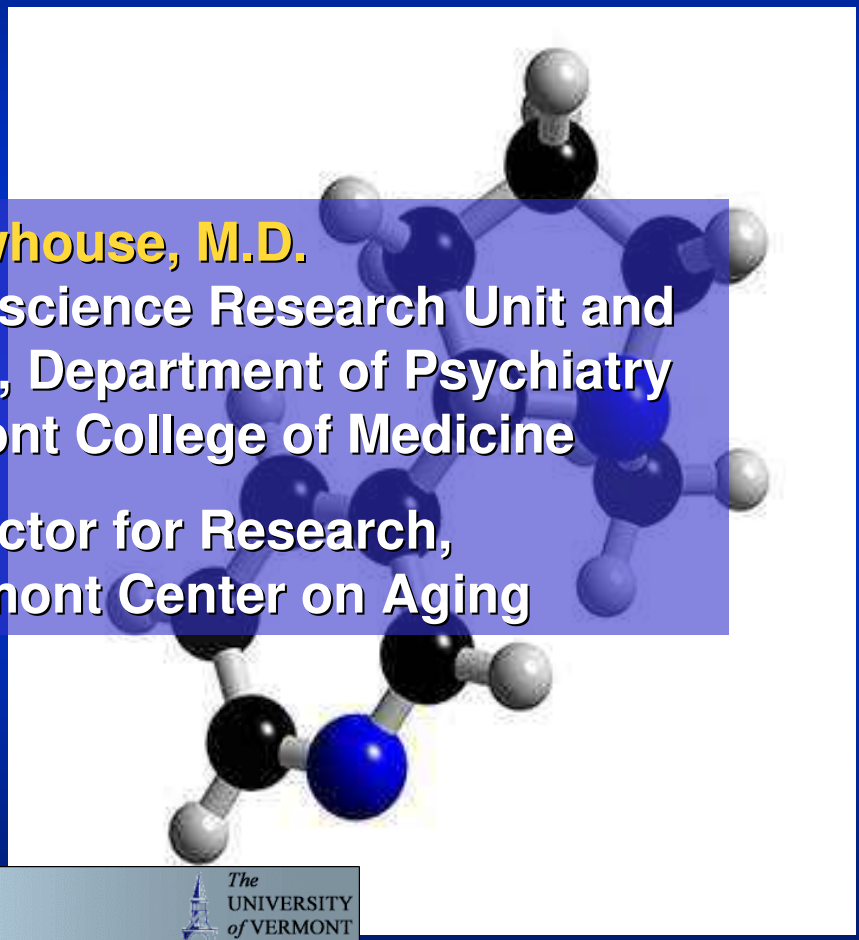
# Transdermal Nicotine Treatment of Mild Cognitive Impairment (MCI)

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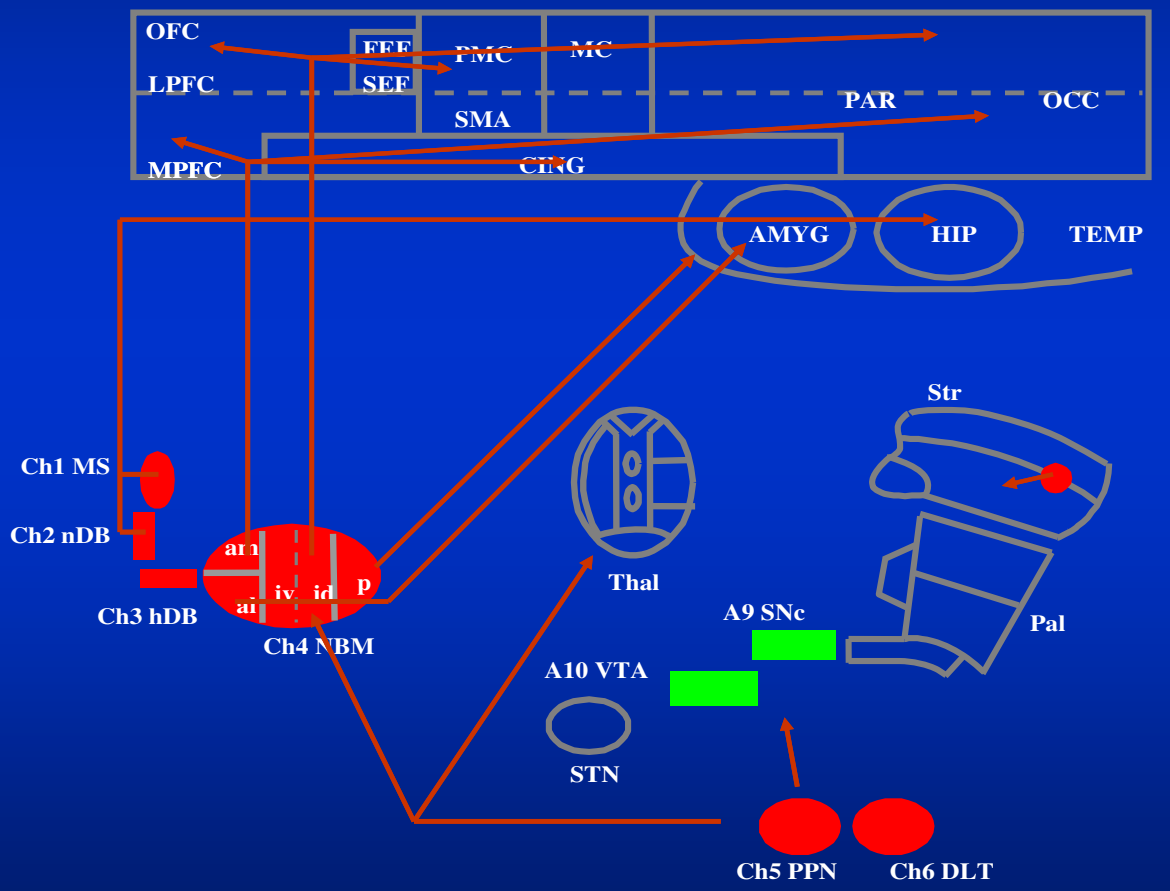
University of Vermont College of Medicine

Associate Director for Research,
University of Vermont Center on Aging


# Cholinergic System and Cognition

The cortical cholinergic input system is a necessary neuronal system for the mediation of a wide range of attentional functions, ranging from sustained to selective and divided attention.

## Central Cholinergic Pathways

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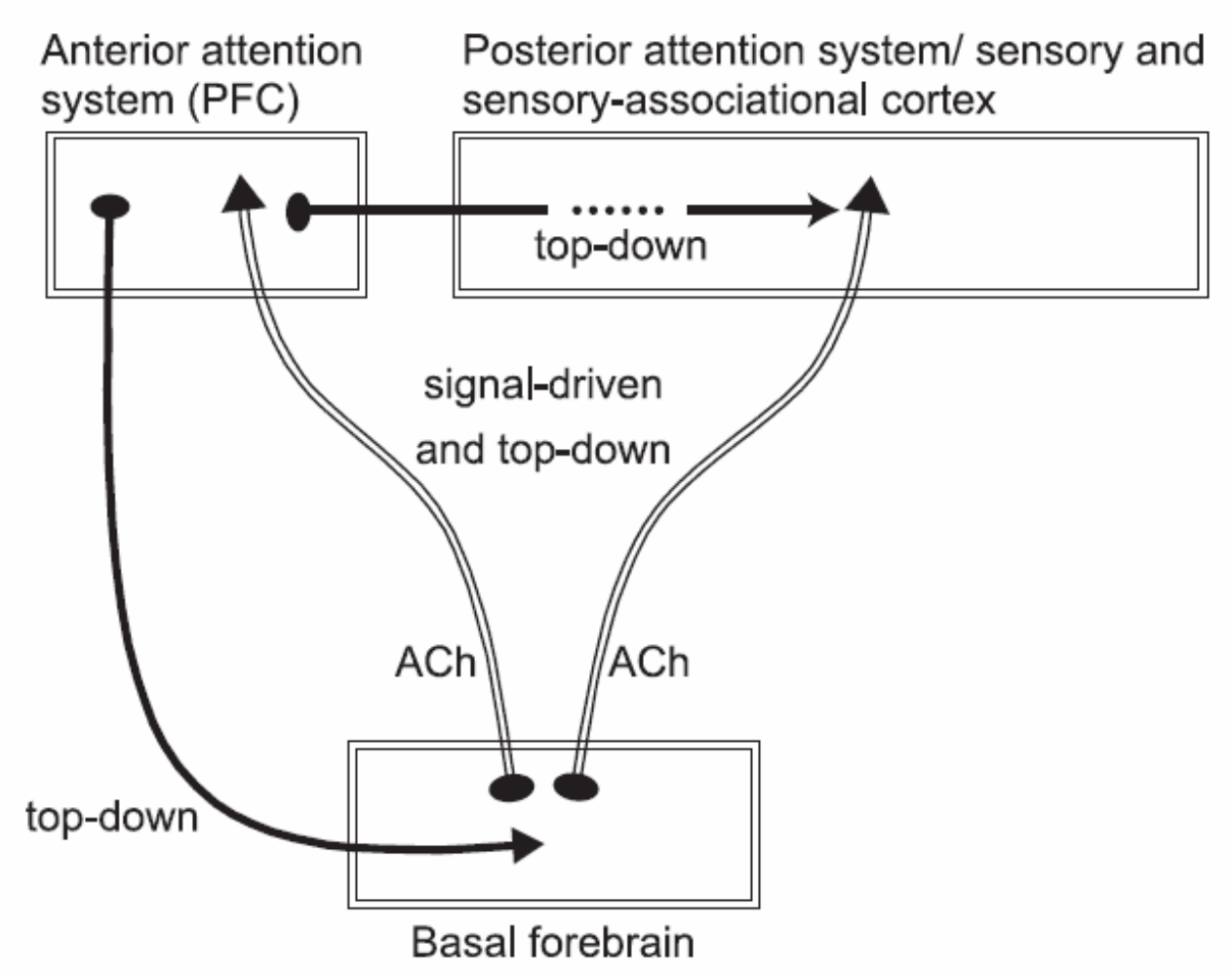
# Role of the Cholinergic System: Top-down and Bottom-up regulation of attentional functions

- Knowledge-based optimization of input processing and filtering; prefrontal efferent neuronal circuitry mediates top-down optimization of attentional functions *(top-down).*
- Modulates or biases stimulus-specific processing of sensory information in extrastriate cortical areas *(Signal Driven-bottom-up)*.
- Hippocampal and frontal memory-specific regions activated, especially in initial encoding.
- Cholinergic system activation affects performance on resource demanding tasks that require the allocation of attention

# Cholinergic System and Attention: Top-down and Bottom-up




Schematic illustration of the components of the cholinergic modulation of input processing or signal detection

*Sarter et al, Brain Research Reviews 48 (2005) 98–111*

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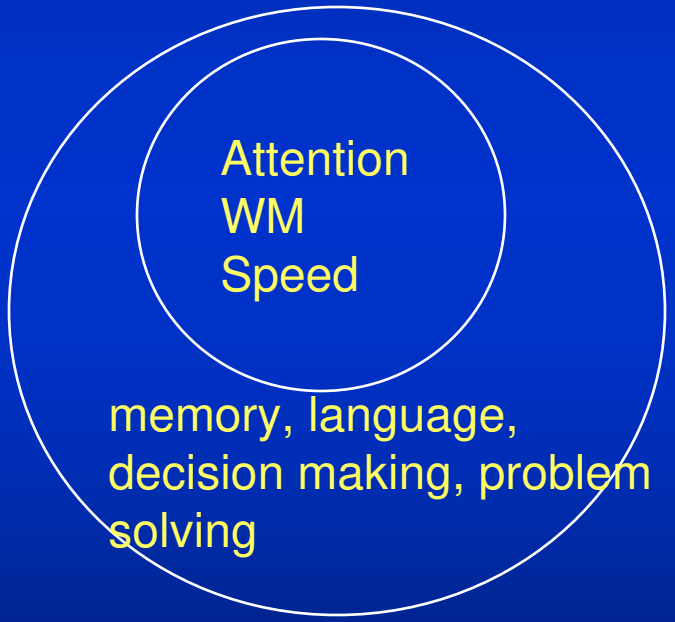
•Decline in the integrity, of the cortical cholinergic input system results in very robust and persistent impairments in attentional abilities, ranging from sustained to divided attention.

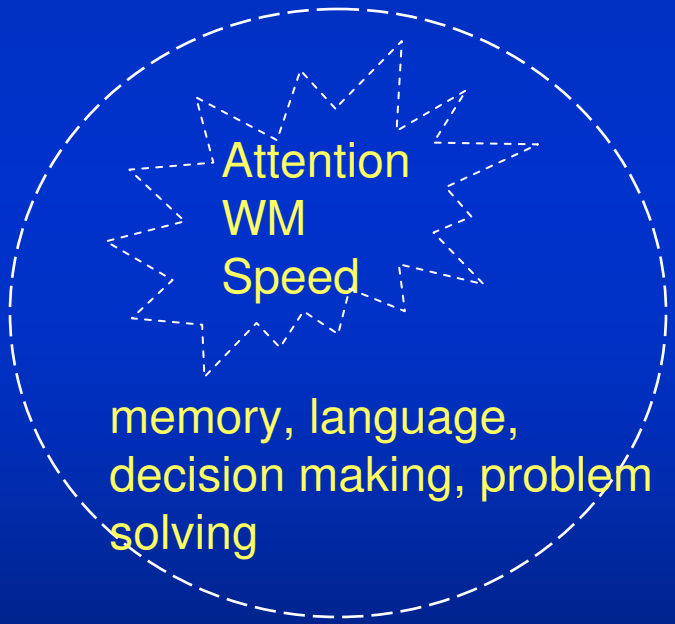
•Such declines will inevitably result in a broad variety of cognitive and behavioral impairments *including memory*.

# Cognitive Aging
## Resource Reduction Hypotheses

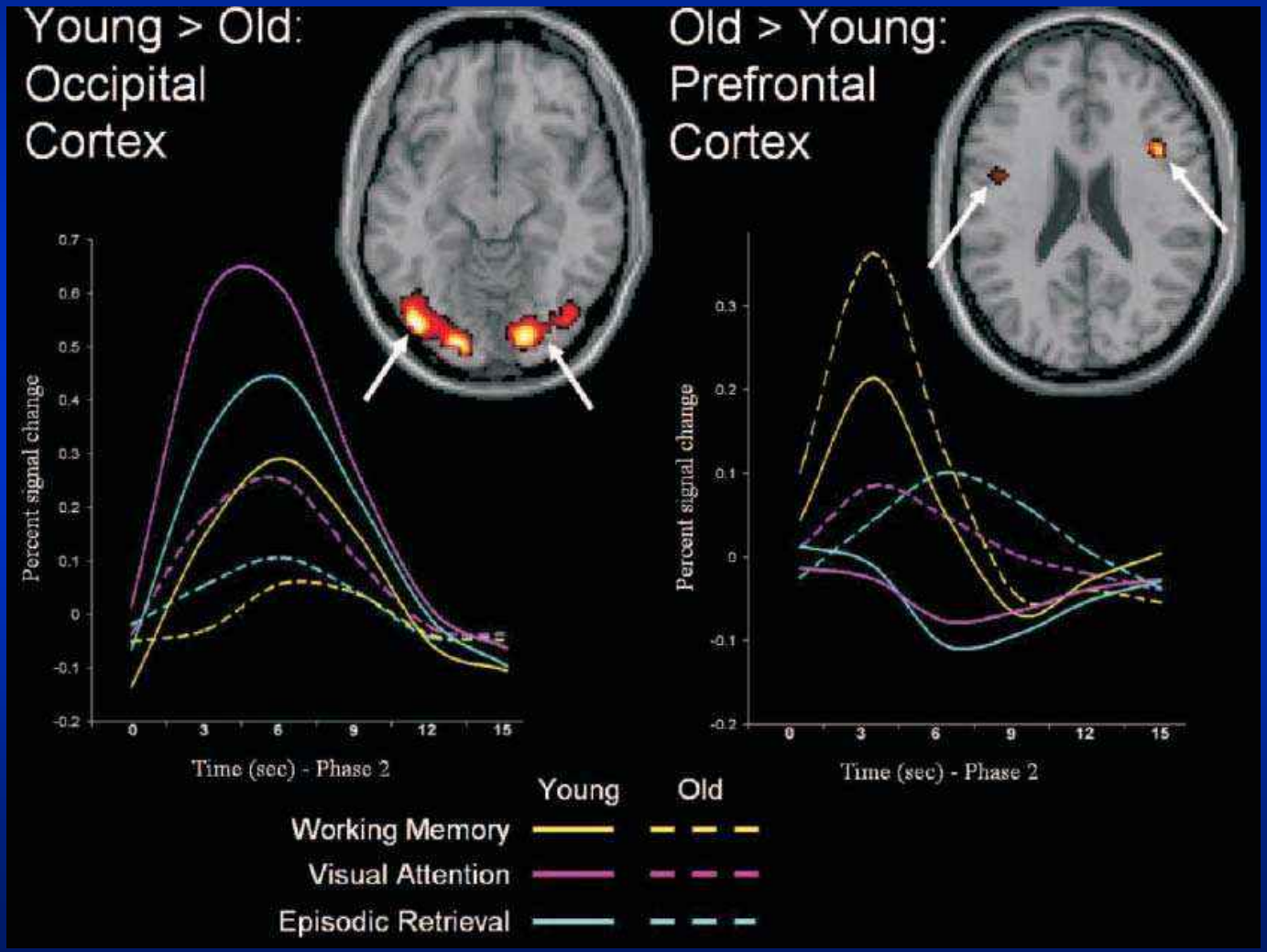
**Younger Adults**



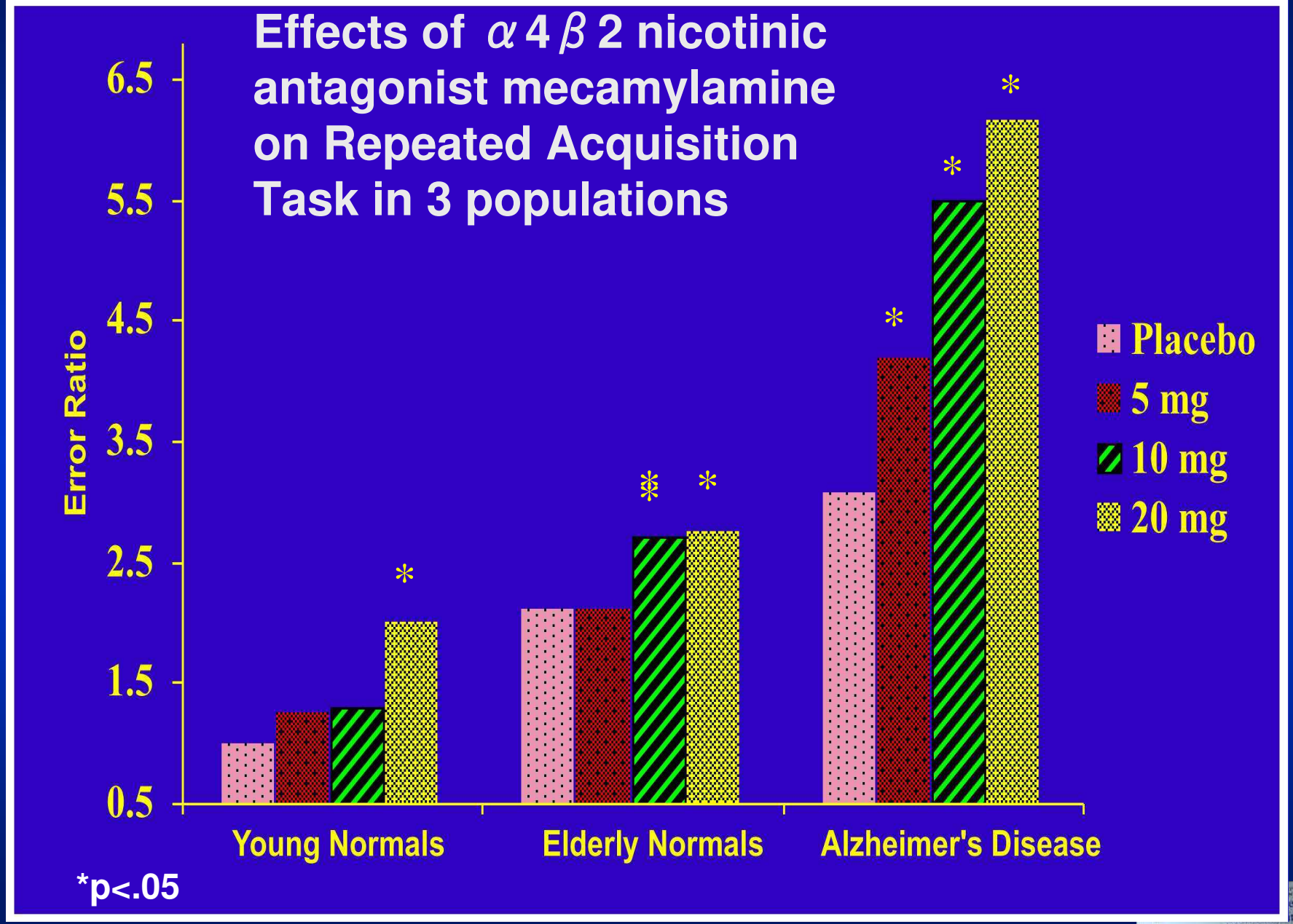

**Older Adults**



# Shift of activity from occipital to prefrontal with normal aging (PASA)

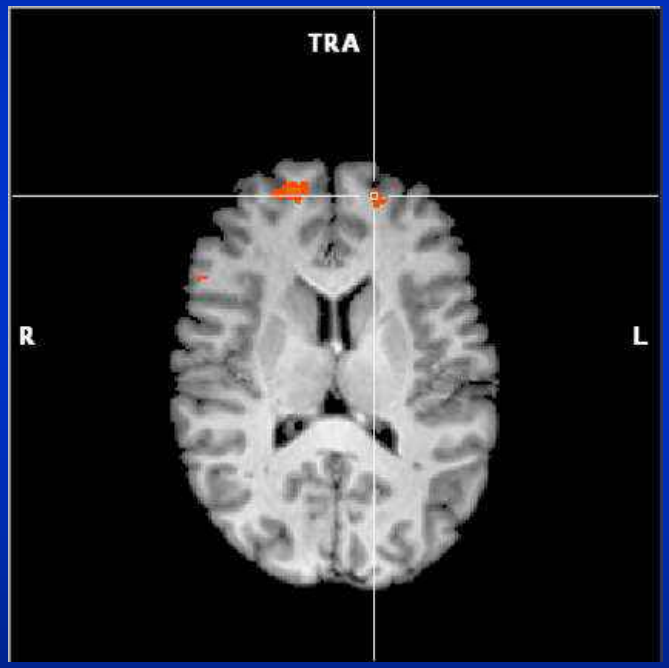


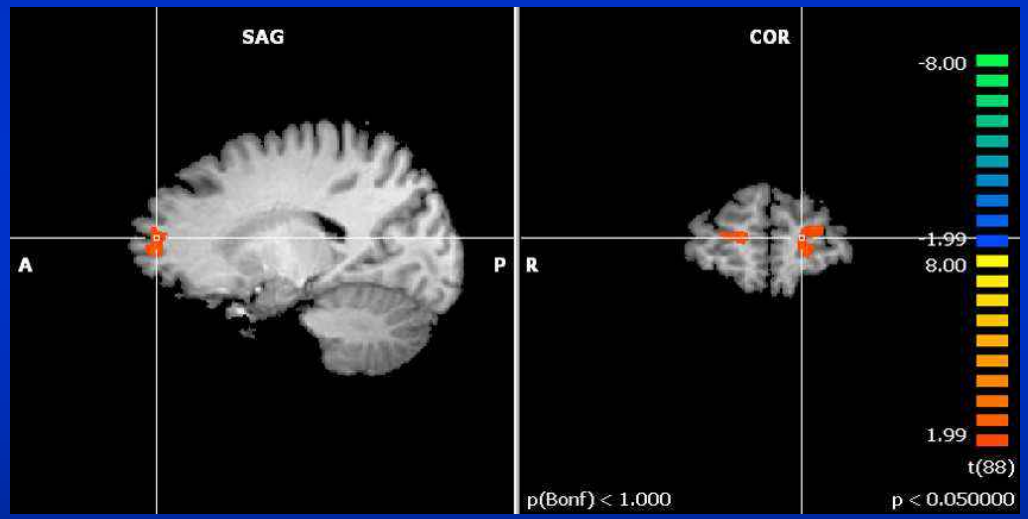

Cabeza et al. 2004




Newhouse et al, Biol Psych, 49: 268, 2001

# Nicotinic Blockade with Mecamylamine Increases Frontal Cortical Activity Associated with Working Memory Processing




Dumas and Newhouse, 2010

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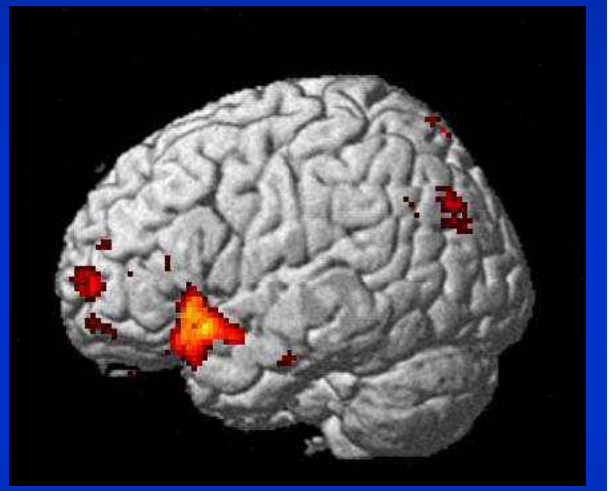
# MCI vs Muscarinic and Nicotinic Blockade on Working Memory

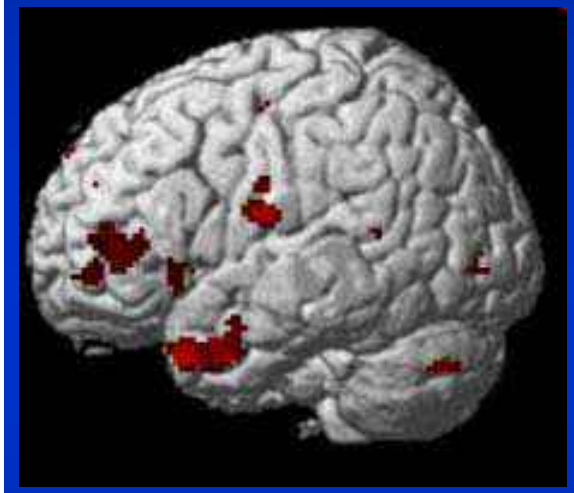
MCI < Control



Group Difference, 2>0, *p<.01*

*Saykin et al, 2006*

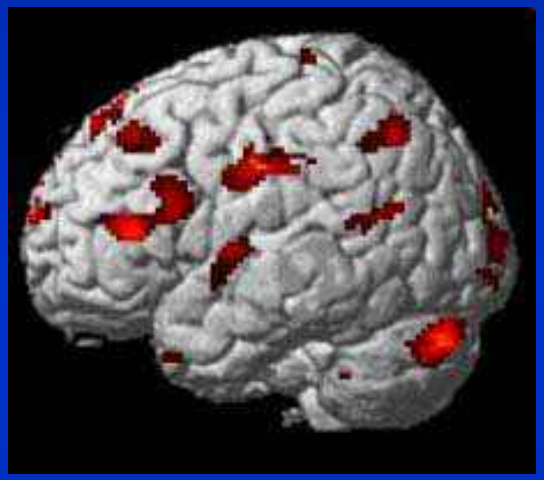
Anti-Muscarinic



(2.5 $\mu$ g/kg, IV) scopolamine vs. placebo, *p <.05*

*Dumas et al., 2008*

Anti-Nicotinic



(20 mg, oral) Mecamylamine vs. placebo, *p <.05*

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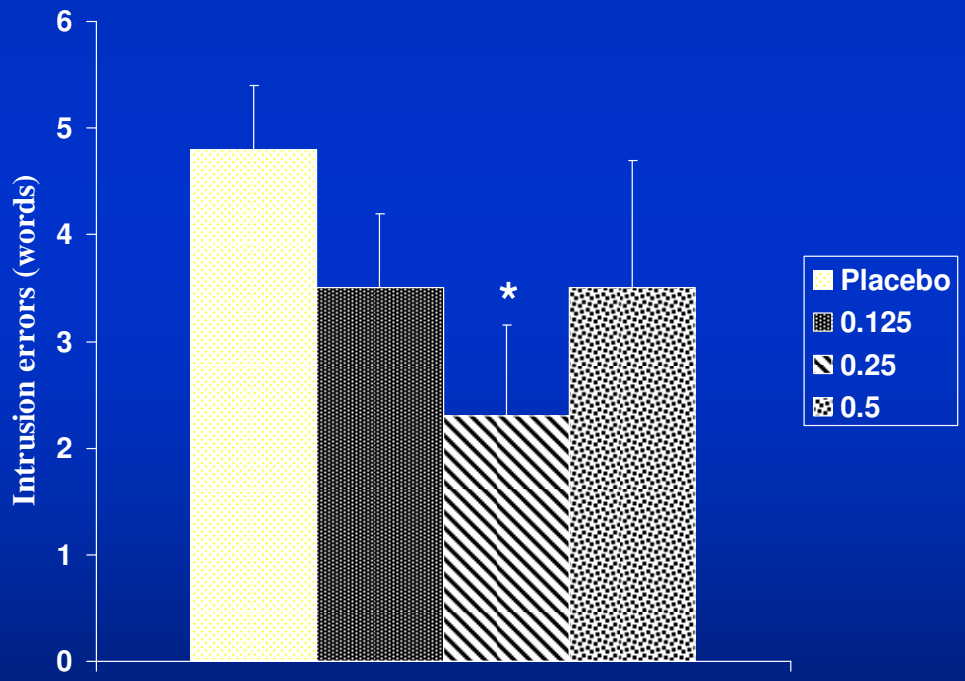
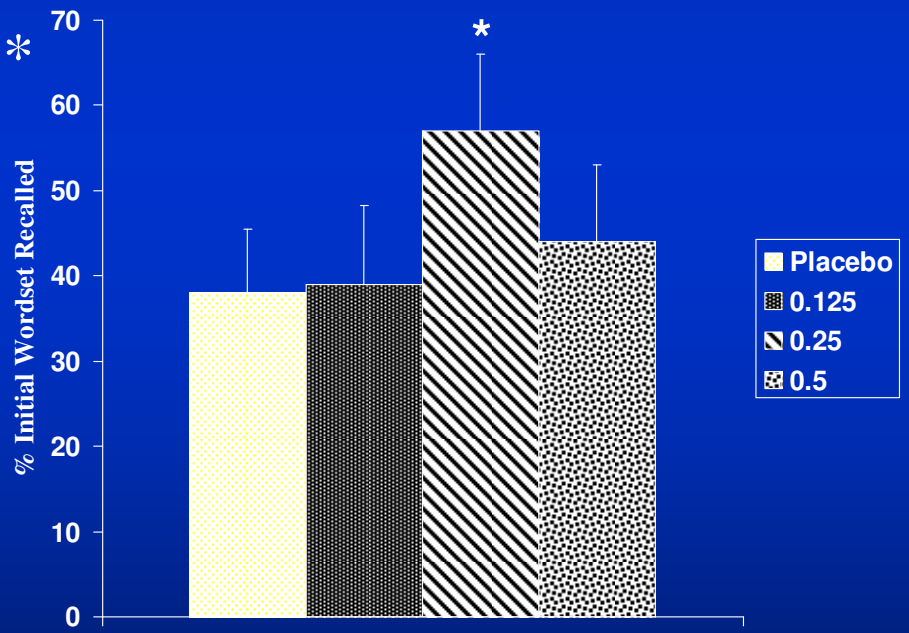
# Treatment of Alzheimer's Disease

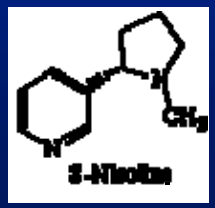
## IV Nicotine Effects on Verbal Memory

### Errors




### Long-Term Recall




* p<.05

**Dose (μg/kg/min)**

Newhouse et al, 1988

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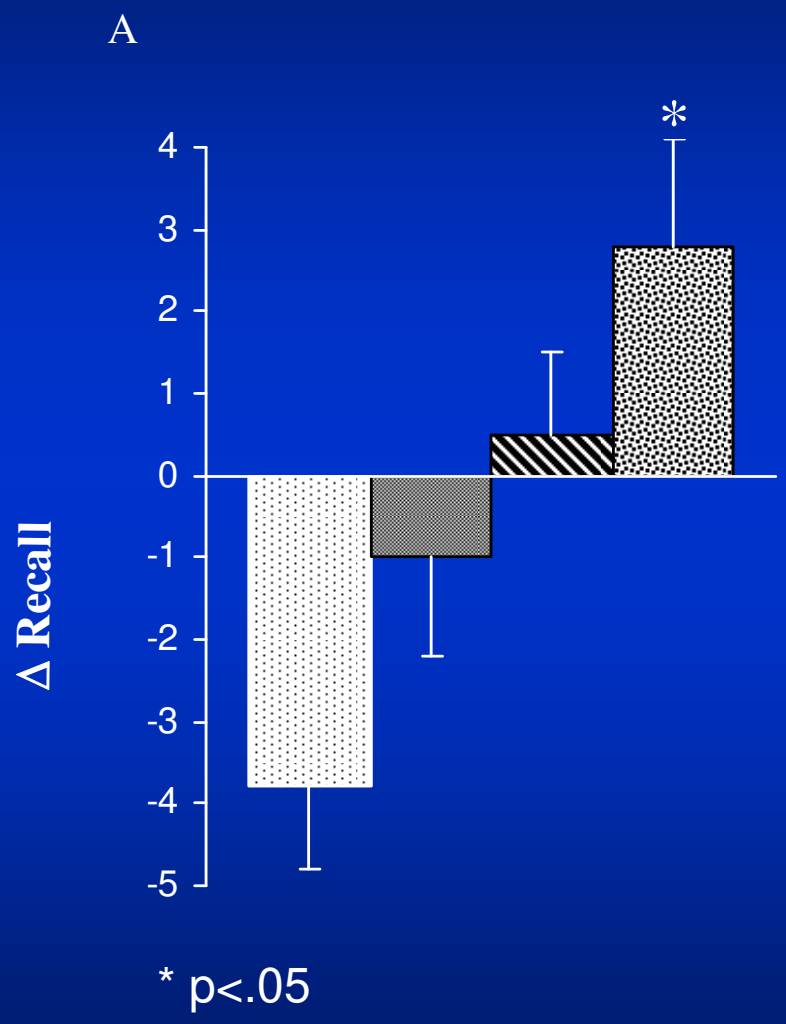
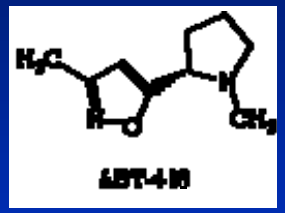
# Single Dose α4β2 Agonist (ABT-418) in AD

## Effects on Verbal Learning: SRT







Placebo | 6 mg | 12 mg | 23 mg

Adapted from Newhouse et al., 2001

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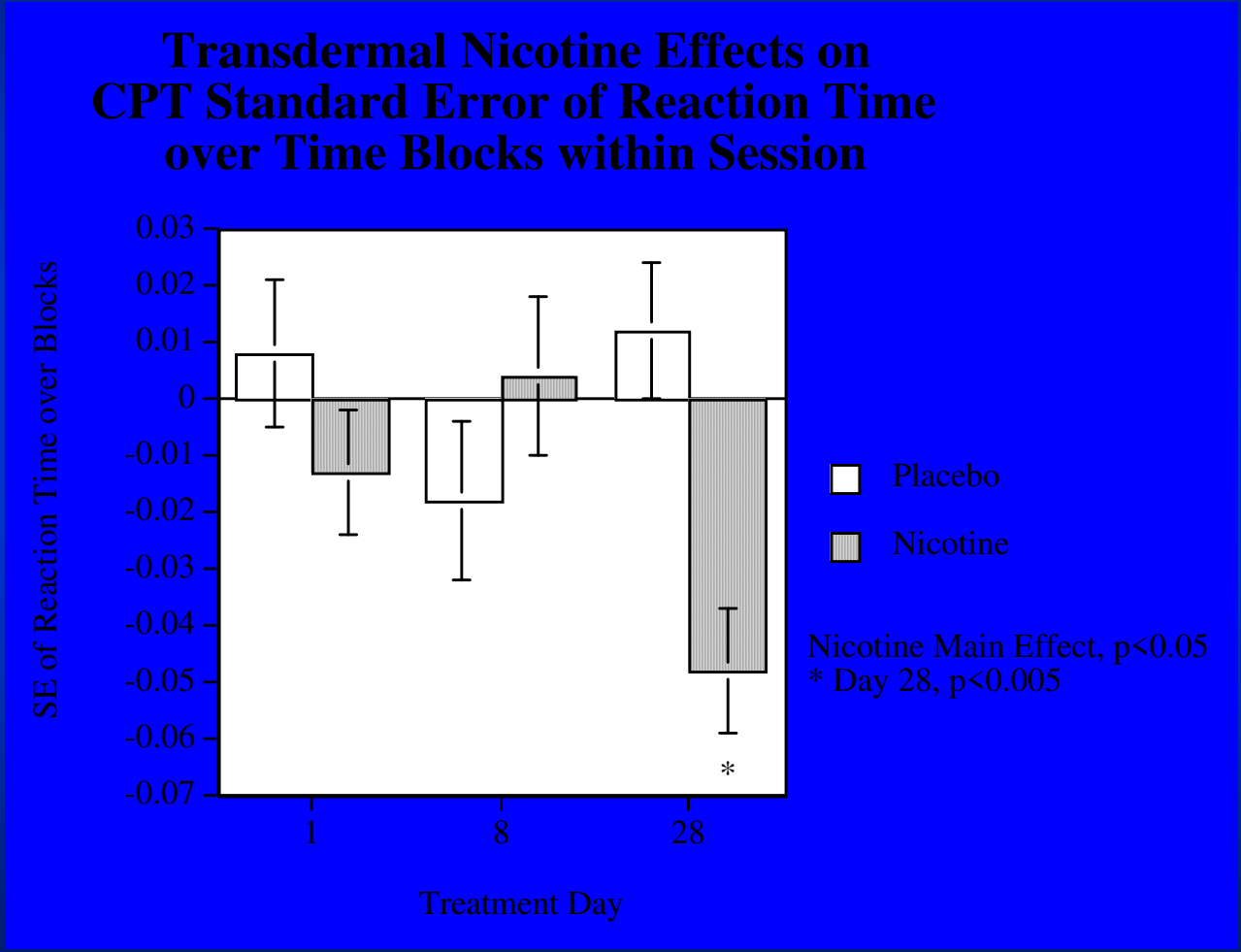
# Nicotine Effects in AAMI: One Month Transdermal Treatment




**White and Levin 2003**

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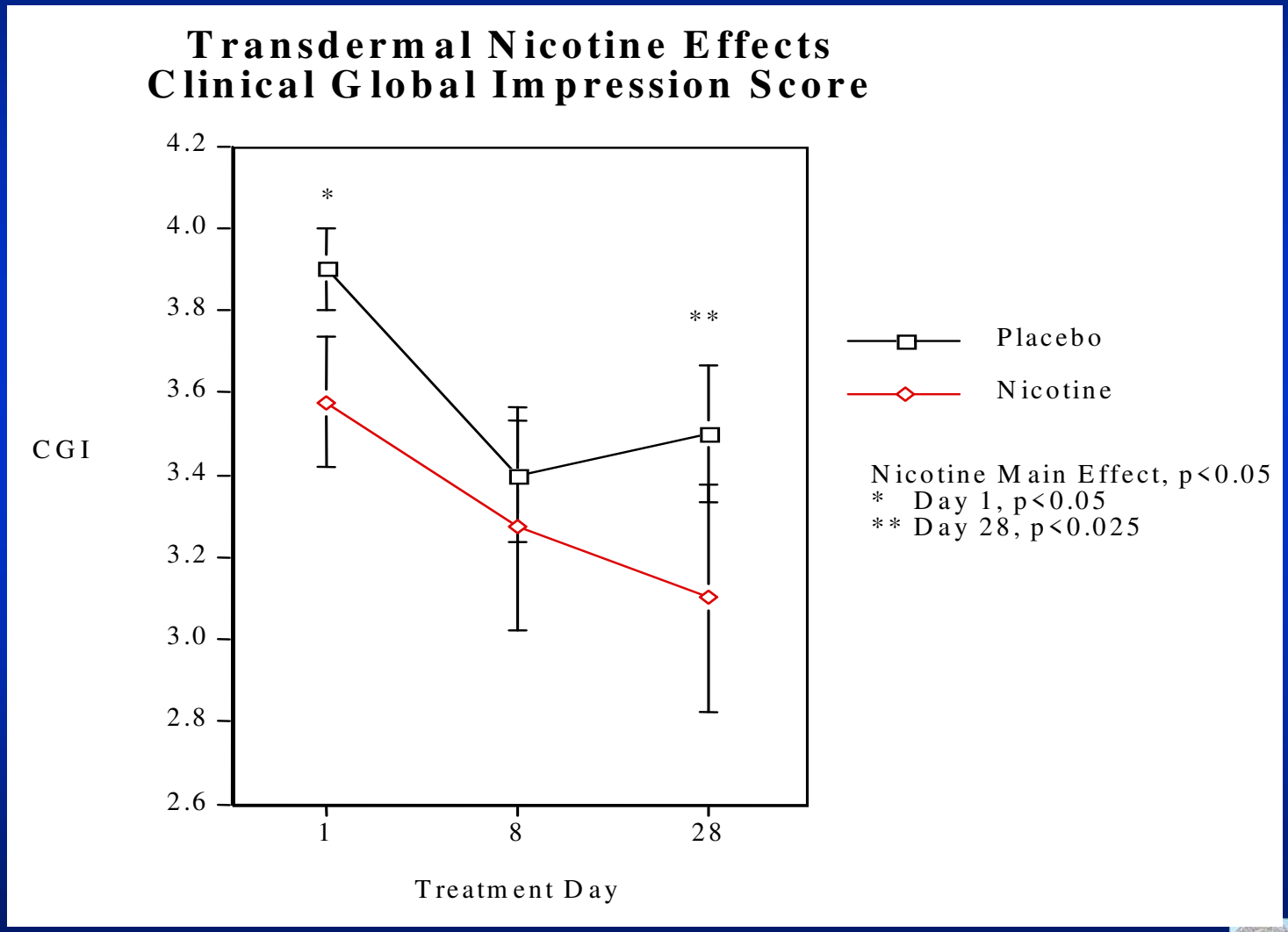
# Nicotine Effects in AAMI: One Month Transdermal Treatment




White and Levin 2003

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# Multicenter Pilot Trial of Transdermal Nicotine for Symptomatic Improvement in MCI

**Goals/Hypotheses:**

- **To examine whether transdermal nicotine is safe and tolerable over extended periods in non-smokers**
- **To examine whether transdermal nicotine produces cognitive symptomatic improvement in amnestic MCI subjects**


- **Funded by National Institute on Aging (R01 AG022462)**


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# Transdermal Nicotine Treatment of MCI Pilot Study

Subjects:

- 74 nonsmoking subjects at with amnestic MCI at 3 sites.
- University of Vermont (coordinating site), Duke University, Georgetown University

Diagnostic Criteria for Amnestic MCI (ADCS):

- Memory complaints/difficulties verified by an informant.
- Abnormal memory function documented by scoring below the education adjusted cutoff on the Delayed Paragraph Recall from the Wechsler Memory Scale.
- Mini-Mental State Exam score from 24 to 30.
- Clinical Dementia Rating of 0.5; memory box score of 0.5 or 1.0.
- Does not meet criteria for Alzheimer's Disease.
- No significant cerebrovascular disease: Modified Hachinski score of less than or equal to 4.

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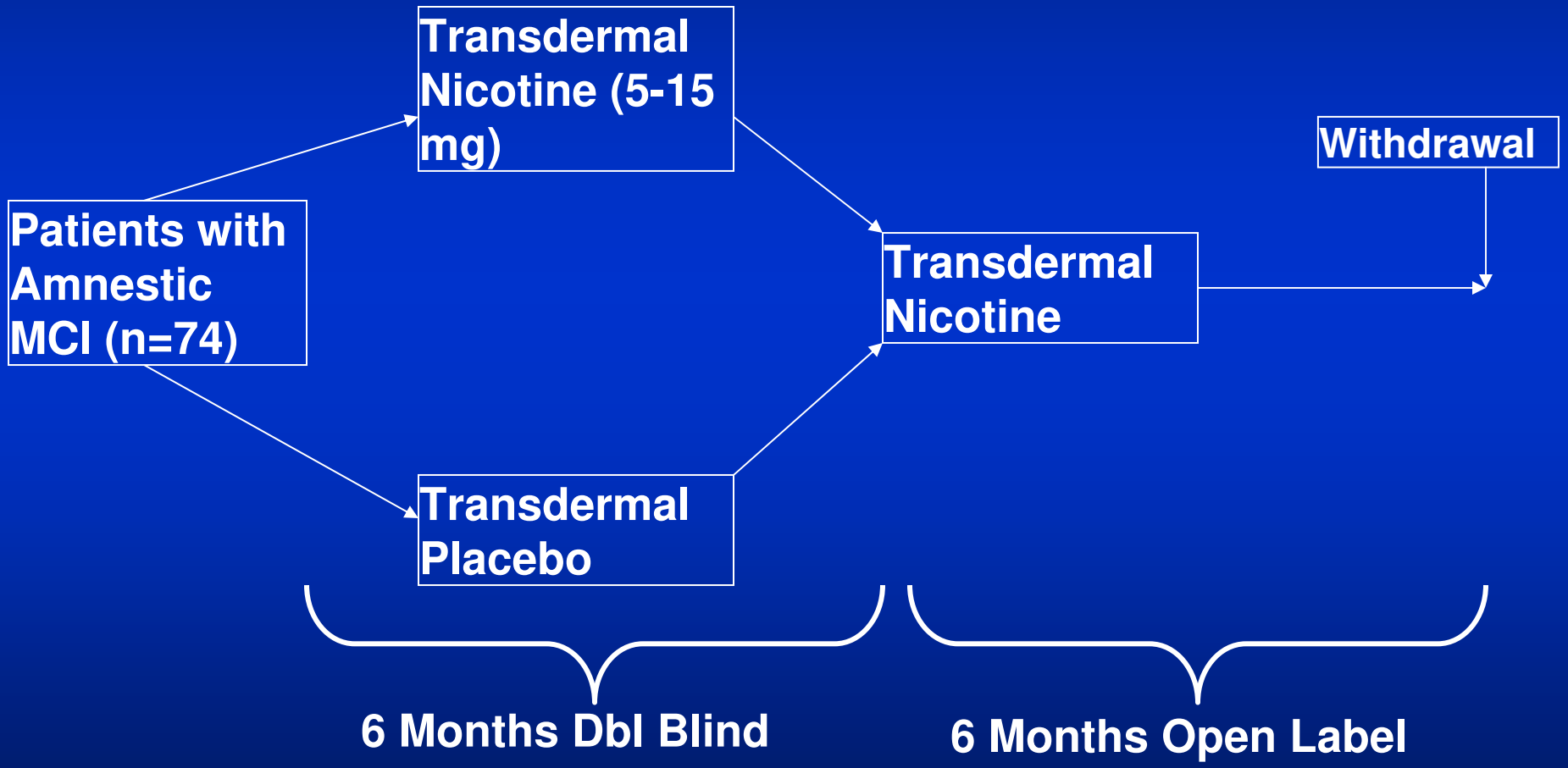
# Transdermal Nicotine for MCI: Study Plan

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# Nicotine MCI Trial: Demographics

| | Nicotine (N=39) | Placebo (N=35) |
|---|---|---|
| **Demographics** | | |
| Gender | | |
| Male (N=45) | 25 (64%) | 20 (57%) |
| Female (N=29) | 14 (36%) | 15 (43%) |
| Age | 75.7 | 75.1 |
| Weight (kg) | 76.9 | 73.9 |
| Education (years) | 15.6 (2.9) | 16.2 (2.4) |
| **Genetics** | | |
| ApoE4 Genotypes (N=70) | | |
| ApoE4 present (N=30) | 14 (38%) | 18 (51%) |
| ApoE4 absent (N=40) | 23 (62%) | 17 (49%) |

Data are mean (SD) or numbers (%). No significant differences on measures between treatment groups.

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# Nicotine MCI Trial:

## *Baseline Cognitive/Behavioral Assessment*

| | Nicotine (N=39) | Placebo (N=35) |
|---|---|---|
| **Psychological assessment** | | |
| CDR | 0.5 | 0.5 |
| Sum of boxes | 1.4 (0.7) | 1.5 (0.8) |
| DRS | 132 (7.6)* | 133 (7.6)† |
| GDS | 2 (0.2) | 2 (0.2) |
| HAM-D Total | 2.7 (2.5) | 3.7 (3.6) |
| MMSE | 27.4 (1.9) | 27.6 (2.1) |
| Hachinski | 0.92 (1.1) | 0.85 (1.0)* |
| MNA | 13.2 (1.2) | 13.2 (1.1) |
| WMS | | |
| Immediate | 7.4 (3.6) | 7.6 (3.8) |
| Delayed | 4.4 (3.2) | 5.0 (3.7) |
| WTAR Standard | 112 (11) | 113 (13) |
| Predicted | 108 (8.1) | 110 (6.9) |
| WAIS | | |
| Verbal | 112 (9.5) | 114 (11) |
| Performance | 109 (7.5) | 111 (8.6) |
| Full Scale | 112 (9.4) | 114 (11) |

Data are mean (SD) or numbers (%). * Data missing for 1 patient. † Data missing for 2 patients. No significant differences on measures between treatment groups.

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# Outcome Measures

- Safety:
  - Adverse Events (AE's)
  - Vital Signs
  - Mini-Nutritional Assessment
  - Activities of Daily Living (ADL's)
  - Self and Informant Multi-Dimensional Assessments (OABCL and OASR)

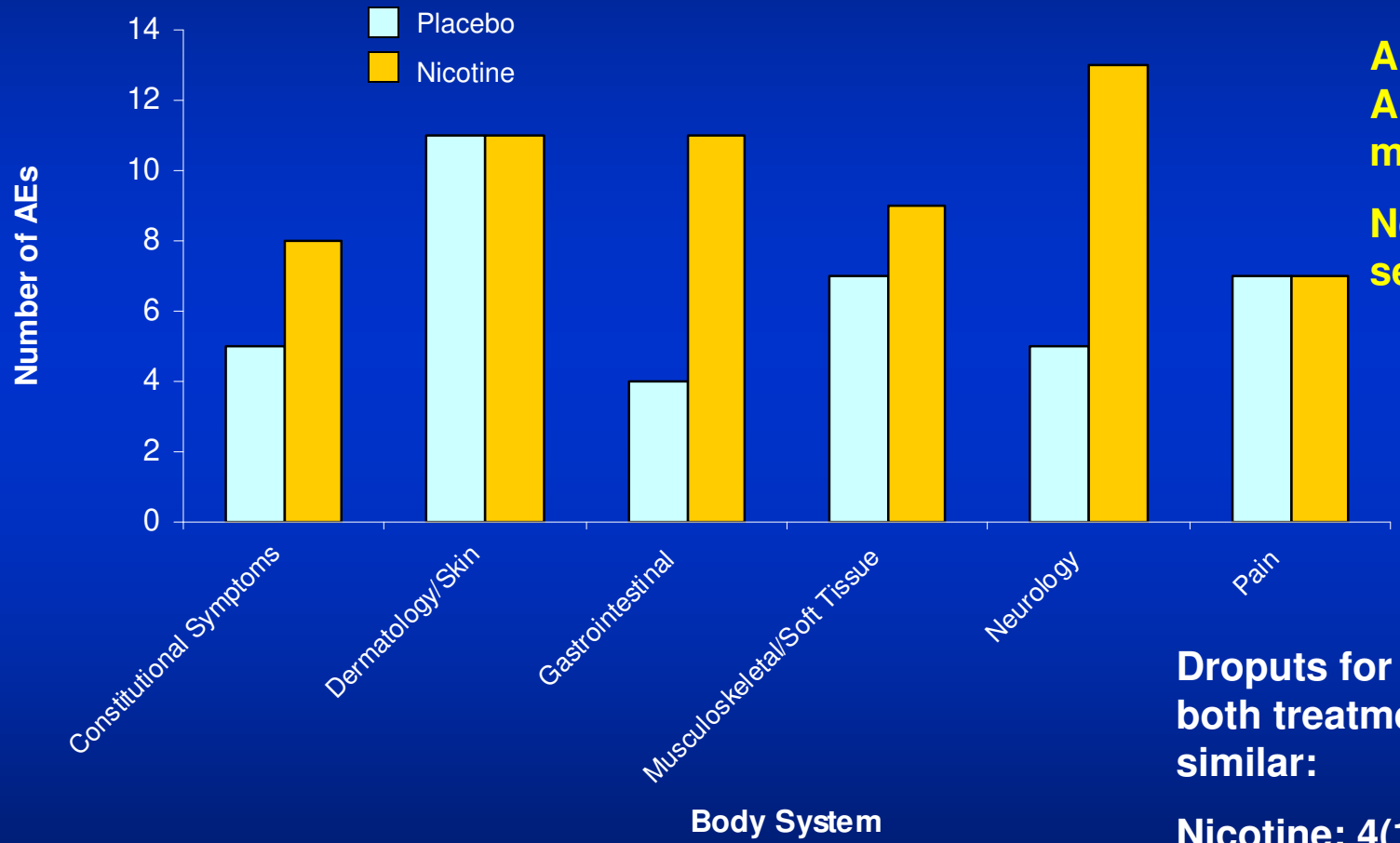
- Efficacy:
  - Clinical Global Impression of Change
  - Clinical Dementia Rating
  - Cognitive Testing:  Cognitive Drug Research (CDR) Battery; Paragraph recall; Continuous Performance Test, Digit-Symbol Substitution Task

# Results: Safety

- Double-Blind Phase:
  - Nicotine:
    - 39 Randomized
    - 35 Completed double blind phase
  - Placebo:
    - 35 Randomized
    - 33 Completed double-blind phase
- Open Label Phase:
  - 67 Entered
  - 54 Completed
  - No withdrawal symptoms reported

# Adverse Events by Body System: Double Blind Phase

Adverse events reported by greater than 10% of patients




**All drug-related AEs were mild-mod**

**No drug-related serious AE's**

**Droputs for AEs for both treatments were similar:**

**Nicotine: 4(10%);**

**PLC: 2 (6%).**

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# Nicotine MCI Trial: Adverse Events by Body System

Adverse events reported by greater than 10% of patients

| | Double-Blind Phase | | |
|---|---|---|---|
| **Body System** | **Placebo** | **Nicotine** | **Open-Label Nicotine** |
| Constitutional Symptoms | 5 | 8 | 11 |
| Dermatology/Skin | 11 | 11 | 22 |
| Itching | 1 | 4 | 11 |
| Rash | 2 | 2 | 3 |
| Gastrointestinal | 4 | 11 | 8 |
| Constipation | 0 | 2 | 0 |
| Diarrhea | 2 | 2 | 0 |
| Gas | 1 | 0 | 1 |
| Nausea | 0 | 3 | 1 |
| Vomiting | 1 | 1 | 0 |
| Pain | 0 | 1 | 0 |
| Musculoskeletal/Soft Tissue | 7 | 9 | 7 |
| Neurology | 5 | 13 | 19 |
| Headache | 3 | 1 | 3 |
| Dizziness | 0 | 4 | 3 |
| Anxiety | 0 | 1 | 0 |
| Agitation | 1 | 1 | 2 |
| Depression | 0 | 2 | 5 |
| Other | 1 | 4 | 5 |
| Pain | 7 | 7 | 9 |

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# Nicotine MCI Trial: Adverse Events by Body System

| | Double-Blind Phase | | |
|---|---|---|---|
| Body System | Placebo | Nicotine | Open-Label Nicotine |
| Allergy/Immunology | 1 | 0 | 0 |
| Auditory/Ear | 0 | 0 | 1 |
| Blood/bone marrow | 0 | 1 | 0 |
| Cardiac Arrhythmia | 1 | 0 | 0 |
| Cardiac General | 2 | 4 | 4 |
| Constitutional Symptoms | 5 | 8 | 11 |
| Dermatology/Skin | 11 | 11 | 22 |
| Itching | 1 | 4 | 11 |
| Rash | 2 | 2 | 3 |
| Gastrointestinal | 4 | 11 | 8 |
| Constipation | 0 | 2 | 0 |
| Diarrhea | 2 | 2 | 0 |
| Gas | 1 | 0 | 1 |
| Nausea | 0 | 3 | 1 |
| Vomiting | 1 | 1 | 0 |
| Pain | 0 | 1 | 0 |
| Hemorrhage/Bleeding | 2 | 1 | 0 |
| Infection | 1 | 0 | 0 |
| Lymphatics | 1 | 0 | 1 |
| Metabolic/Laboratory | 0 | 4 | 4 |
| Musculoskeletal/Soft Tissue | 7 | 9 | 7 |
| Neurology | 5 | 13 | 19 |
| Headache | 3 | 1 | 3 |
| Dizziness | 0 | 4 | 3 |
| Anxiety | 0 | 1 | 0 |
| Agitation | 1 | 1 | 2 |
| Depression | 0 | 2 | 5 |
| Other | 1 | 4 | 5 |
| Ocular/visual | 1 | 2 | 6 |
| Pain | 7 | 7 | 9 |
| Pulmonary/Upper Respiratory | 1 | 5 | 4 |
| Renal/GenitoUrinary | 1 | 3 | 4 |

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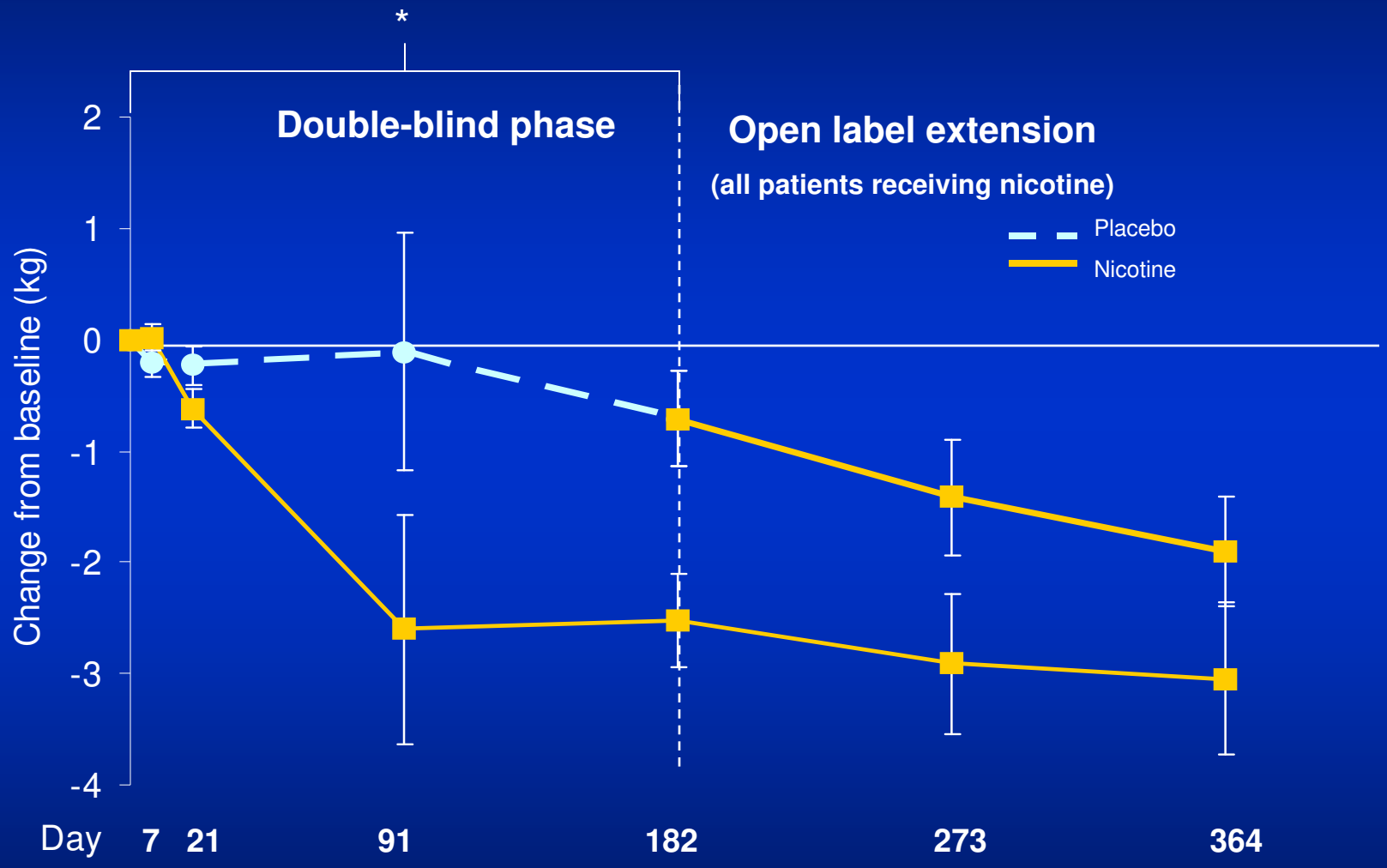
# Nicotine MCI Trial: Weight




* Main effect of treatment, F(1,71)= 5.72, *p*= 0.02

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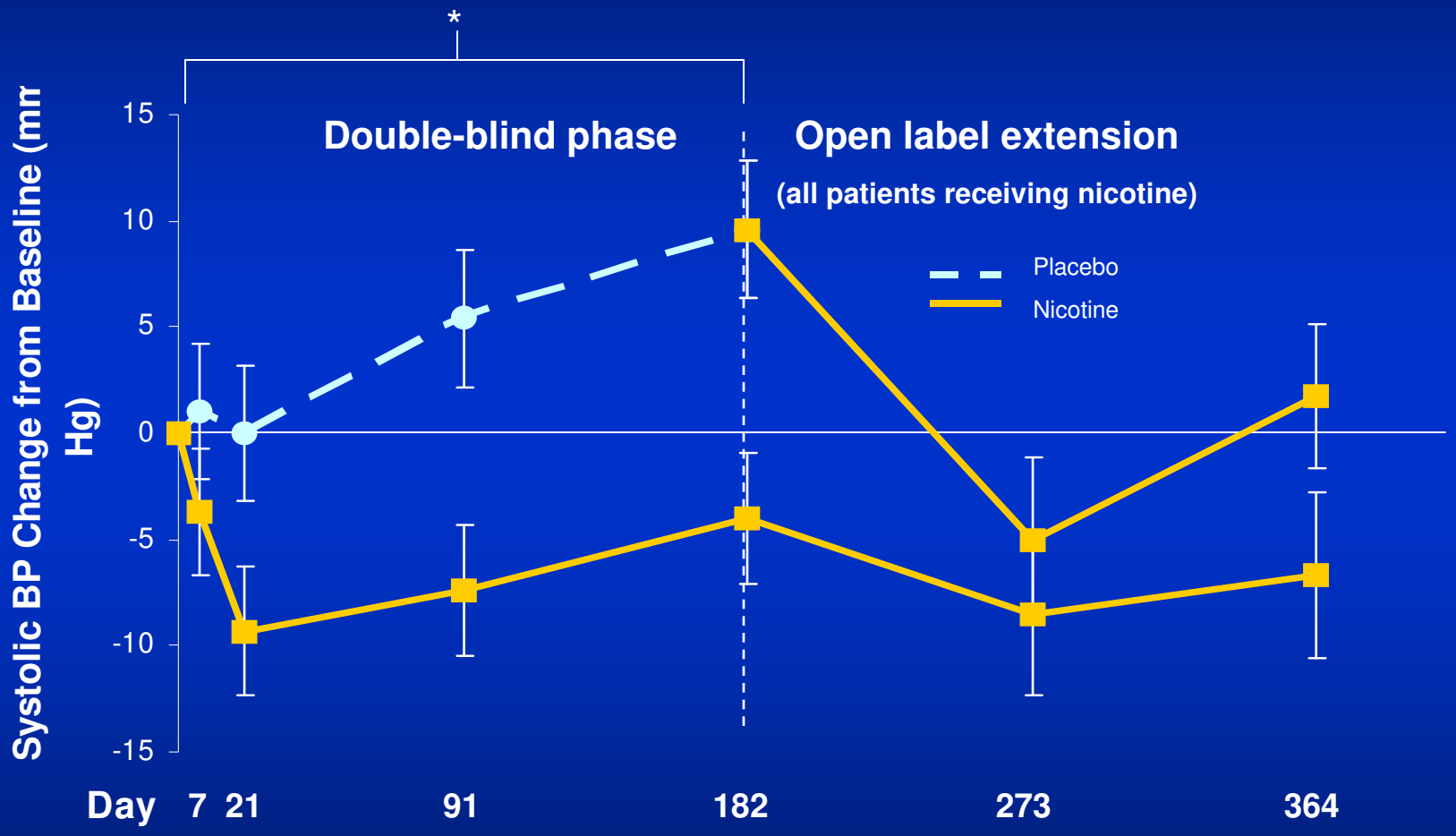
# Nicotine MCI Trial: Systolic Blood Pressure




* Main effect of treatment, F(1,71)= 9.01, *p*= 0.004

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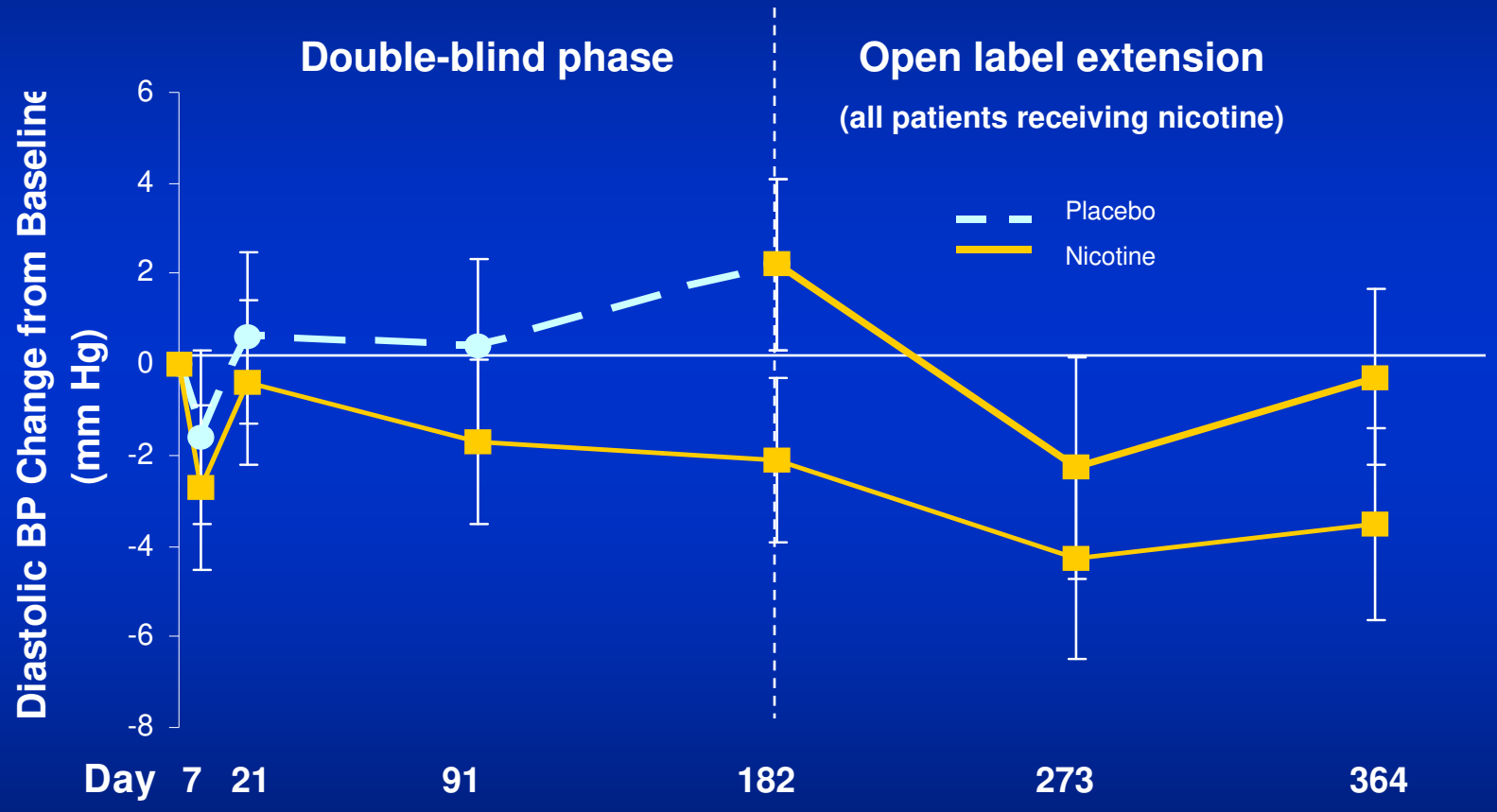
# Nicotine MCI Trial:
# Diastolic Blood Pressure

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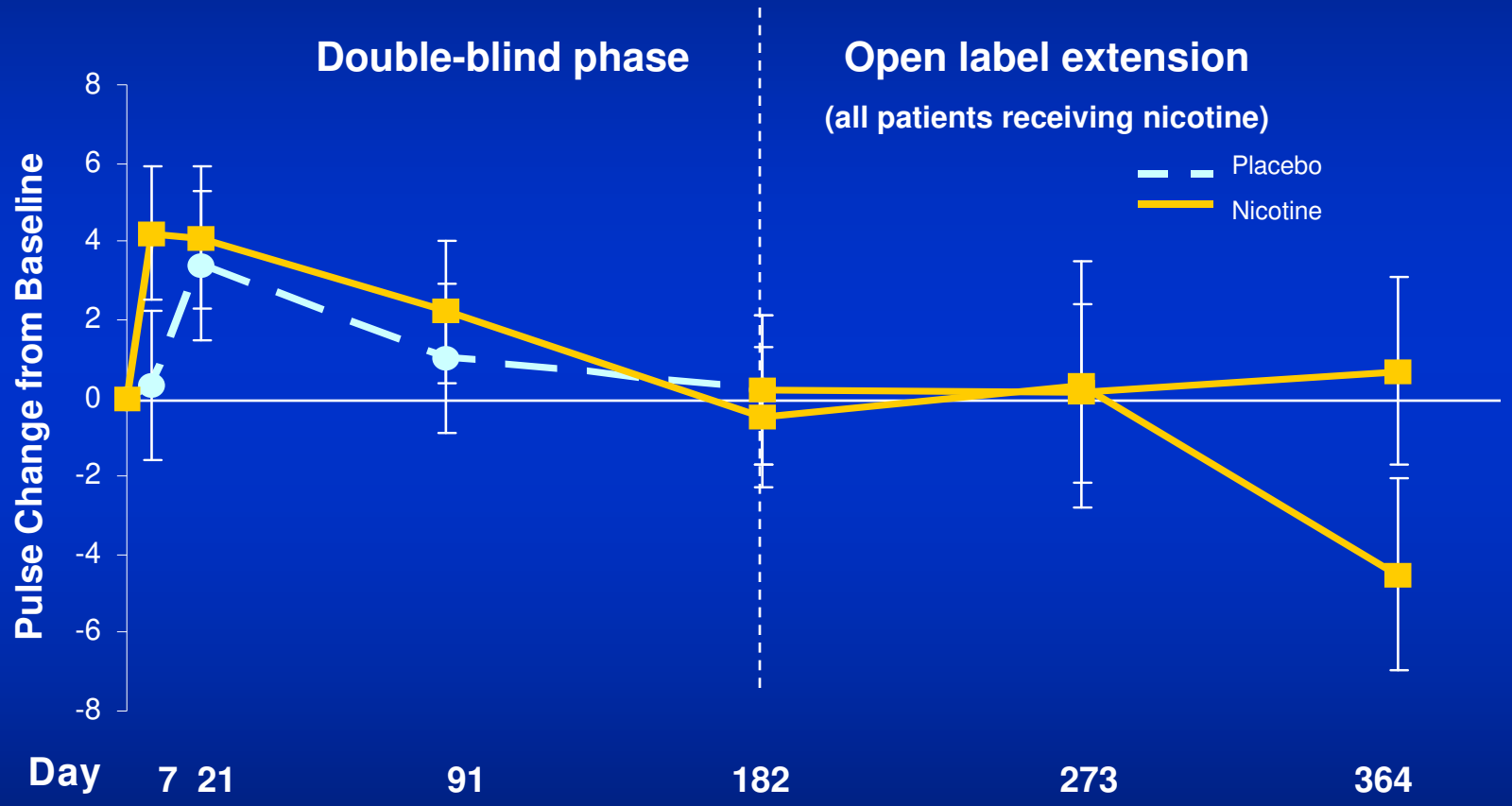
# Nicotine MCI Trial:
## Pulse




| | | |
|---|---|---|
| Nicotine | n = 34 | n = 29 |
| Placebo | n = 33 | n = 25 |

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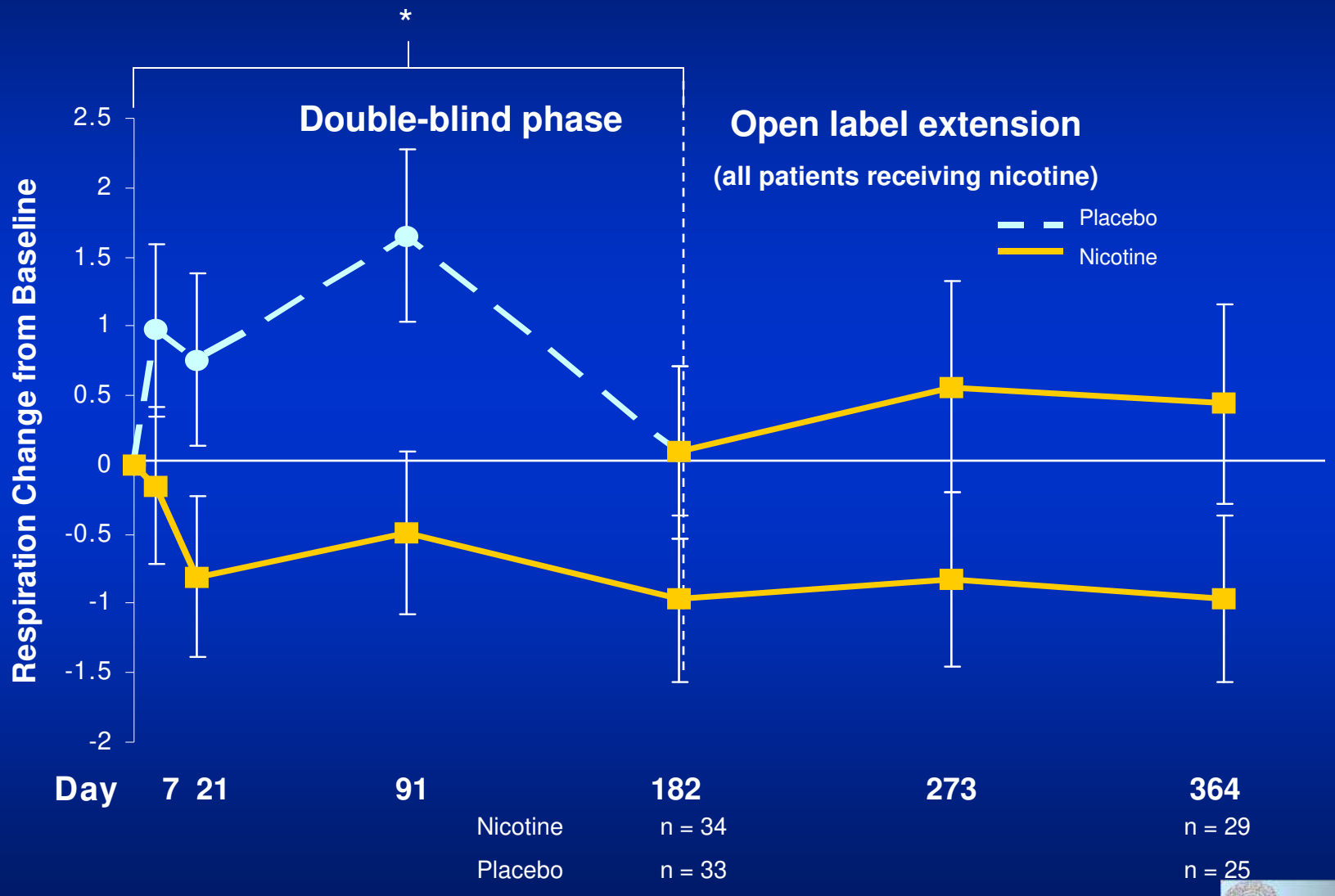
# Nicotine MCI Trial: Respiration




* Main effect of treatment, F(1,71)= 5.16, *p*= 0.03

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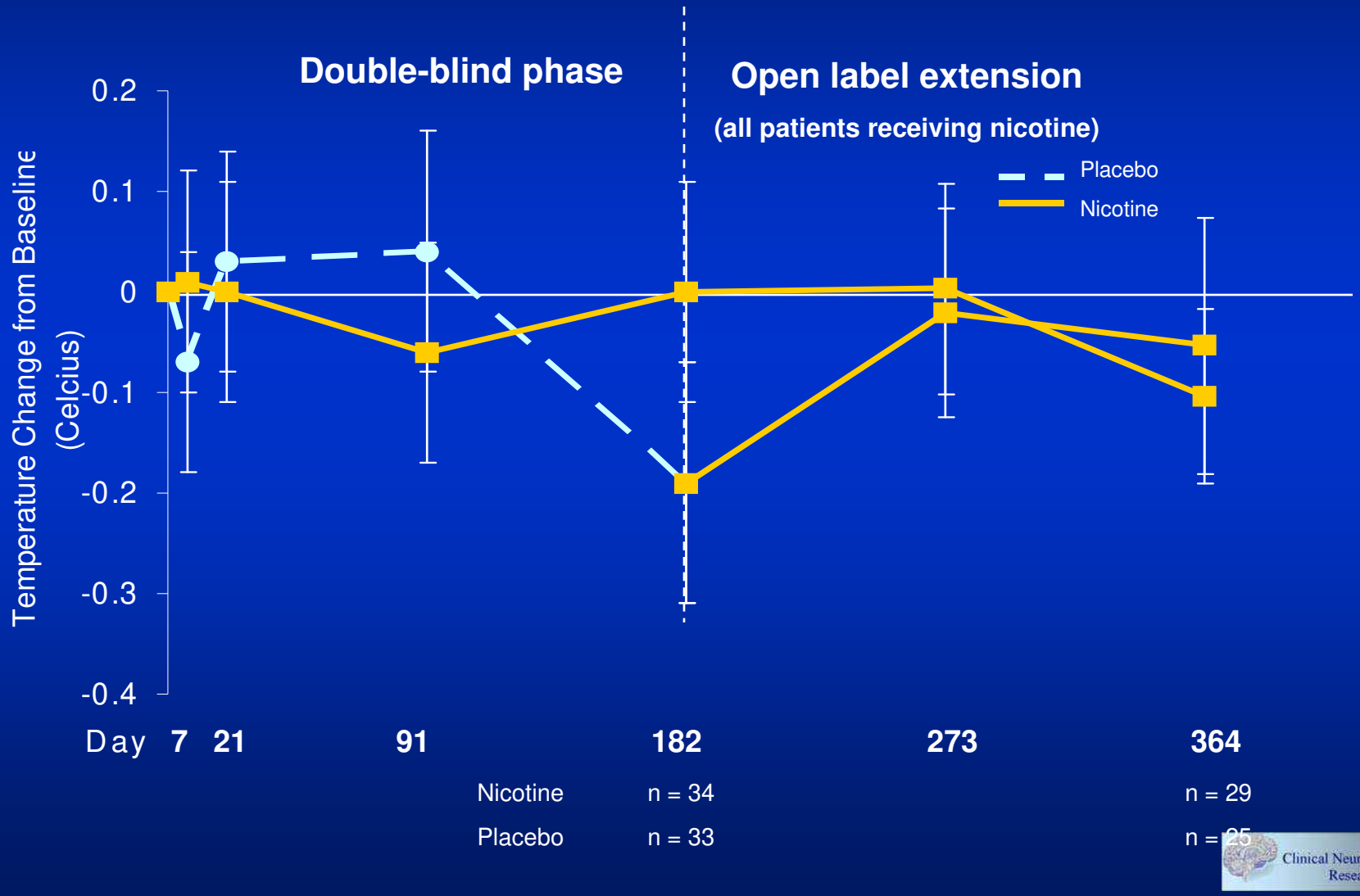
# Nicotine MCI Trial: Oral Temperature

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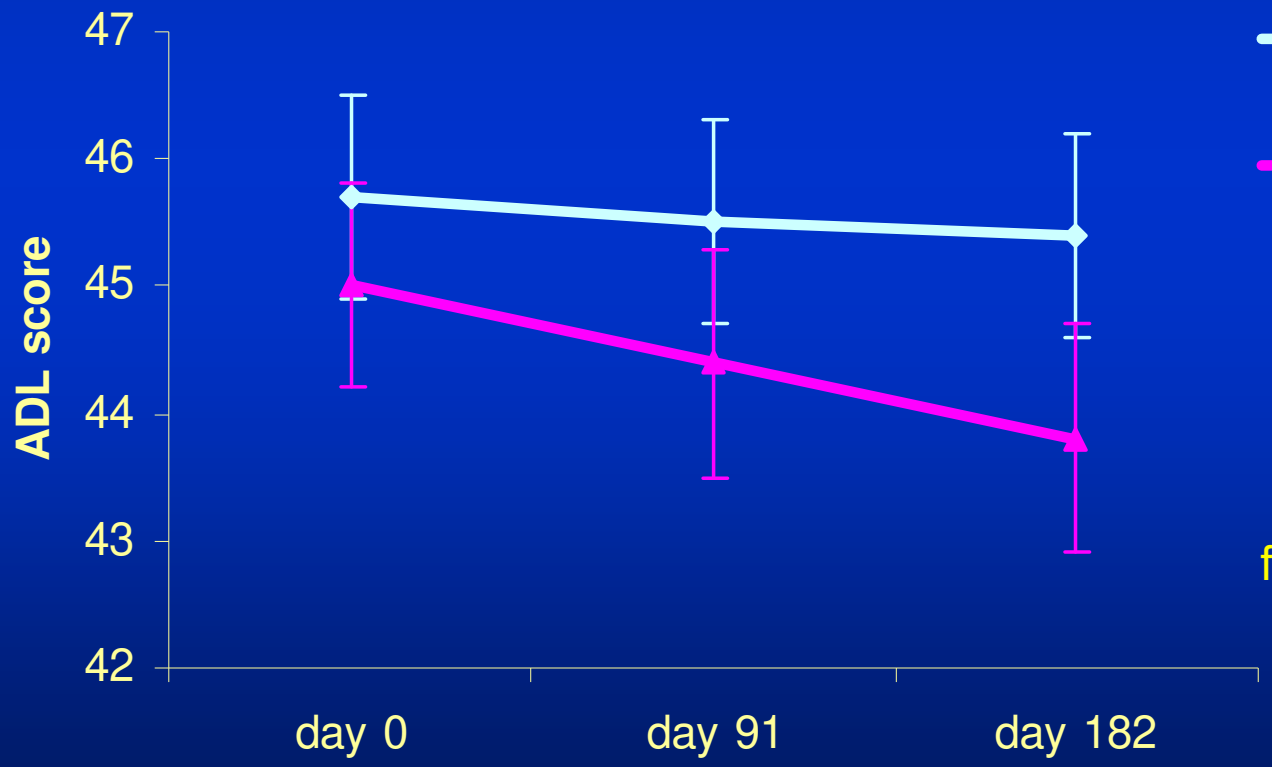
# Transdermal Nicotine Treatment of MCI

**Activities of Daily Living: 74 subjects**




p=.29
for Treatment
p=.74
for Treatment x Day

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# Study Withdrawals

**Blind Phase**

- Dropouts for AEs for both treatments were similar: Nicotine: 3(8%); PLC: 4 (11%).
  - GI (2)
  - Dermatologic
  - CV (2)
  - Progression to AD (2)

**Open Label Phase**

- 13 dropouts
- Causes:
  - Progression to AD (4)
  - Fatigue
  - Insomnia/Mood disturbance
  - Vertigo; light-headedness
  - CV (3)
  - GI (2)
  - Cancer

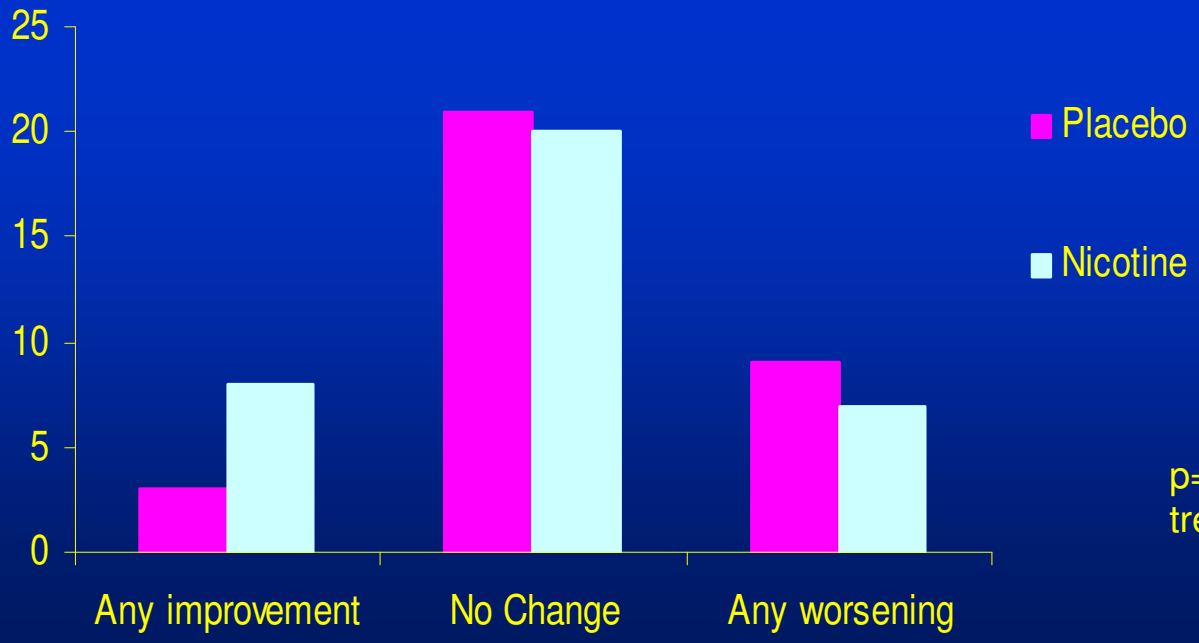
# Summary: Safety Data

- Transdermal nicotine was very well tolerated in an older non-smoking population.
- Adverse event rates similar between nicotine and placebo.
- No serious AE's judged secondary to nicotine.
- No significant adverse effects on vital signs from nicotine other than decrease in weight.

# Efficacy

# Transdermal Nicotine Treatment of MCI: CGIC

| CGI | Placebo (n=33) | Nicotine (n=35) |
|---|---|---|
| Any improvement | 3 (9.1%) | 8 (22.9%) |
| No Change | 21 (63.6%) | 20 (57.1%) |
| Any worsening | 9 (27.3%) | 7 (20.0%) |




p= .12 for nicotine treatment effect

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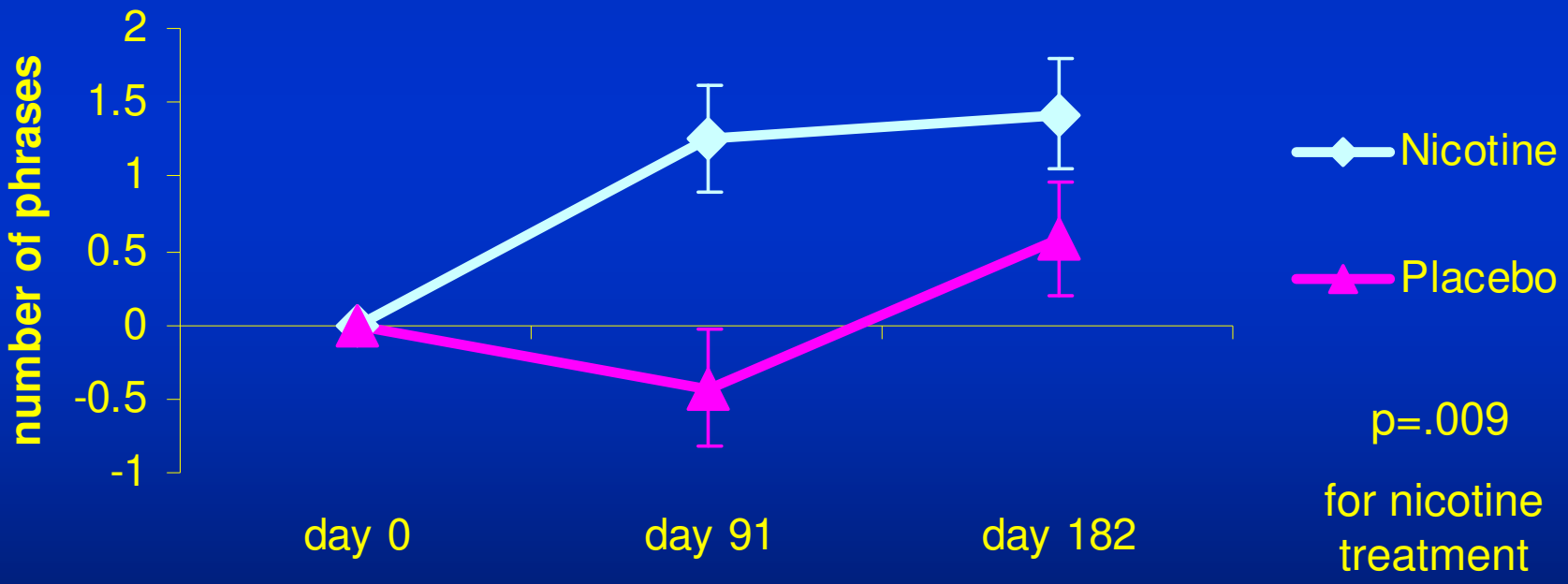
# Transdermal Nicotine Treatment of MCI

**Paragraph Immediate Recall: Change Score**

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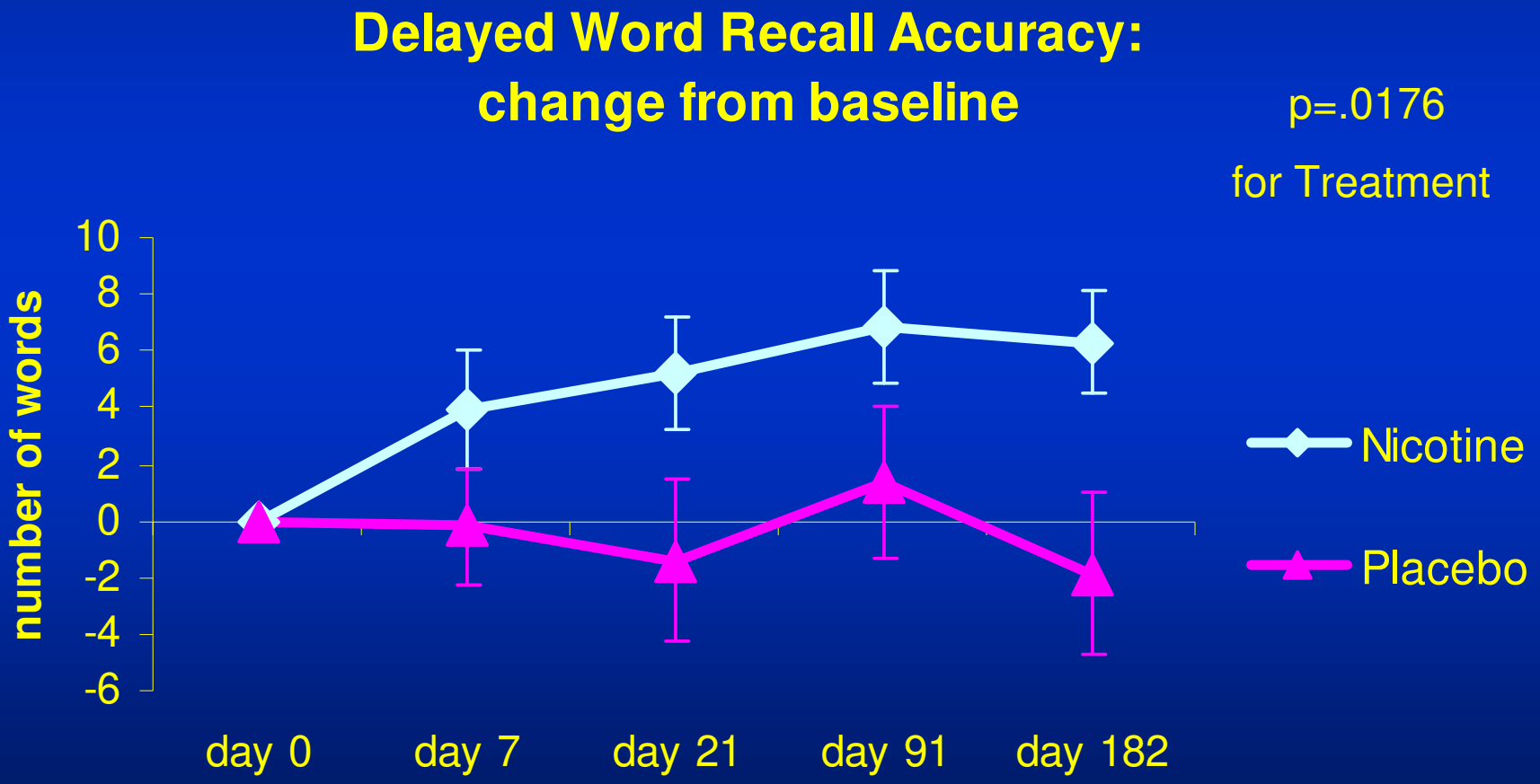
# Transdermal Nicotine Treatment of MCI:

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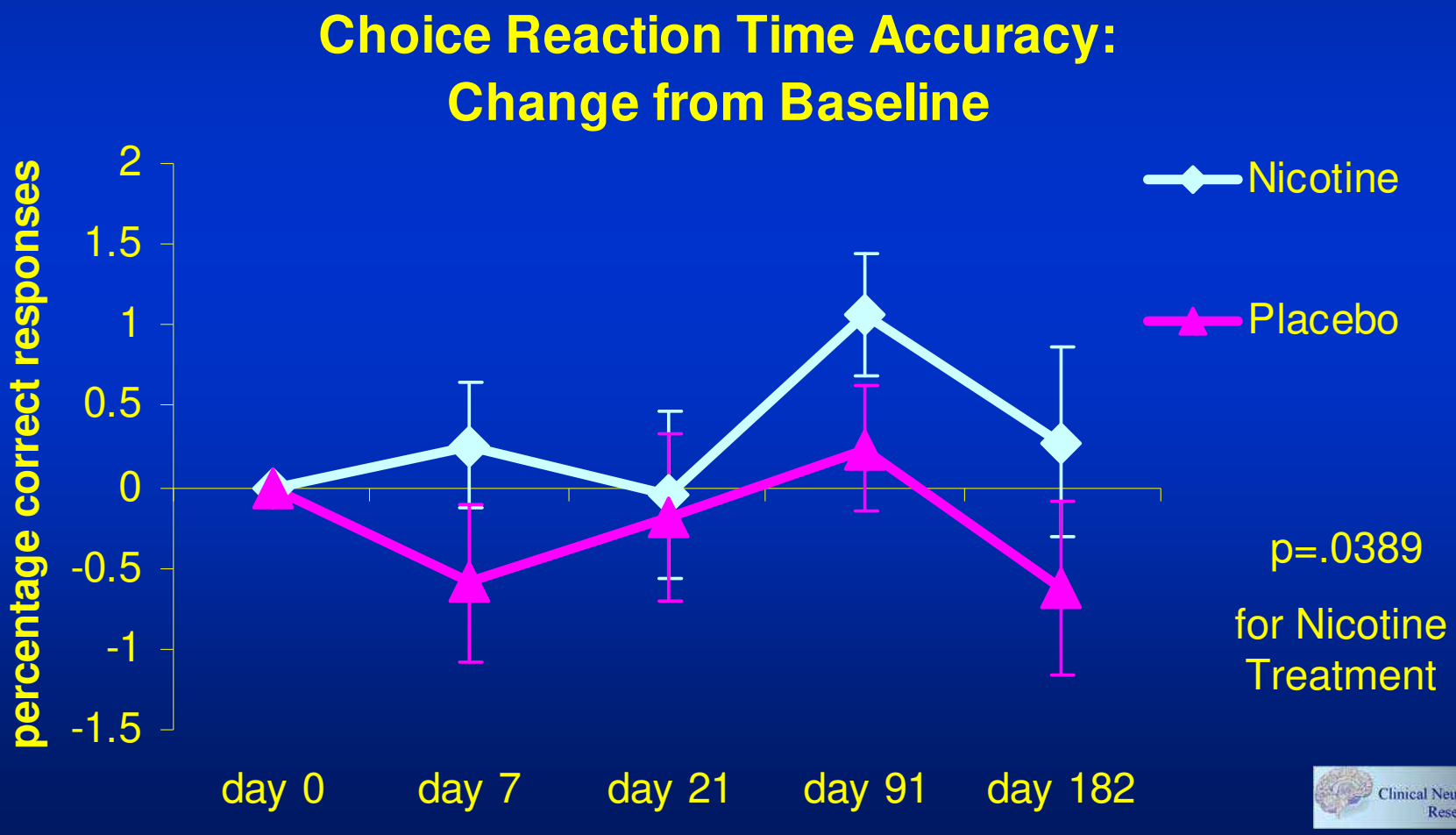
# Transdermal Nicotine Treatment of MCI

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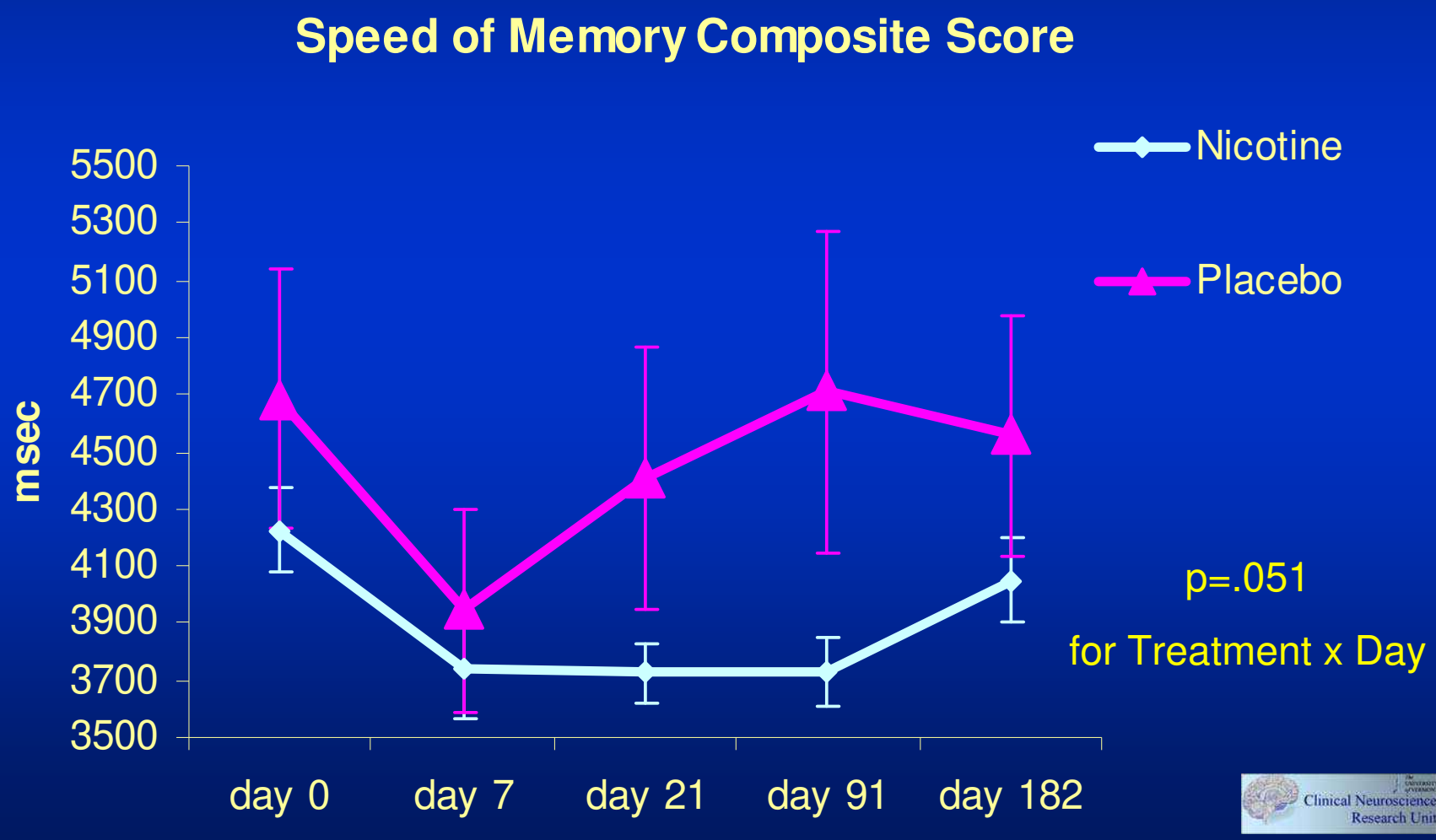
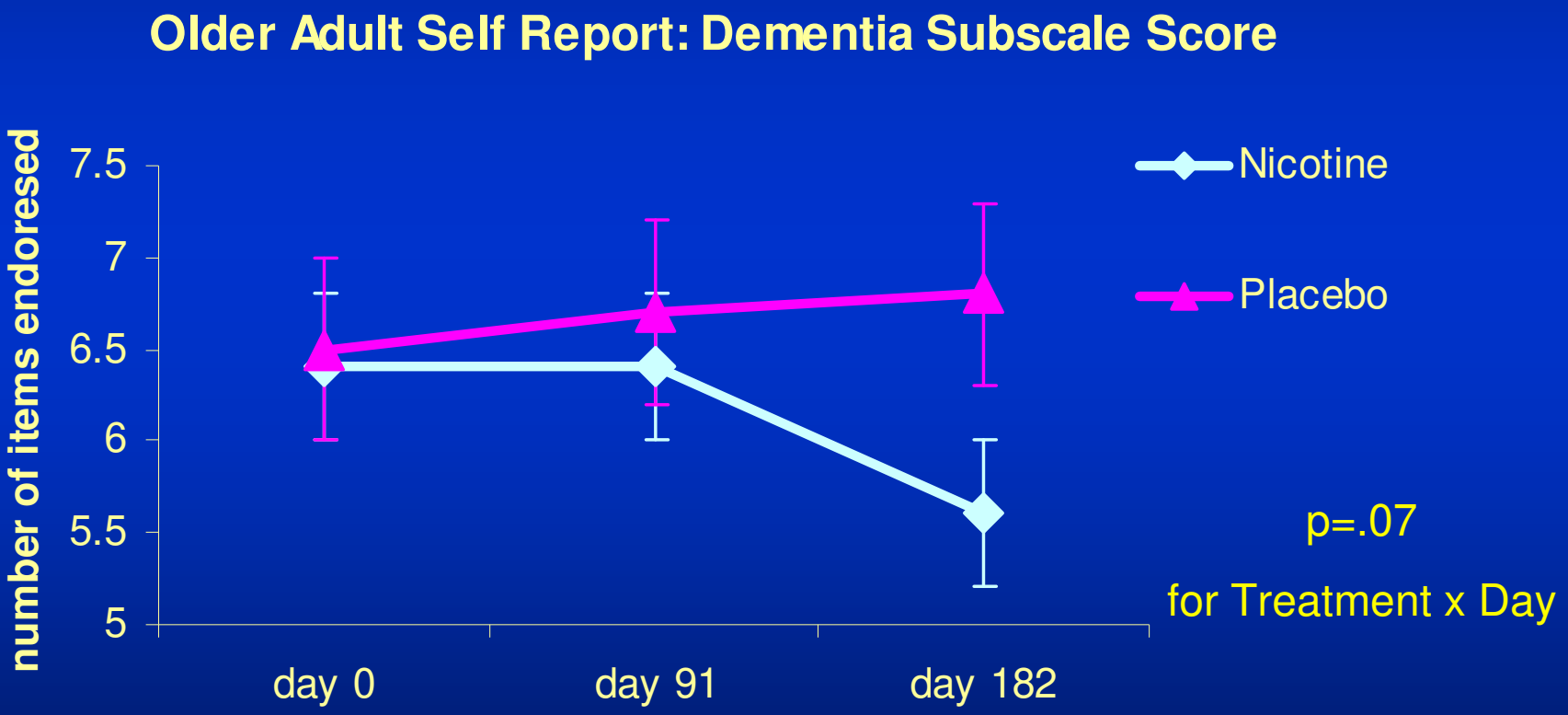
# Transdermal Nicotine Treatment of MCI



# Transdermal Nicotine Treatment of MCI

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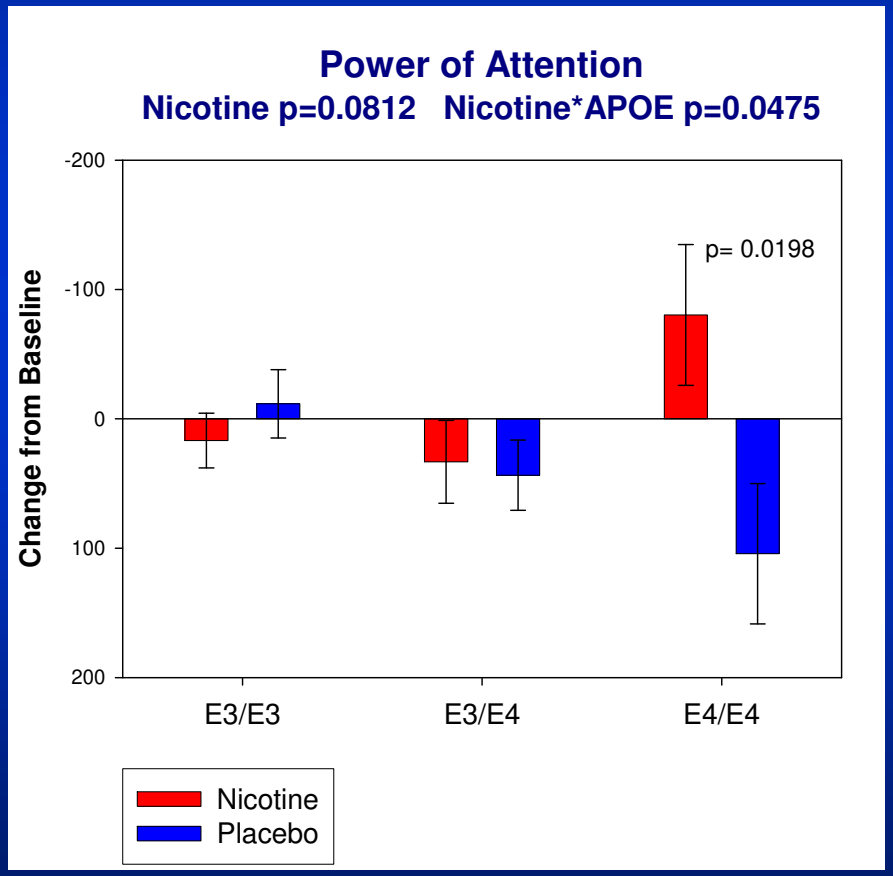
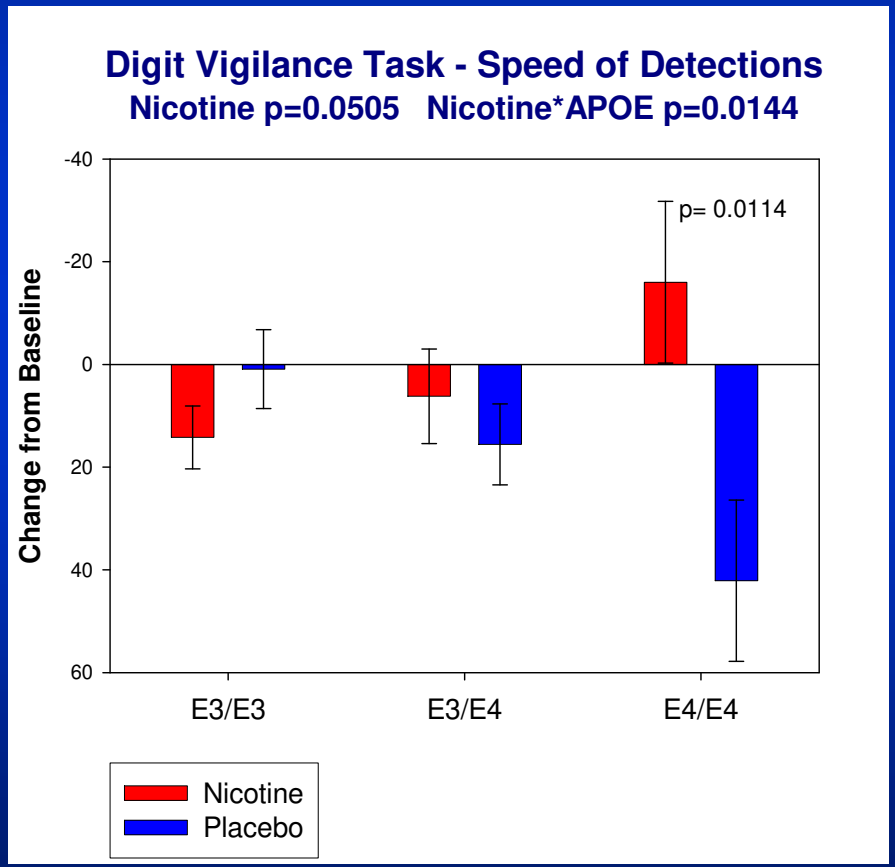
# APOE Genotype Modulates Nicotine Effect

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# Summary

- **Transdermal nicotine:**
  - **is well tolerated and safe in older non-smoking patients with MCI for up to one year.**
  - **Improvement seen by 6 months in verbal episodic memory and psychomotor speed, trends for CGIC.**
  - **In those cognitive domains that improve, no loss of efficacy is seen after 6 months.**
  - **APOE genotype may influence magnitude of the nicotinic effect.**
- **Alterations in the activity of the nicotinic cholinergic system may be compensatory for age-related alterations in sensory and/or associational processing.**

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