



Philadelphia VA PADRECC

*Parkinson's Disease Research,
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Initiation of therapy should be delayed until symptoms become disabling or bothersome: No

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Essential Question:

Do the possible disease modifying aspects of treatment outweigh the risk of side effects or the potential for long term complications?

MODIFYING PARKINSON'S DISEASE

REDUCE MOTOR COMPLICATIONS

Early DA Therapy
Continuous Dopaminergic Stim
Deep Brain Stimulation
Anti-dyskinesia drugs
amantadine, dopamine transport inhib, gaba and glutamatergic drugs

SLOW DISEASE PROGRESSION

Block Neurodegenerative process

oxidative stress
protein aggregation
apoptosis, necrosis

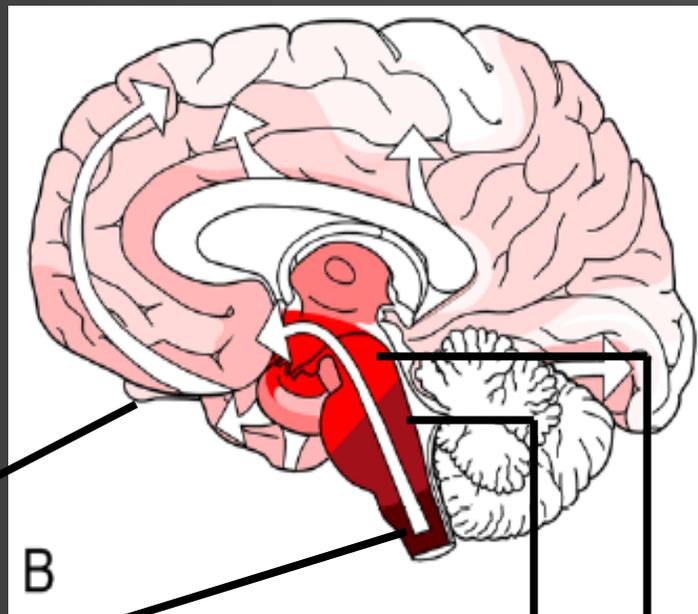
Restorative Therapies

cells, genes, trophic factors

LIMIT COGNITIVE AND NON-DOPAMINERGIC SYMPTOMS

Dementia
Depression
Postural Instability
Freezing
Autonomic failure

Preclinical phase of Parkinson's disease



100%
80%
60%
40%
20
0%

Striatal dopamine

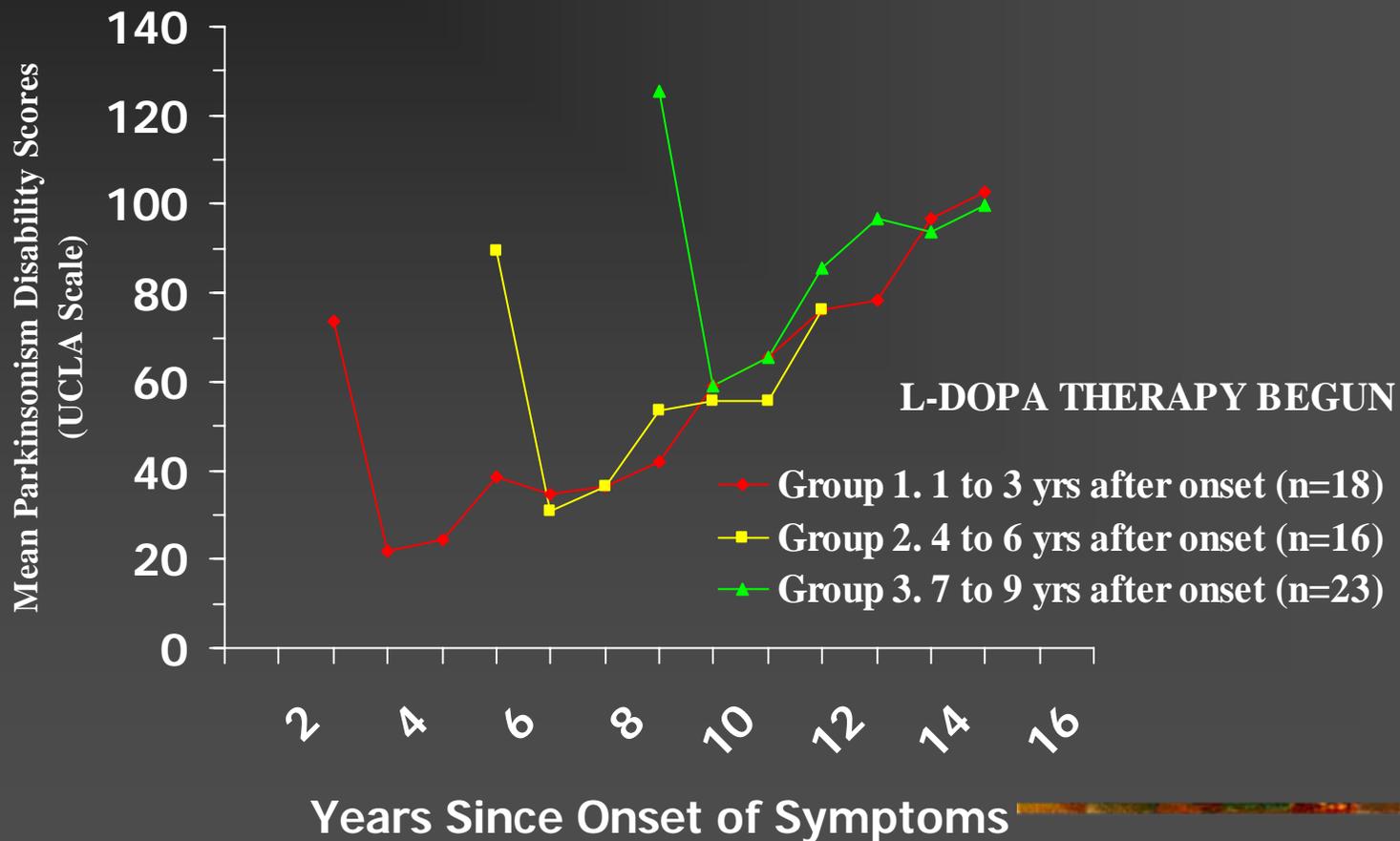
4 to \geq 13
Years

Diagnosis



Courtesy of Web Ross, MD

Disability Scores on the UCLA Scale



IS LEVODOPA TOXIC?

- *In vitro* evidence indicates that levodopa can be protective or toxic to dopaminergic neurones depending on the experimental conditions
- *In vivo* studies show no evidence of levodopa toxicity
- There is no clinical evidence that levodopa causes or accelerates neuronal cell death

In 2002 a panel of 28 experts in PD concluded that levodopa toxicity has not been convincingly demonstrated in animal models, and almost certainly does not occur in people with PD

ELLDOPA Study

Primary Objective

- To assess the effect of levodopa on the course of Parkinson's Disease

Primary Outcome

- Change between baseline and 42 weeks in the total score on the UPDRS

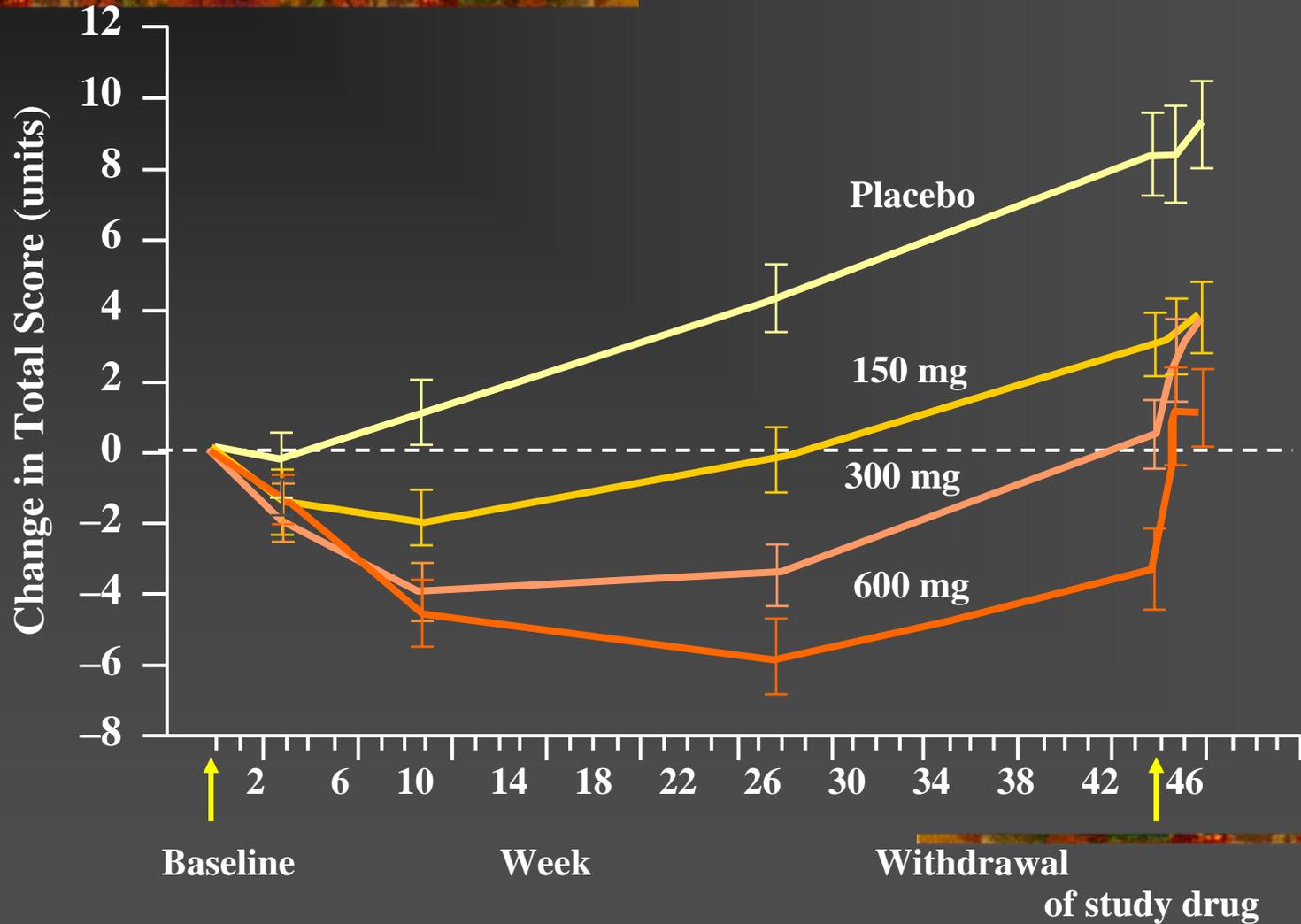
Secondary Objectives

- **Secondary Objectives: To assess:**
 1. **The change in the dopamine transporter in the striatum, based on β -CIT SPECT scans at base line (N=143) and just prior to the Week-40 visit**
 2. **When the long-duration response to levodopa is lost**
 3. **If the dosage of levodopa is a factor in the loss of the long-duration response**
 4. **The presence of fatigue is in patients with early disease and how severe it is; and**
 5. **How early initiation or the dosage of levodopa affects signs and symptoms of PD, the quality of life, and fatigue.**

ELLDOPA TRIAL (PSG)

- 360 never treated PD patients in 35 centers
 - UPDRS outcome measure
 - 40 weeks of treatment randomized to:
 - Placebo
 - 32.5/100 mg/day
 - 75/300 mg/day
 - 150/600 mg/day
 - Given in divided doses three times per day
 - Last assessment after 2 week washout
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Changes in Total UPDRS Scores from Baseline through Evaluation at Week 42



RESULTS

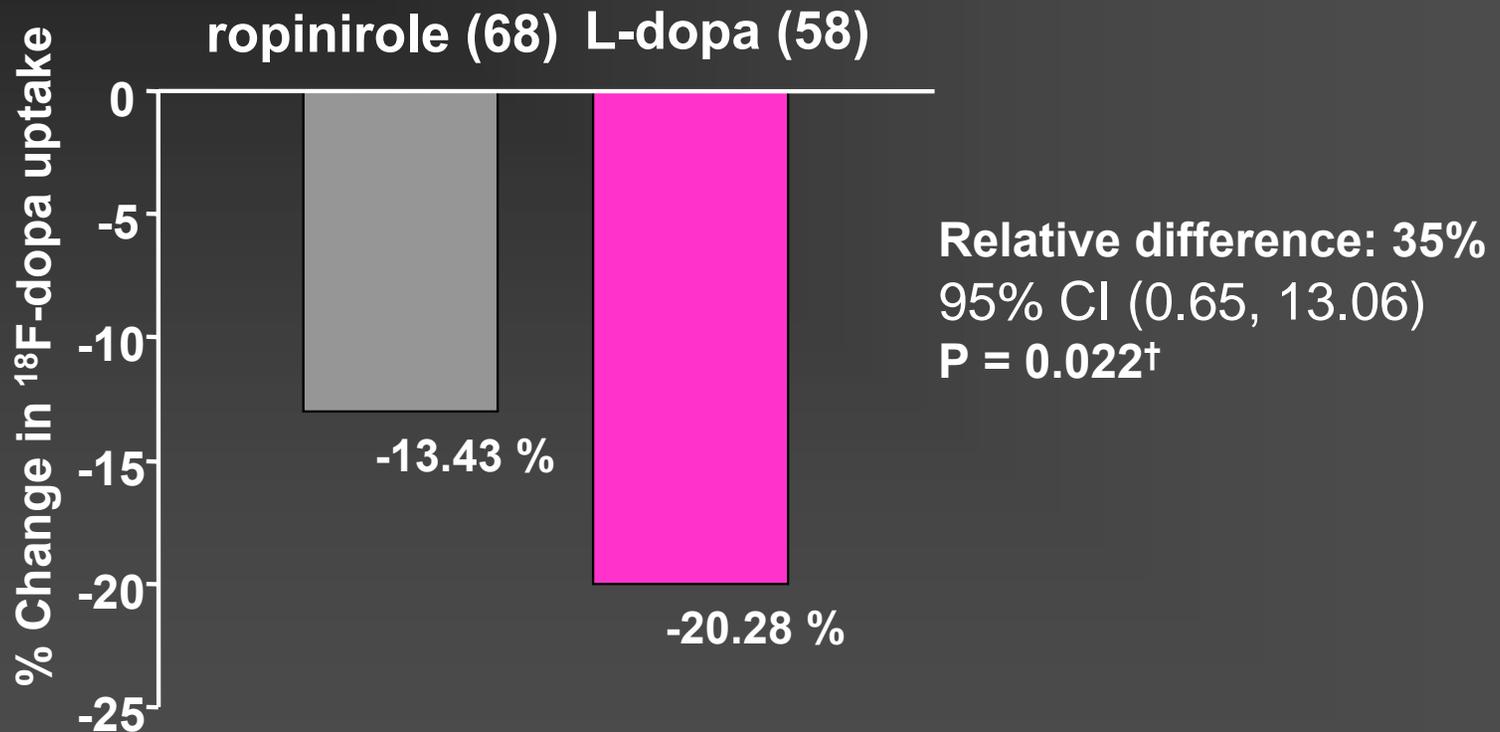
- Patients in all treatment groups were improved relative to placebo during treatment and after 2 week washout
- Highest levodopa group had lowest UPDRS disability score
- However, wearing off and dyskinesias were more common in the highest-dose group and β -CIT data suggested that levodopa accelerates the loss of nigrostriatal dopamine nerve terminals
- Does not support “levodopa toxicity” theory or aggressive delay in levodopa treatment

Can dopamine agonists be thought of as neuroprotective: Neuroimaging assessment of PD progression

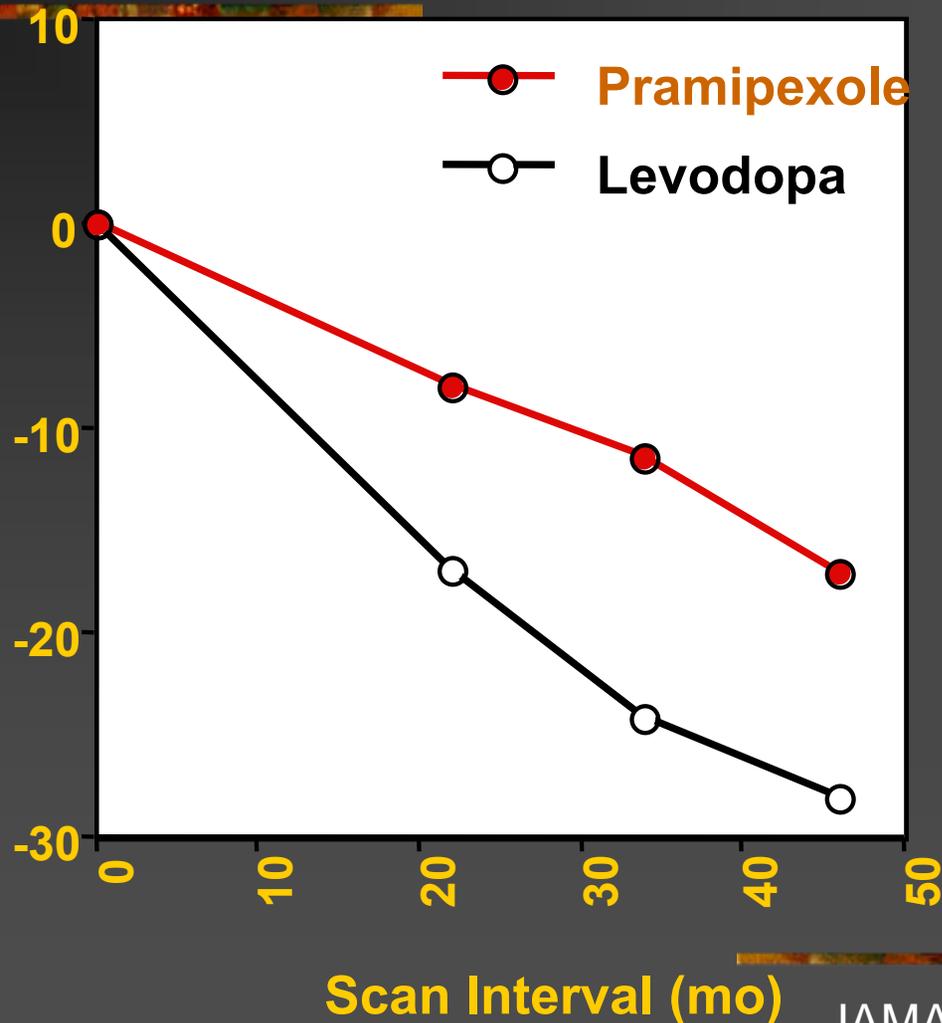
- **Trials: REAL-PET and CALM-PD**
- **Compare ropinirole and pramipexole to levodopa in patients with early, previously untreated PD**
- **Differential rate of PD progression measured with functional imaging**
 - **REAL-PET – F-dopa PET**
 - **CALM-PD – β -CIT SPECT**

Real-PET: % Change in Putamen ^{18}F -dopa Uptake from Baseline by Treatment

Left & right putamen averaged % change in K_i



CALM-PD : % Change in Putamen β -CIT Uptake from Baseline by Treatment



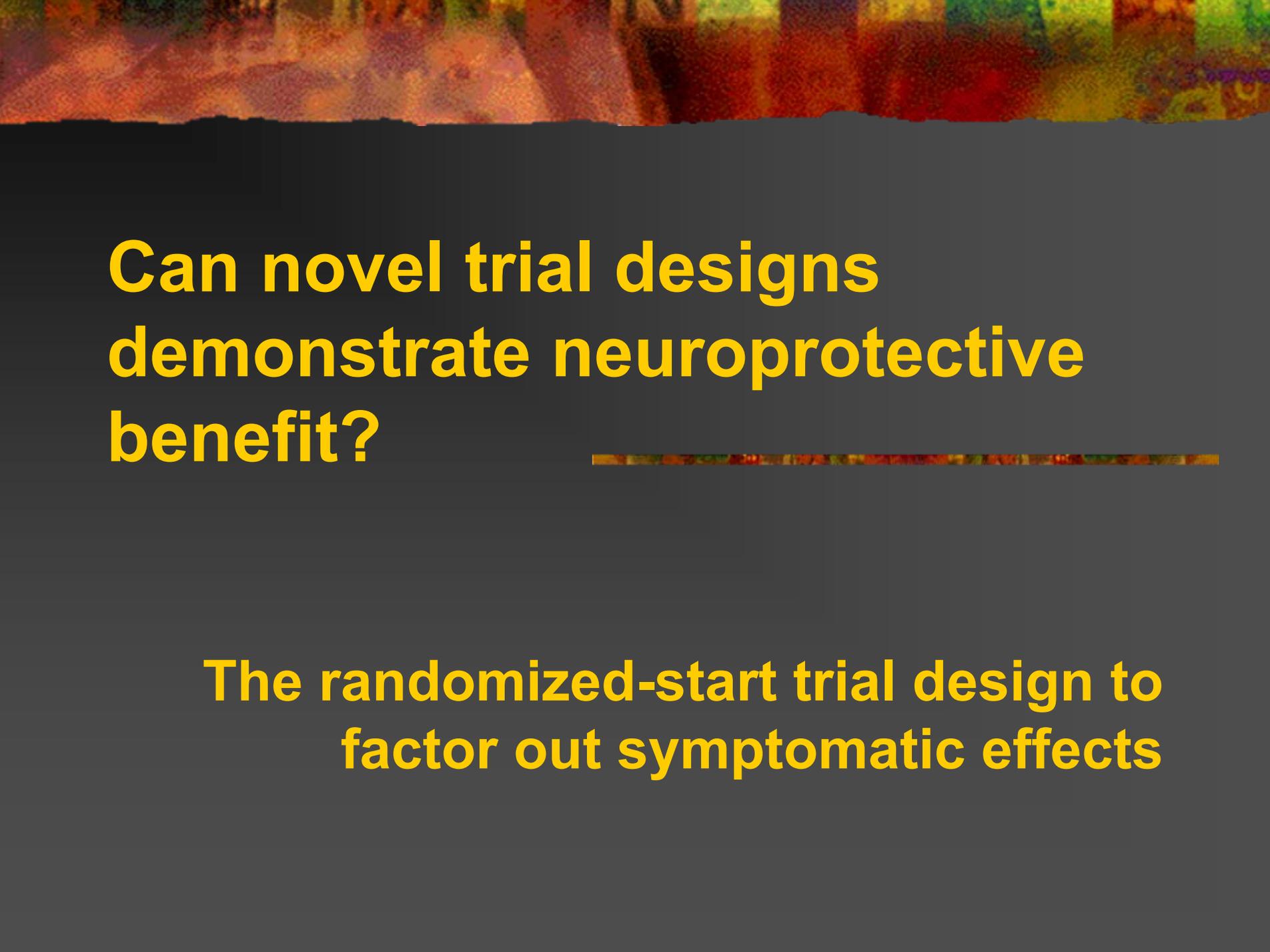
P=0.03 at 46 months

Conclusions

- In both REAL-PET and CALM-PD, patients treated with a dopamine agonist had 35-40% less loss of dopaminergic function by imaging
 - These results could be interpreted as a neuroprotective effect for dopamine agonist therapy relative to levodopa
 - These results do not support neuroprotection relative to no therapy
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Concerns about results from REAL-PET and CALM-PD

- Pharmacological effect of agonists on the dopamine transporter and/or flourodopa uptake
- Lack of corresponding motor improvement
- All of the difference between groups accumulates in the first 22 months (CALM-PD)
- Initial therapy with levodopa followed by adjunctive therapy with a dopamine agonist and reduction in levodopa dose at the onset of motor complications might yield the same benefit as initial therapy with a dopamine agonist



Can novel trial designs demonstrate neuroprotective benefit?

**The randomized-start trial design to
factor out symptomatic effects**

Randomized start design

Group 1 starts
treatment

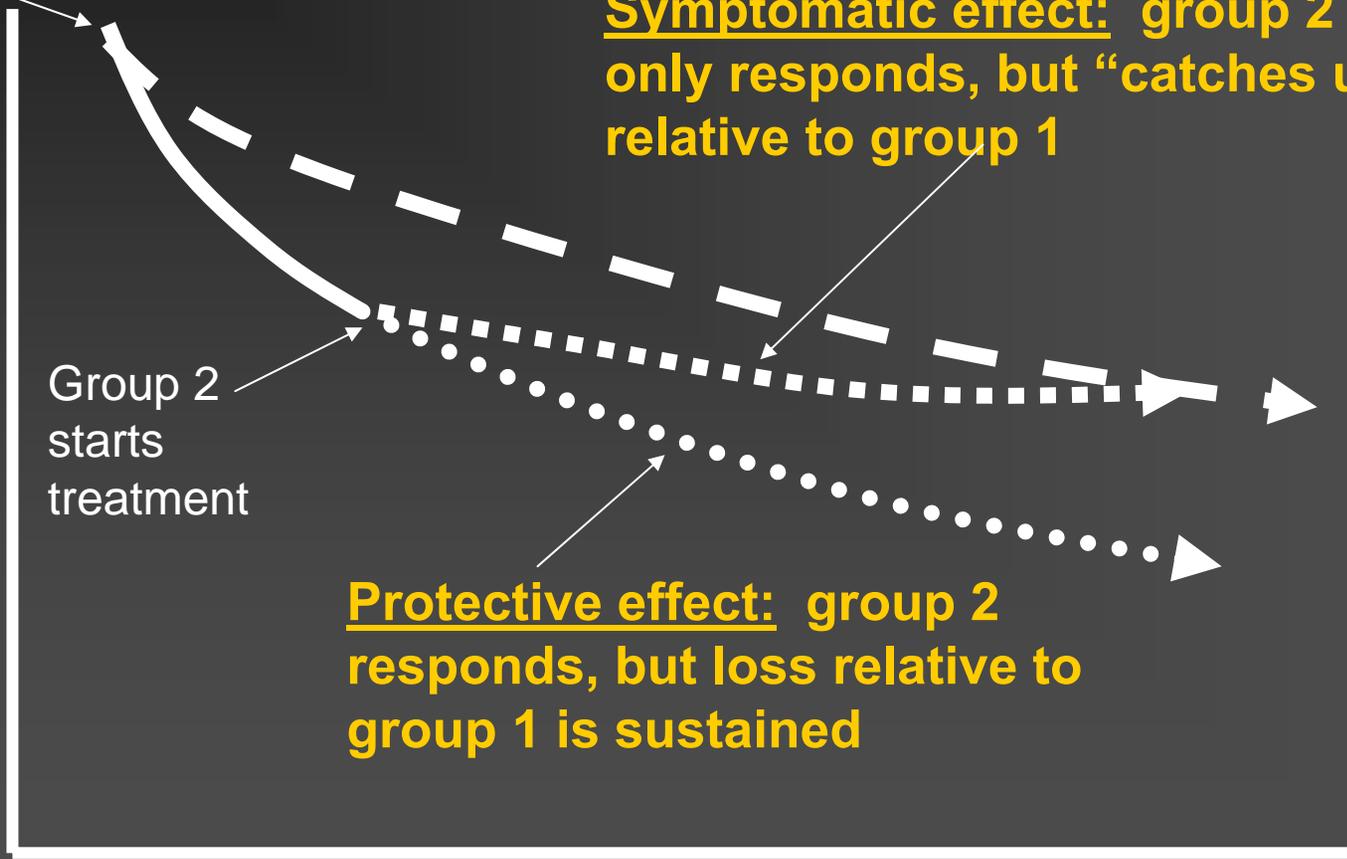
performance

Group 2
starts
treatment

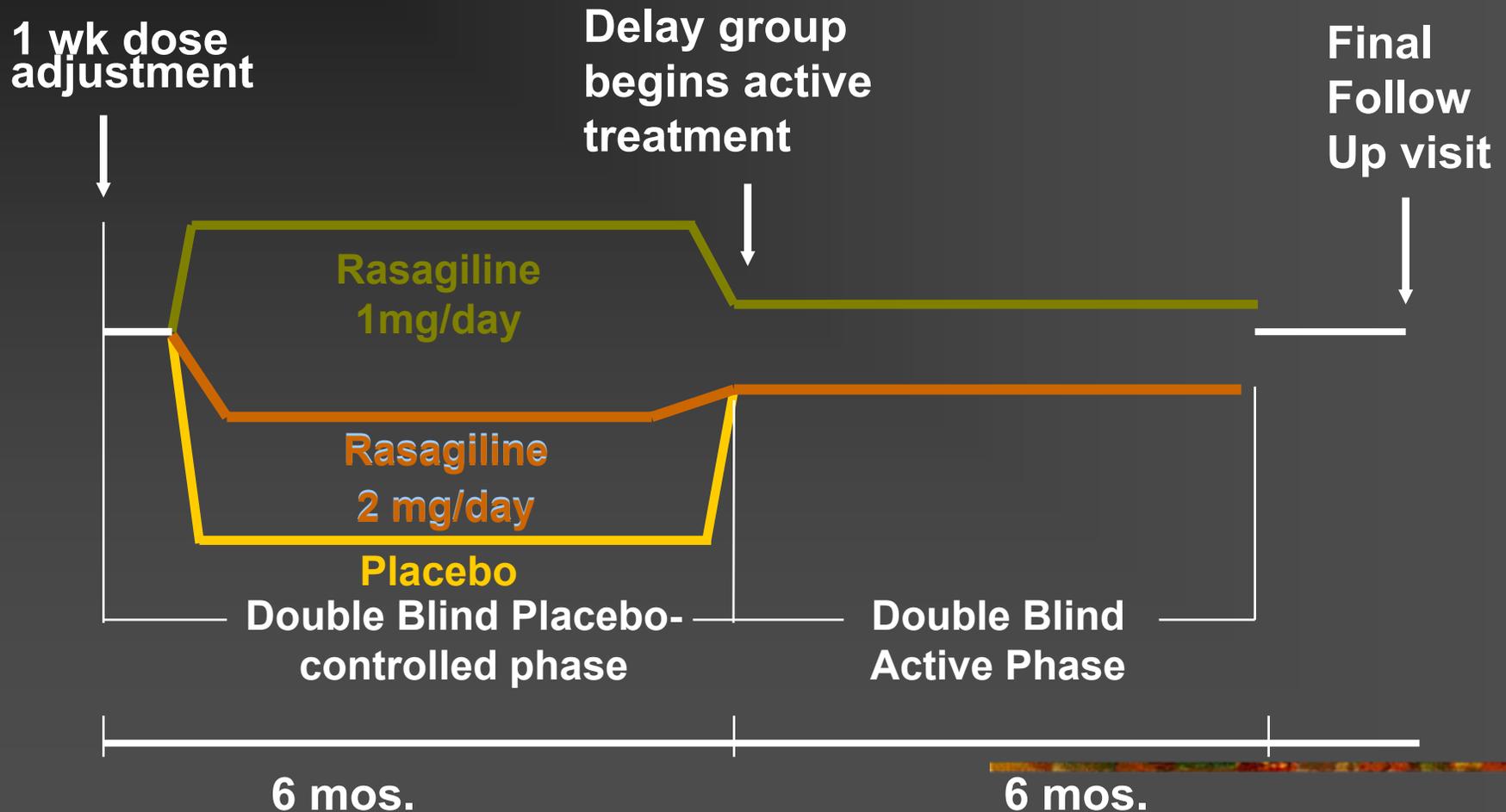
Symptomatic effect: group 2 not only responds, but “catches up” relative to group 1

Protective effect: group 2 responds, but loss relative to group 1 is sustained

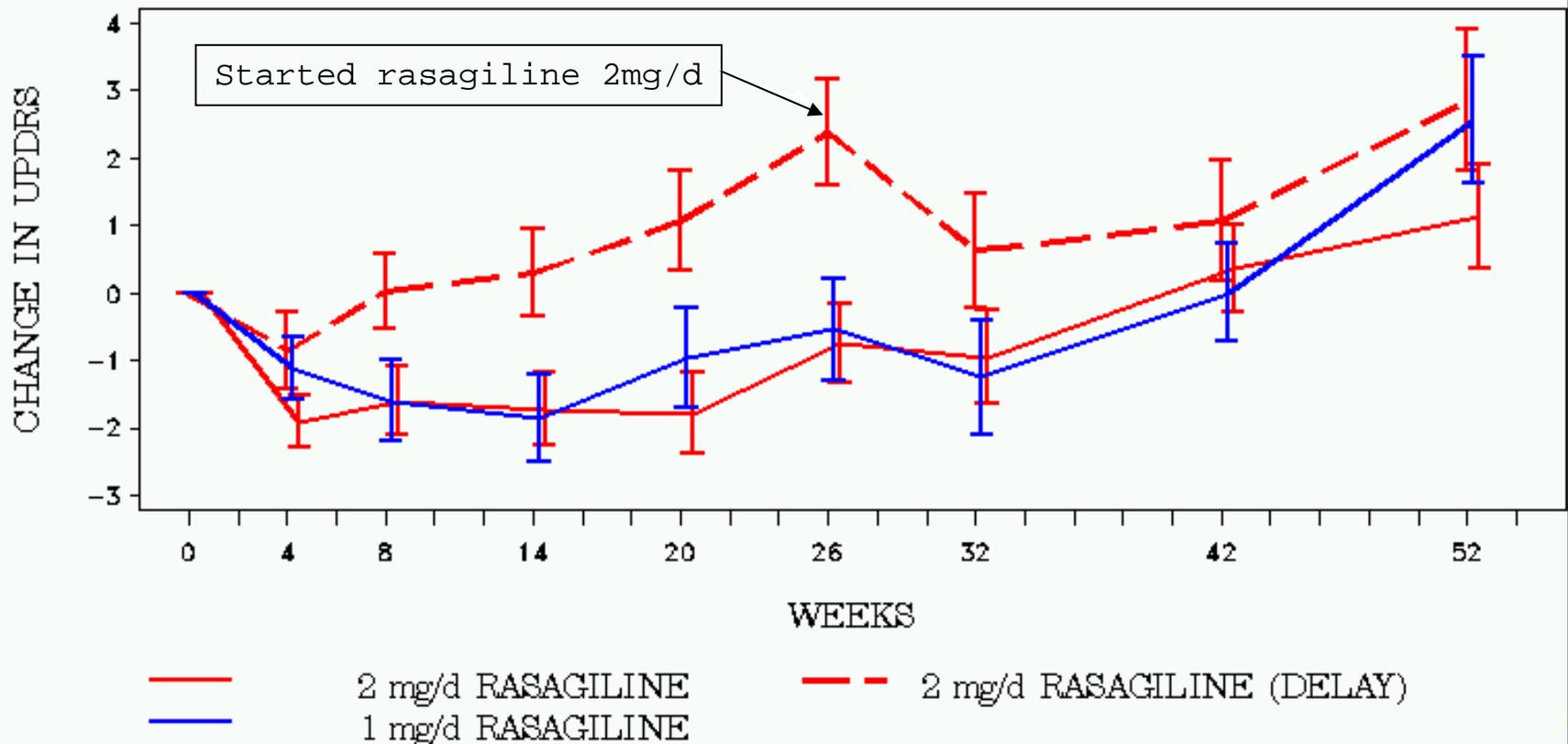
time



TEMPO Trial of Rasagiline in early PD



Mean change from baseline total UPDRS for subjects completing 52 weeks without starting additional therapy (n=249)



ADAGIO trial

- a randomized, double-blind, placebo-controlled study prospectively examining rasagiline's potential disease-modifying effects in 1,176 de novo PD patients
- Patients were randomized to early-start treatment (72 weeks rasagiline 1 or 2 mg once daily) or delayed-start treatment (36 weeks placebo followed by 36 weeks rasagiline 1 or 2 mg once daily)
- Primary analyses were based on total UPDRS scores
 - Superiority of slopes in weeks 12-36 (-0.05; $p=0.013$, 95%CI -0.08,-0.01)
 - Change from baseline to week 72 (-1.7 units; $p=0.025$, 95%CI -3.15,-0.21)
 - Non-inferiority of early-start vs. delayed-start slopes in weeks 48-72 (0.0; 90%CI -0.04,0.04)

Conclusions and concerns with the randomized start trials of rasagiline

- Delayed start trial design is a potentially powerful tool for separating symptomatic effects from neuroprotection and is probably preferable to wash-out designs
- There may be selection biases in trials potentially requiring patients to stay untreated for 6-9 months
- These trials are powered to detect small differences in Total UPDRS scores that may not be clinically significant
- It is possible that dopaminergic therapy of any kind may prevent potentially deleterious physiological mechanisms that compensate for the loss of dopaminergic neurons

Conclusions

- At the current time there are no proven neuroprotective therapies in PD
 - However, there is growing evidence that delaying the initiation of dopaminergic therapy after diagnosis of PD is detrimental
 - Therefore, the decision whether to treat before symptoms become bothersome or disabling should be based upon careful consideration of many factors with the patient but the possible benefits may outweigh the risks
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