

SERMs: Cognitive Outcomes

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Background: SERMS and Cognition

- Selective estrogen receptor modulators (SERMs) have differential tissue-dependent effects...estrogen partial agonists at some sites and antagonists at others.
- Also different affinities for ER alpha and beta.
- Complex interactions with ligand-ER and co-regulators (repressors or activators)
- ? Effect on CNS.
- In the future, more women on SERMs.
- In light of WHI, need to determine if SERMs are harmful or beneficial to cognitive outcomes.

SERMs and Cognition/Dementia

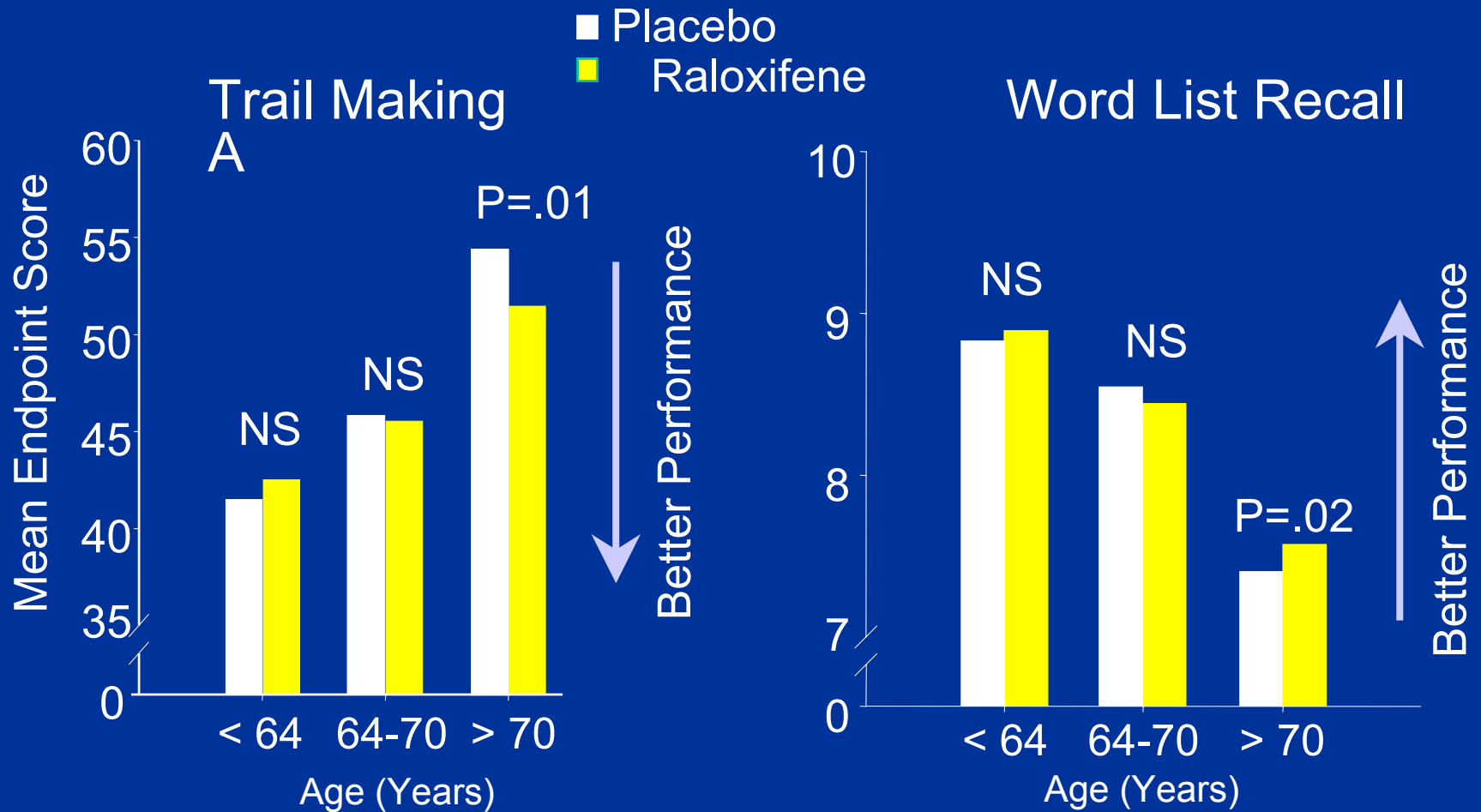
- SERMs have neurotrophic effects *in vitro*
- Increases in choline acetyltransferase activity
- Increases in hot flushes with most SERMs
- 12-month trial of raloxifene in 148 postmenopausal women with no effect on cognition (Nickelsen, 1999)
- Trial of RLX for patients with AD...prelim beneficial.
- Observational studies of tamoxifene primarily negative but usually in patients with breast cancer

The MORE Trial

- Multiple Outcomes of Raloxifene Evaluation (MORE) trial funded by Eli Lilly, Inc.
- A RCT of 7700 postmenopausal women (67 years); main outcome was osteoporosis
- Subjects completed a battery of 6 cognitive tests at baseline and annually for 4 years
- 5386 in sites participating in dementia study

Effect of Raloxifene on Trails A and Word List Recall Scores by Age Tertile

MORE Trial - 3 Years



Risk of Developing Cognitive Decline*

Cognitive Test	Relative Risk*	(95% CI)
Short Blessed	1.0	0.9 - 1.3
Trails A	0.8	0.7 - 1.0
Trails B	1.1	0.9 - 1.2
Word List Memory	1.0	0.9 - 1.2
Word List Recall	0.8	0.6 - 1.0
Word List Fluency	1.0	0.8 - 1.2

*worse 10th decline

*Relative risk compared to placebo group

Conclusions: MORE Cognitive Study

- No overall effect on 3-year cognitive scores
- In women >70 years old, slight improvement in attention and verbal memory tests with raloxifene (pooled doses)
- Lower risk of decline in attention and verbal memory tests with raloxifene, not in 4 other tests
- No effect of hot flushes on cognitive scores

Raloxifene Dementia Study

- Cognitive battery on all subjects in MORE trial
- Based on Year 3 Short Blessed score (worse 10% by country) or clinical impression
- Referred to Dementia Diagnostic Evaluation
- Two Phases
 - I To evaluate presence of dementia
 - II To evaluate type of dementia

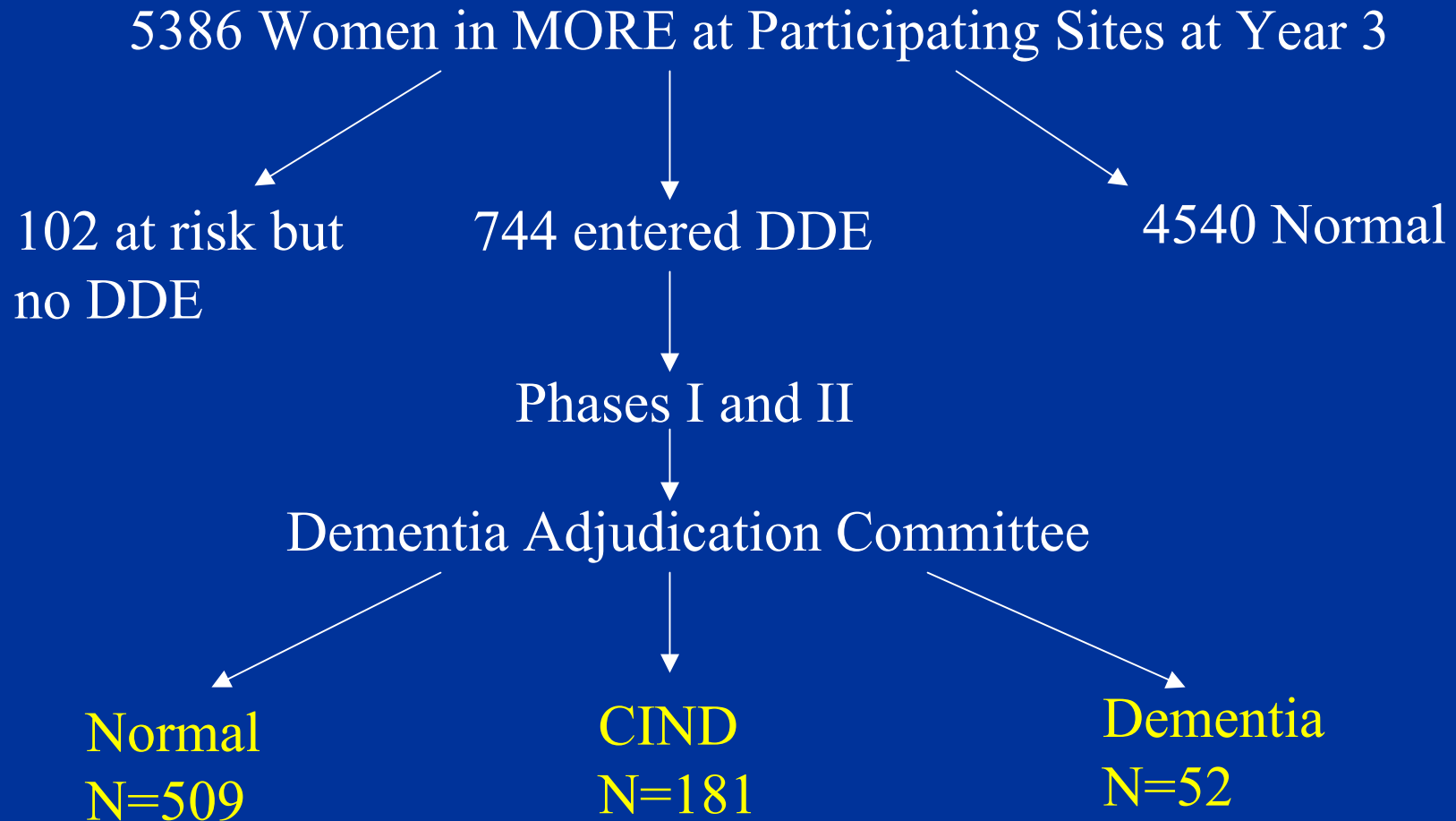
Raloxifene Dementia Study (cont)

- Phase I
 - Interviews with patient and caregiver
 - History, general and neurological exam
 - MMSE
 - Geriatric Depression Scale
 - Clinical Dementia Rating Scale (CDR)
 - Hachinski Ischemic Score
- Phase II
 - Brain CT or MRI
 - Dementia Labs

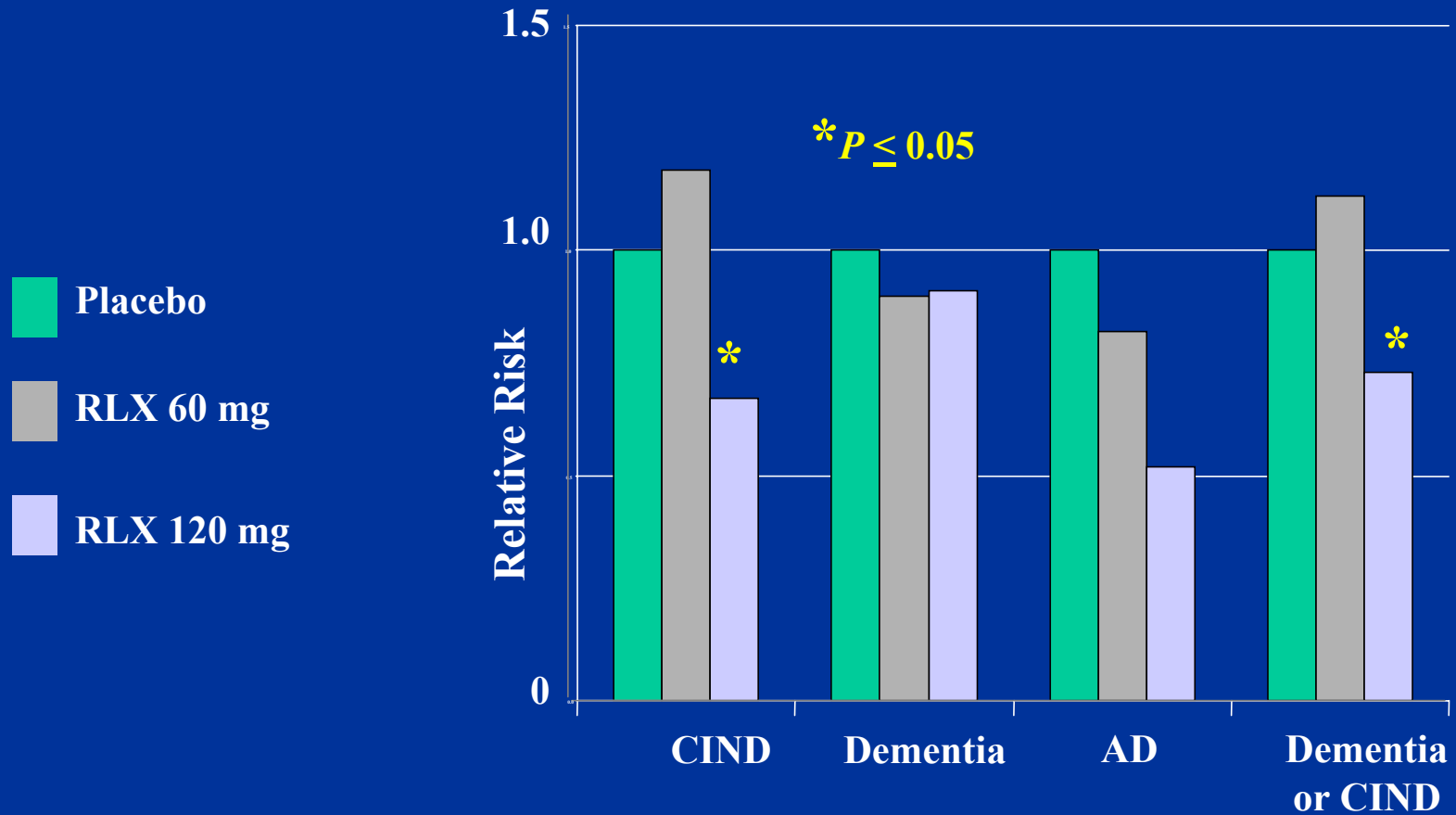
Raloxifene Dementia Study (cont)

- All results from Phases I and II sent to Dementia Adjudication Committee
- Committee members blind to treatment group
- Committee used standard criteria for diagnosis
 - Dementia (DSM IV)
 - AD (NINCDS)
 - Cognitive Impairment not Dementia (CIND)..similar to MCI but not based solely on verbal memory but CDR 0.5

DDE Flow



Risk of CIND and Dementia



Raloxifene and Dementia: Summary

- After 4 years of a randomized trial:
- No effect on risk of dementia or CIND for women taking RLX 60 mg/day
- For women taking RLX 120 mg/day
 - 33% lower risk of developing CIND (p=0.04)
 - 48% lower risk of developing AD (p=0.12)
 - 37% lower risk of developing any cognitive impairment (Dementia plus CIND) (p=0.05)

Lasofoxifene Trial: Prelim Results

- Next generation SERM
- Two phase III trials of lasofoxifene for osteoporosis treatment (doses 0.025-0.5mg)...recently ended.
- Cognitive battery at baseline, annually for 2 years on 267 women.
- Prelim results indicate no benefit or harm on cognitive outcomes.

Other Trials Underway

- Trials of aromatase inhibitors
- Trials of other SERMs
 - Large RCT of arzoxifene and dementia outcome
- Co-STAR: comparing tamoxifen & raloxifene
 - RCT of 1800 women in STAR trial
 - Cognitive testing annually
 - Currently 1000 enrolled

SERMs: Conclusions & Future Directions

- RLX results compatible with hypothesis that SERMs may prevent cognitive impairment but preliminary.....
- Need trials of RLX 120 for women at risk eg. older age or MCI.
- Need trials for other SERMs with cognitive outcomes.
- Premature to prescribe to women for prevention of AD or other cognitive impairment.