- Most patients prefer some dyskinesias over the alternative of akinesia and rigidity

Levodopa/Carbidopa Formulations

	Onset	**Duration**
Immediate Release 10/100, 25/100, 25/250	20-40 min	2-4 hr
Controlled Release 25/100, 50/200	30-60 min	3-6 hr
ODT	dissolves on contact with saliva but no transmucosal absorption	

Pulsatile vs. Tonic DA Receptor Stimulation



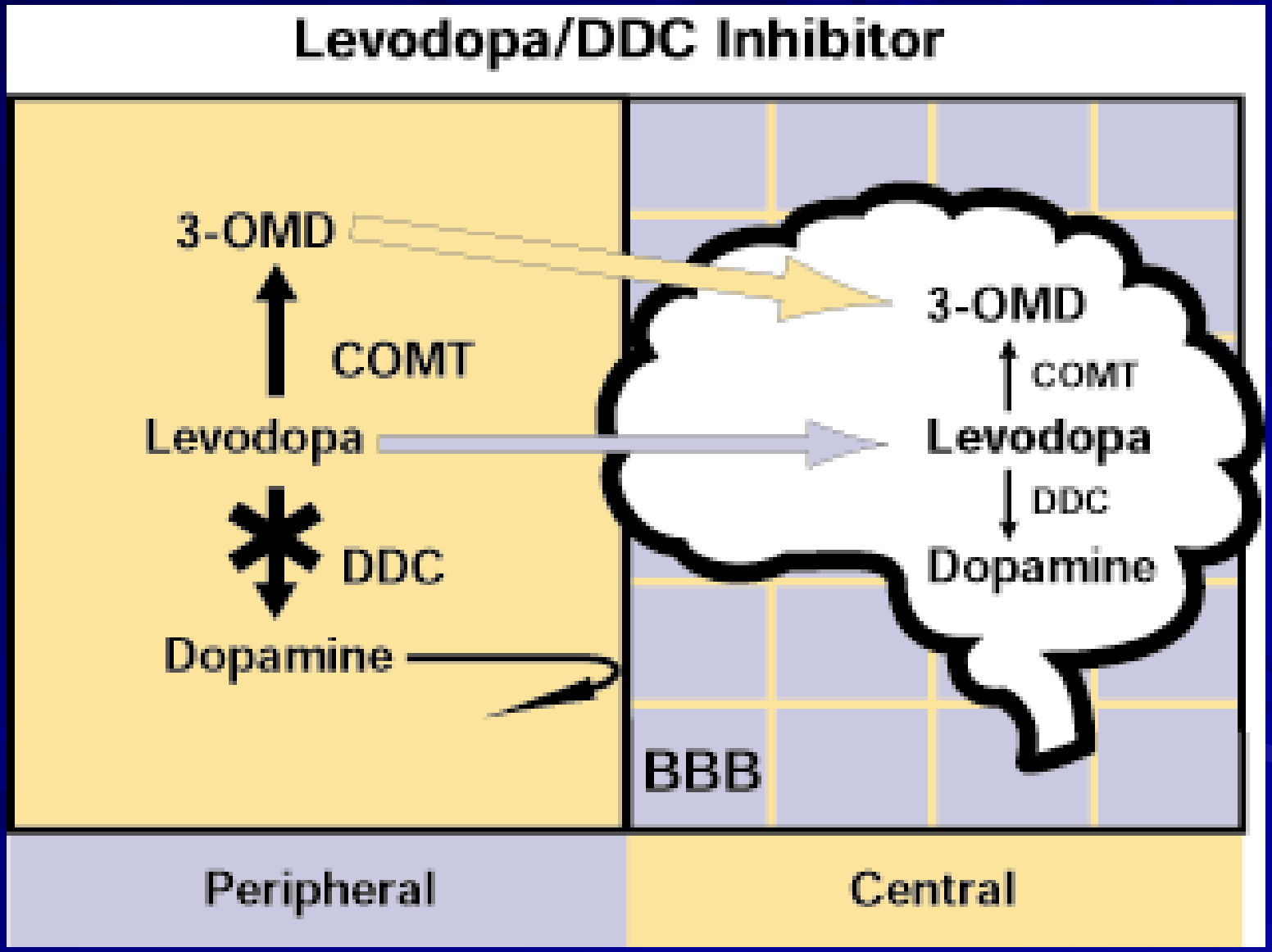
Principles of Managing Fluctuations

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

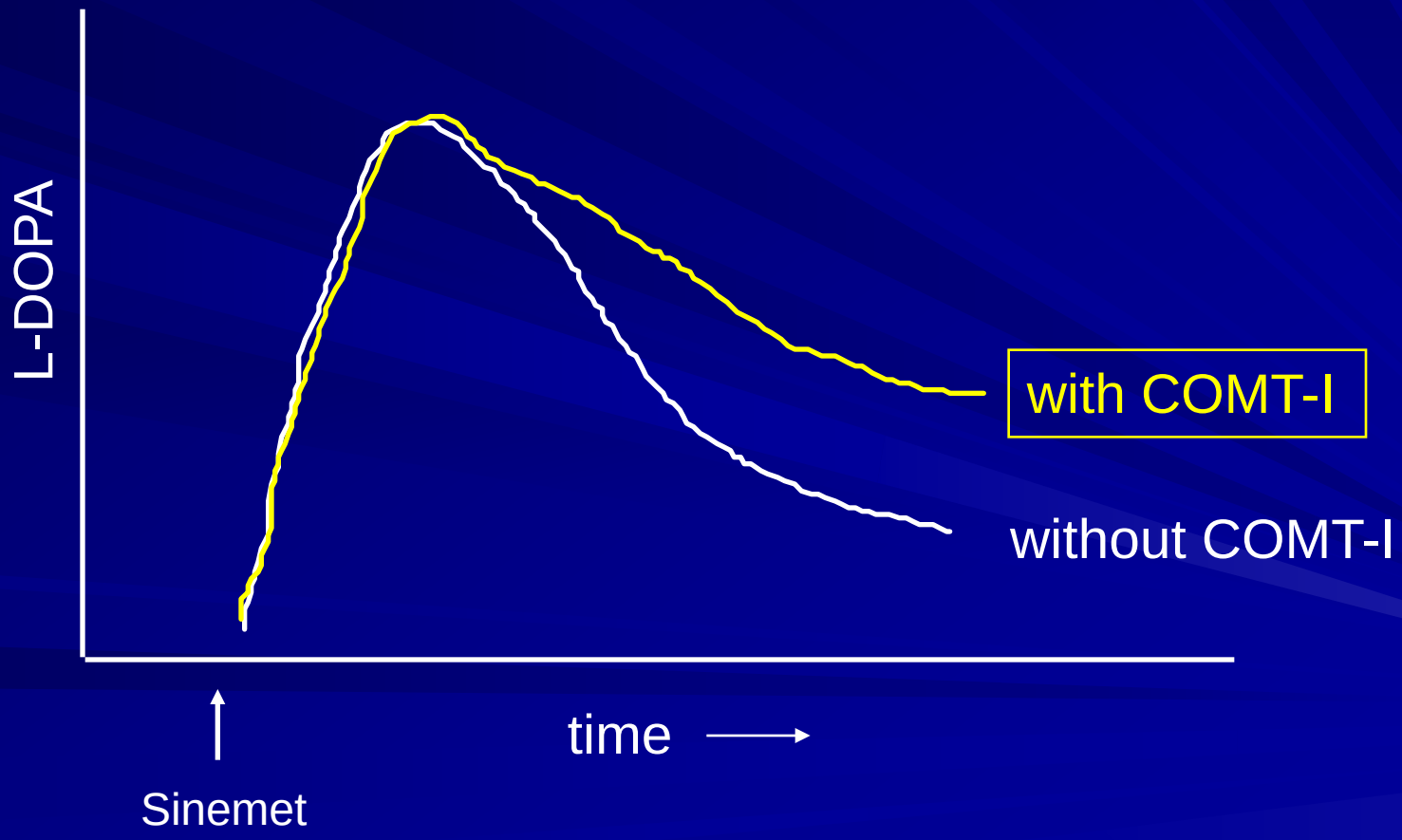
COMT Inhibition

- Increases the half-life of L-dopa plasma concentrations without affecting peak values thus reducing fluctuations in L-dopa concentrations
- Decreases concentration of O-methyl-dopa which may reduce competition for the NAA transporter.

COMT Inhibition



EFFECT OF COMT-I ON PLASMA L-DOPA LEVELS



COMT Inhibitors

- Newest class of antiparkinsonian drugs: tolcapone (use best restricted to PD specialist), entacapone
- MOA similar to dopa decarboxylase inhibitors
- Potentiate LD: prevent peripheral degradation by inhibiting catechol O-methyl transferase
- Reduces LD dose necessary for a given clinical effect
- Helpful for both early and fluctuating Parkinson’s disease
- May be particularly useful for patients with “brittle” PD, who fluctuate between off and on states frequently throughout the day

Entacapone

- Dosage: 200 mg w/each levodopa dose
- Parkinson's Study Group 1997: Increased on time by 5%, more in pts w/least on time
- Rinne et al., 1998: Increased on time by ~10%; decreased levodopa
- Diarrhea, dopaminergic SEs

Amantadine

- Antiviral agent; PD benefit found accidentally
- Tremor, bradykinesia, rigidity & dyskinesias
- Exact mechanism unknown; possibly:
  - enhancing release of stored dopamine
  - inhibiting presynaptic reuptake of catecholamines
  - dopamine receptor agonism
  - NMDA receptor blockade
- Side effects —autonomic, psychiatric
- 200-300 mg/day

Anticholinergics

- Dopaminergic depletion→cholinergic overactivity
- Initially used in the 1950s
- Effective mainly for tremor and rigidity
- Common agents (Start low, go slow):
  - Trihexyphenidyl: 2-15 mg/day
  - Benztropine: 1-8 mg/day
  - Ethopropazine: 10-200 mg/day
- Side effects:
  - Dry mouth, sedation, delirium, confusion, hallucinations, constipation, urinary retention

Apomorphine

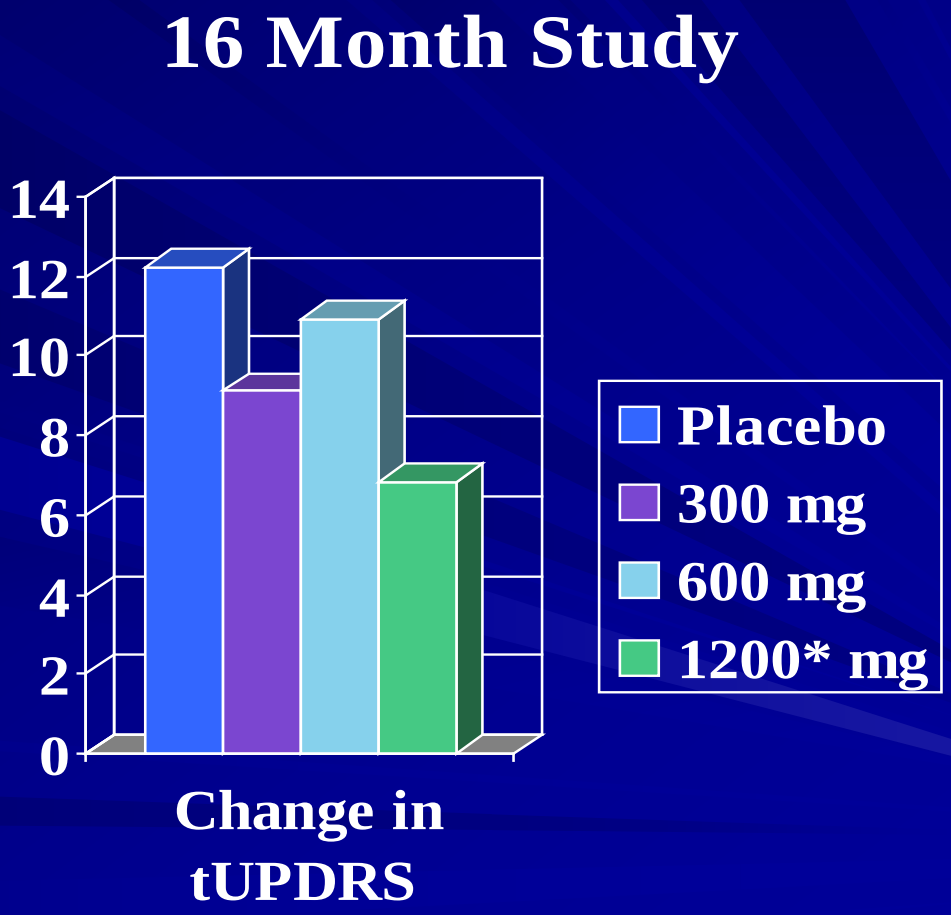
- D1/D2 agonist
- Parenteral delivery (s.c., i.v., sublingual, intranasal, rectal)
- Rapid “off” period rescue
  - 2-5 mg s.c.; pen injection systems
- Treatment of unpredictable, frequent motor fluctuations
  - continuous s.c. infusion via mini-pump
- SE: nausea, vomiting, hypotension
  - trimethobenzamide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

Considerations in Choosing a Medical Regimen

- Sinemet is the most effective medication
- L-Dopa probably doesn’t kill cells and works for more than 5 yrs.
- L-Dopa primes system for motor fluctuations (pulsatile vs tonic use)
- Agonists delay onset of motor fluctuations
- All PD medications have more side-effects in elderly

Co-Enzyme Q10

- Complex I deficiency in PD
- Co-Q10 is a cofactor for Complex I
- Co-Q10 restores activity *in vitro*



Shults et al. 2002

Considerations in Choosing a Medical Regimen

- Potency
- Side-effects
  - Nausea
  - Psychosis (especially in elderly)
  - Orthostatic hypotension
  - Peripheral edema
  - Compulsions ?
- Relative benefits of agonists are often outweighed by SE in elderly

Problems in Advanced Parkinson's Disease

- Motor fluctuations (young onset > older).
- Falls
- Medication-induced psychosis
- Depression
- Sleep
- Cognitive decline

Initiating Therapy