Schizophrenia and Aging: Myths and Reality

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Potential Conflicts of Interest

- **Donation of antipsychotic medications for an NIMH-funded RO1: AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Janssen**
- **Consultant: Solvay/Wyeth, Otsuka, Bristol-Myers Squibb**

Self-Assessment Question 1

Which of the following statements is true?

A. Rate of age-related cognitive decline in late-onset schizophrenia does not differ from that in normal subjects.

B. Remission of schizophrenia in late life appears independent of age or chronicity of illness

C. Positive symptoms in late-onset schizophrenia are as prevalent as in early-onset schizophrenia.

D. Female gender is over-represented among patients with late-onset schizophrenia

E. All of the above

Self-Assessment Question 2

Compared to early-onset schizophrenia, which of the following is true of late-onset schizophrenia?

A. Negative symptoms are more severe
B. Paranoid subtype is more prevalent
C. A smaller percentage of patients have ever been married
D. All of the above
E. None of the above

Self-Assessment Question 3

Which of the following statements is true of neuropsychological findings in patients with late-onset schizophrenia?

A. A wide range of cognitive deficits have been reported
B. Compared to patients with early-onset schizophrenia, less severe deficits in learning and executive functions characterize patients with late-onset schizophrenia
C. The overall pattern of deficits is similar to that seen in early-onset schizophrenia
D. All of the above
E. None of the above

Self-Assessment Question 4
Which of the following is true regarding treatment of late-onset schizophrenia?

A. The cumulative incidence of tardive dyskinesia with conventional antipsychotics is low in elderly patients.
B. Risperidone has been shown to be superior to olanzapine in treating positive and negative symptoms of late-onset schizophrenia.
C. Cognitive Behavioral Social Skills Training has been shown to reduce delusions and hallucinations
D. All of the above
E. None of the above

Self-Assessment Question 5

Which of the following are long-term adverse effects of atypical antipsychotics?

A. Weight gain
B. Type 2 diabetes mellitus
C. Dyslipidemia
D. Increase in strokes and mortality in dementia patients
E. Any of the above

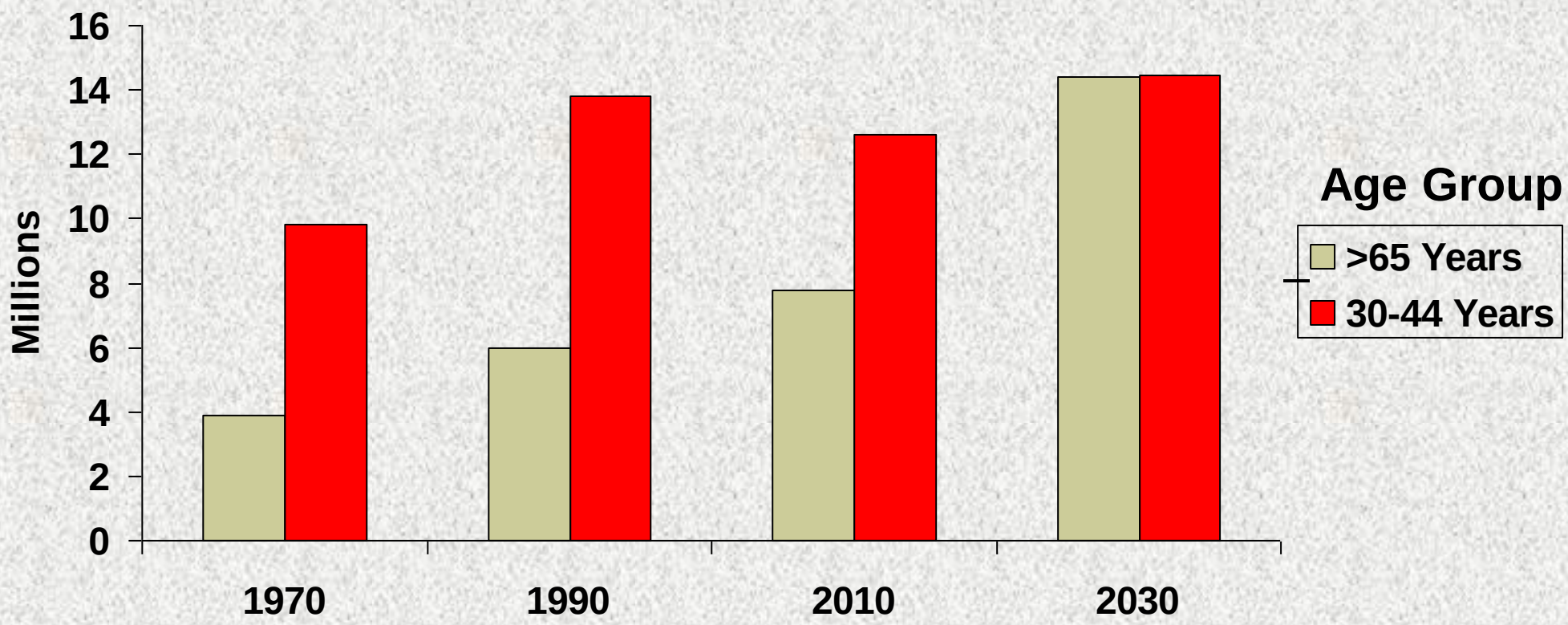
Major Points

- Schizophrenia can manifest for the first time after age 40
- Course of schizophrenia in late life is generally characterized by persistence of negative symptoms, absence of rapid cognitive decline, and modest improvement in positive symptoms
- Very late-onset schizophrenia-like psychosis (with onset after age 60) is a heterogeneous syndrome that includes psychosis of dementia or of other medical conditions, substance use, or psychosis NOS
- Other conditions in differential diagnosis include delusional disorder and psychosis associated with mood disorders
- Treatment with atypical antipsychotics is associated with symptomatic improvement but also potentially hazardous metabolic side effects offset by lower rates of tardive dyskinesia and other extra-pyramidal symptoms
- Psychosocial approaches have been shown to improve functioning and insight but not psychopathology in older patients with schizophrenia.

OUTLINE

- Introduction
- Course of Schizophrenia in Late Life
- Middle-Age-Onset Schizophrenia
- Very Late-Onset Schizophrenia-like Psychosis
- Pharmacologic & Psychosocial Treatments

Estimated Numbers of People with Psychiatric Disorders in USA



Jeste et al., Arch Gen Psychiatry, 1999

UCSD Studies of Late-Life Schizophrenia

- **Over 1200 middle-aged and elderly patients with schizophrenia and related psychoses, and over 250 normal comparison subjects**

- **Longitudinal follow-up with comprehensive clinical, neuropsychological, and functional evaluations**

Course of Schizophrenia in Late Life

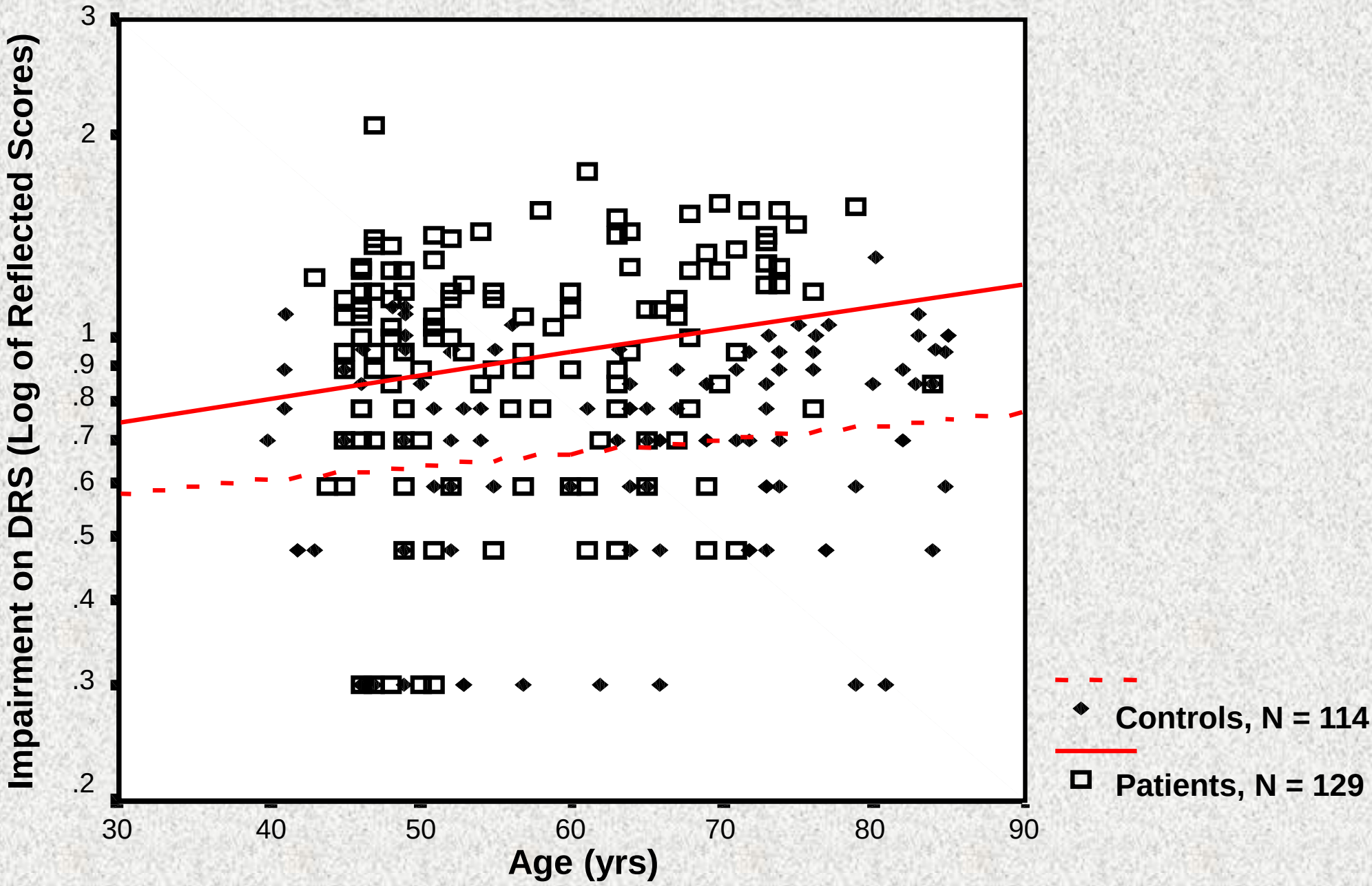
- Relatively stable and non-deteriorating course
- Negative symptoms persist while positive symptoms show a modest improvement
- The rate of age-related cognitive decline is similar in patients and normal subjects

Jeste DV et al., Acta Psychiatrica Scand, 2003

Correlations with Age in Schizophrenia Patients Aged 40-85 (N=192)

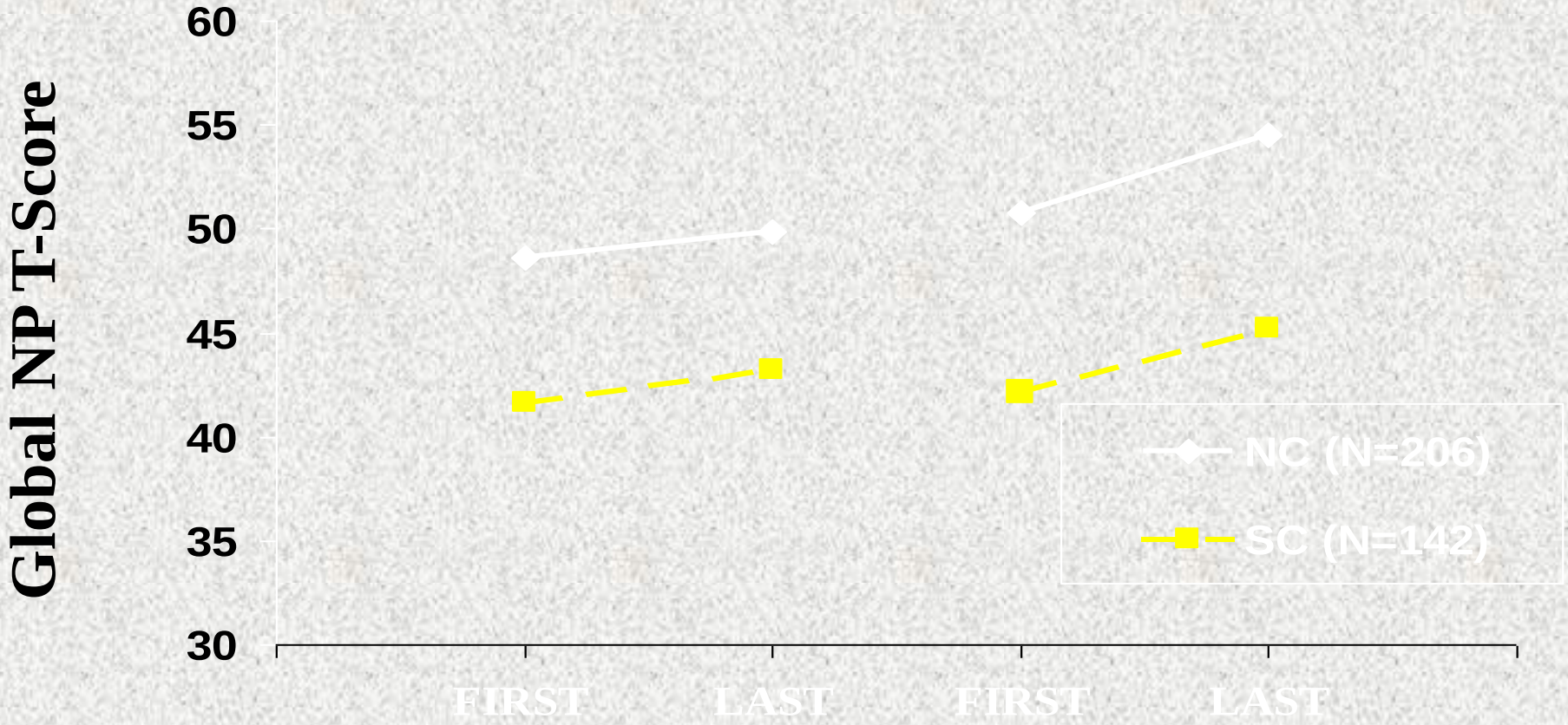
Positive Symptoms:	**SAPS**	**-0.19***
Negative Symptoms:	**SANS**	**-0.15**
Daily Neuroleptic Dose:		**-0.31****
Cognitive Impairment:	**DRS**	**0.21***

***p<0.05; **p<0.01**



Zorrilla E, et al., Am J. Psychiatry, 2000

Stability of Neuropsychological Performance



(Heaton et al., Arch. Gen. Psychiatry, 2001)

Remission of Schizophrenia: Earlier Studies

- Reported rates of remission or recovery range from 3% to 68%
- Variable use and definitions of terms: Cure, Recovery, Remission
- Bias in sample selection
- Inconsistent diagnostic criteria for schizophrenia
- Subjective evaluations

UCSD Criteria for Sustained Remission

- Met DSM-IV criteria for schizophrenia in past, but not currently;
- No hospitalization for last 5 years;
- Living independently; and
- Neuroleptic-free or on low dose of an antipsychotic

Auslander L & Jeste DV, Am J Psychiatry, 2004

Remission Study Conclusions

- **8% of the older schizophrenia patients living in the community met criteria for persistent symptomatic remission**
- **Remitted patients had somewhat impaired cognition & functioning suggesting that remission in schizophrenia may reflect a return to pre-morbid functioning rather than to "normal level"**

Predictors of Sustained Remission from the Literature

- **Social support**
- **Greater cognitive / personality reserve**
- **Early initiation of treatment**
- **NOT age or duration of illness**

Late-Onset Schizophrenia: A Controversial Entity

Age of onset and diagnosis of schizophrenia in USA:

DSM-III (1980)
DSM-III-R (1987)
DSM-IV (1994)

European terminology:

Paranoia
Paraphrenia
Late paraphrenia

Questions

1. **Can schizophrenia manifest after age 45?**

   If it can,

2. **Why do these patients develop schizophrenia?**

   and

3. **What protects them from developing schizophrenia until late in life?**

Diagnosis

DSM-III-R or DSM-IV diagnosis with SCID

Age of onset of prodromal symptoms of schizophrenia

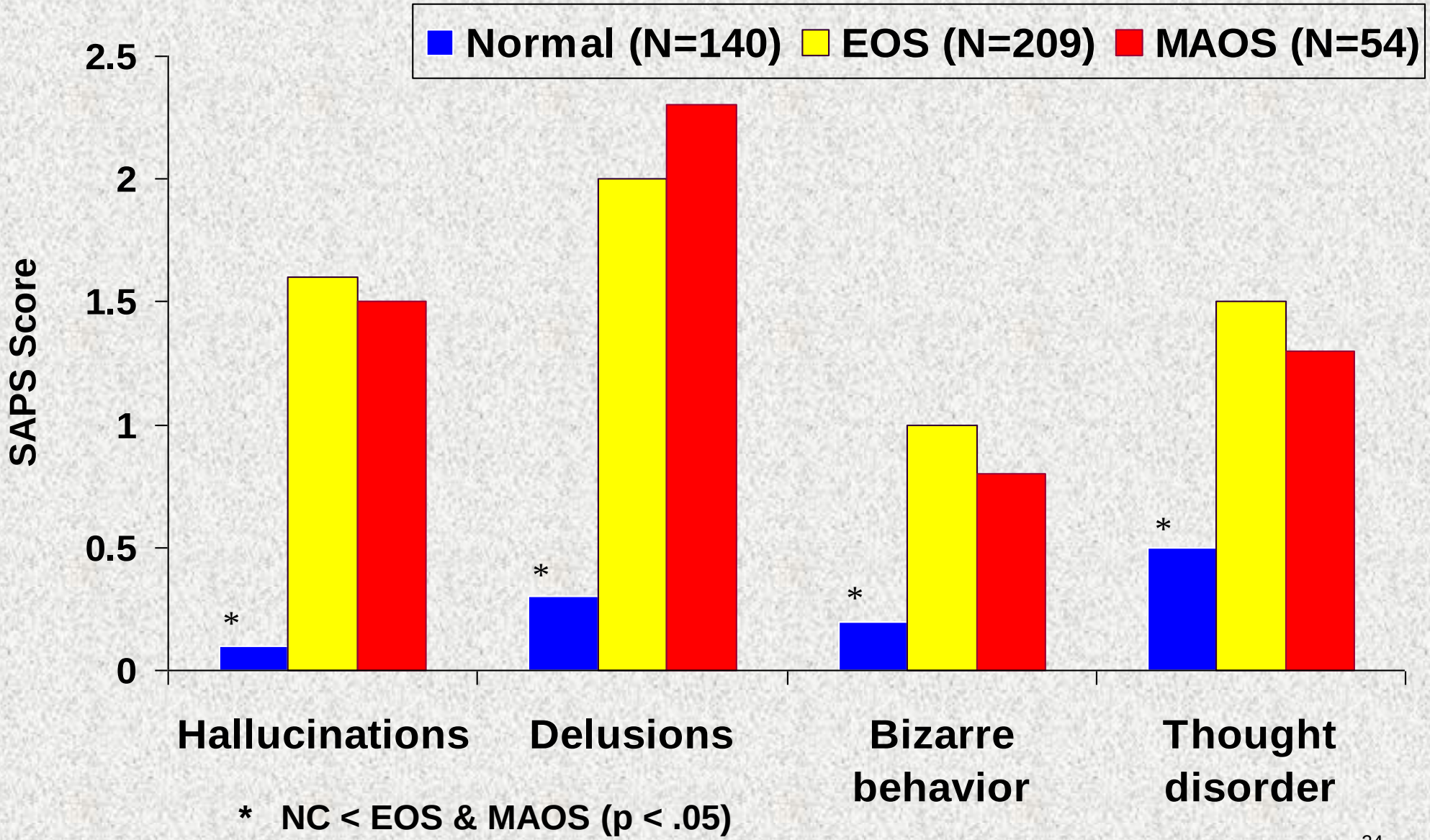
Specific inclusion and exclusion criteria

Diagnostic stability over follow-up period

Patient Characteristics

	Early-Onset Schizophrenia (EOS) (N=253)	Middle-Age Onset Schizophrenia (MAOS) (N=65)
Age of onset of schizophrenia	25 (7)	51 (8)
Duration of illness	31 (11)	10 (8)
Neuroleptic dose (mg CPZE/day)	250	126 *

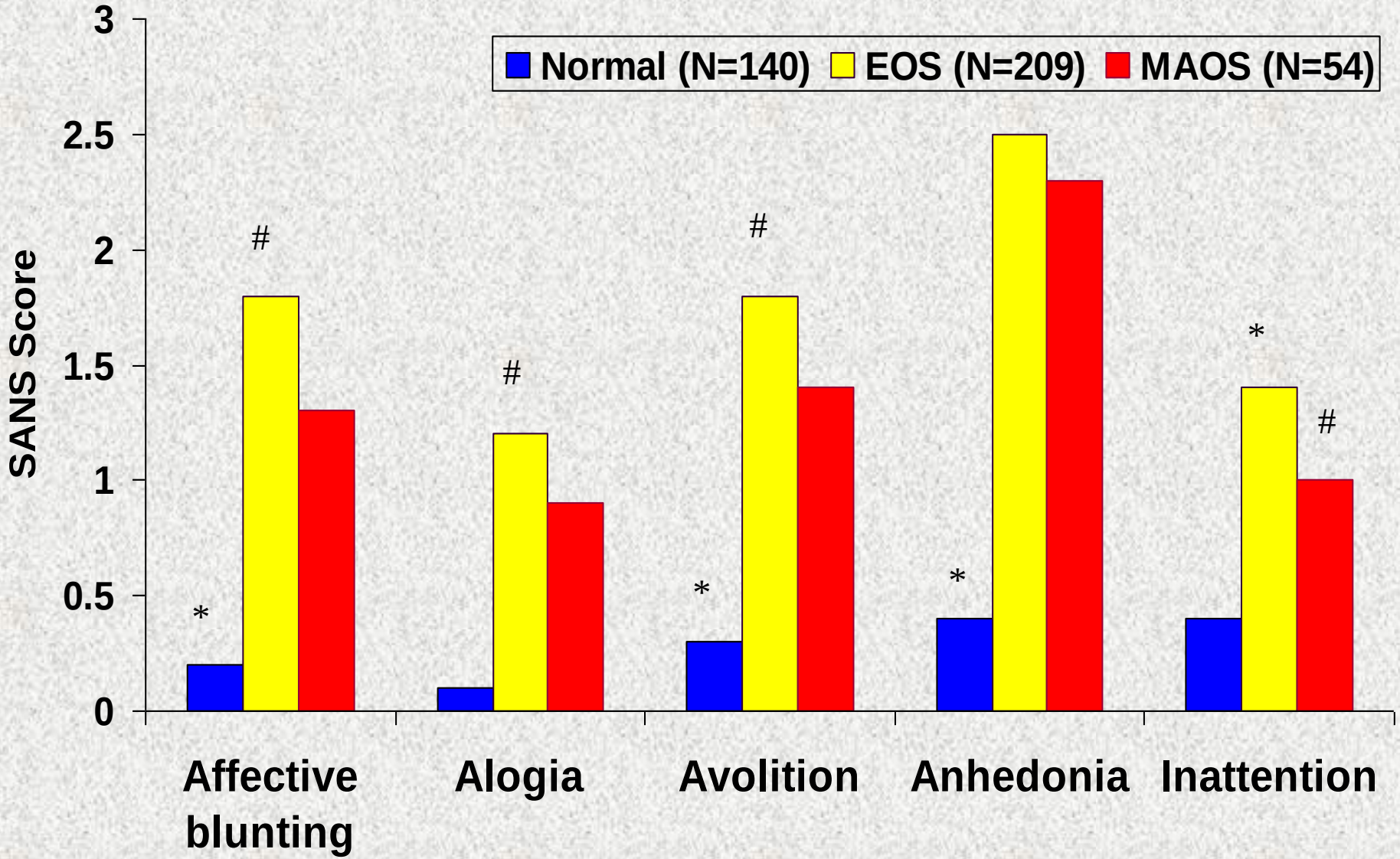
SAPS Subscale Scores



* NC < EOS & MAOS ($p < .05$)

Palmer B, et al., Harvard Review of Psychiatry, 2001

SANS Subscale Scores



* NC < EOS & MAOS (p < .05) # EOS > MAOS (p < .05)

Palmer B, et al., Harvard Review of Psychiatry, 2001

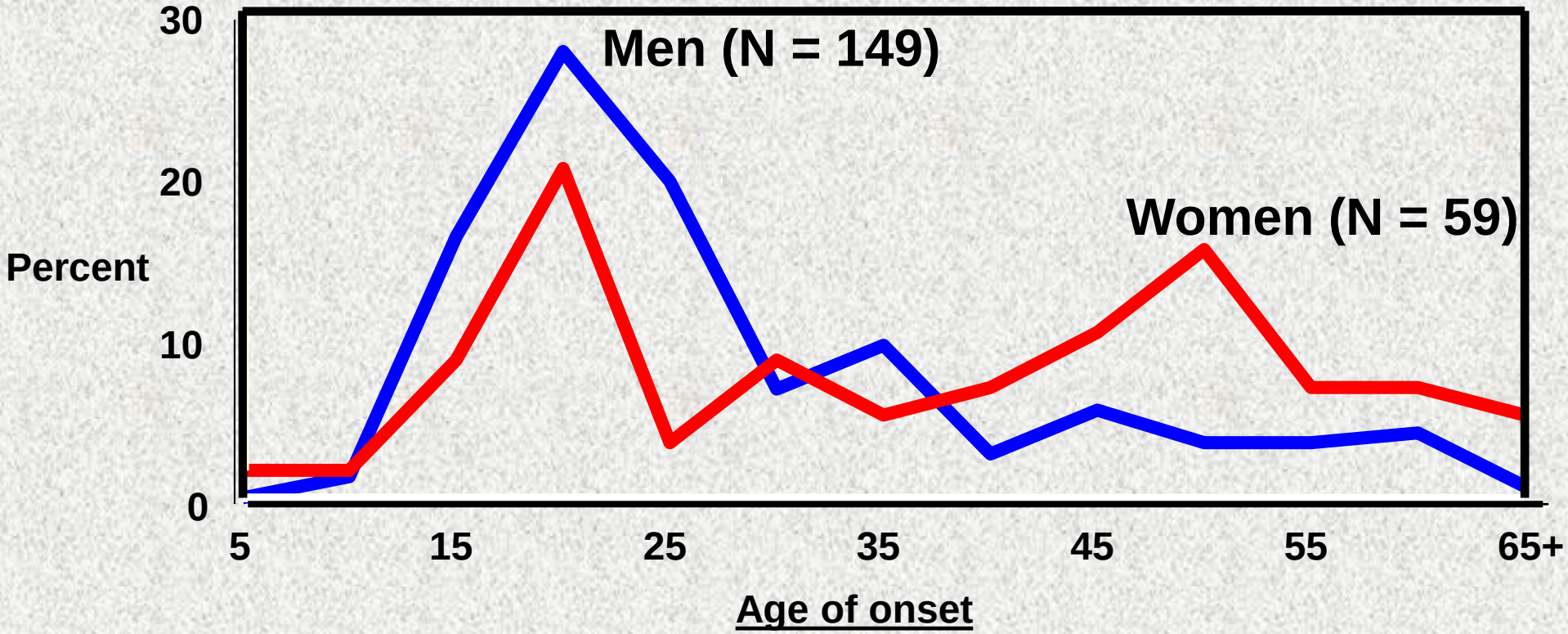
MAOS: Similarities with EOS

(I) Clinical

1) Severity of positive symptoms
2) Family history of schizophrenia
3) Minor physical anomalies
4) Childhood maladjustment
5) Sensory impairment

Jeste et al., Am Psychiatry, 1995; Am J Geriat Psychiatry, 1997

Age of Onset of Schizophrenia by Gender (Age > 45)



Kolmogorov-Smirnov pvalue < .0001

Lindamer et al., Psychopharm. Bull., 1997

MAOS: Differences from EOS

(I) Clinical

1) More common in women
2) Less severe negative symptoms
3) Mostly paranoid subtype
4) Greater % of patients ever married

Jeste et al., Am J Psychiatry, 1995; Am J Geriat Psychiatry, 1997

Psychosocial Factors

- **Premorbid Functioning: Suboptimal without being grossly psychopathological;**

  Premorbid personality may show paranoid or schizoid traits but not disorder.

- **Psychosocial Stressors: Retirement, bereavement, financial loss, physical disability, etc. may serve as precipitants and/or maintainers of psychosis.**

Neuropsychological Assessment

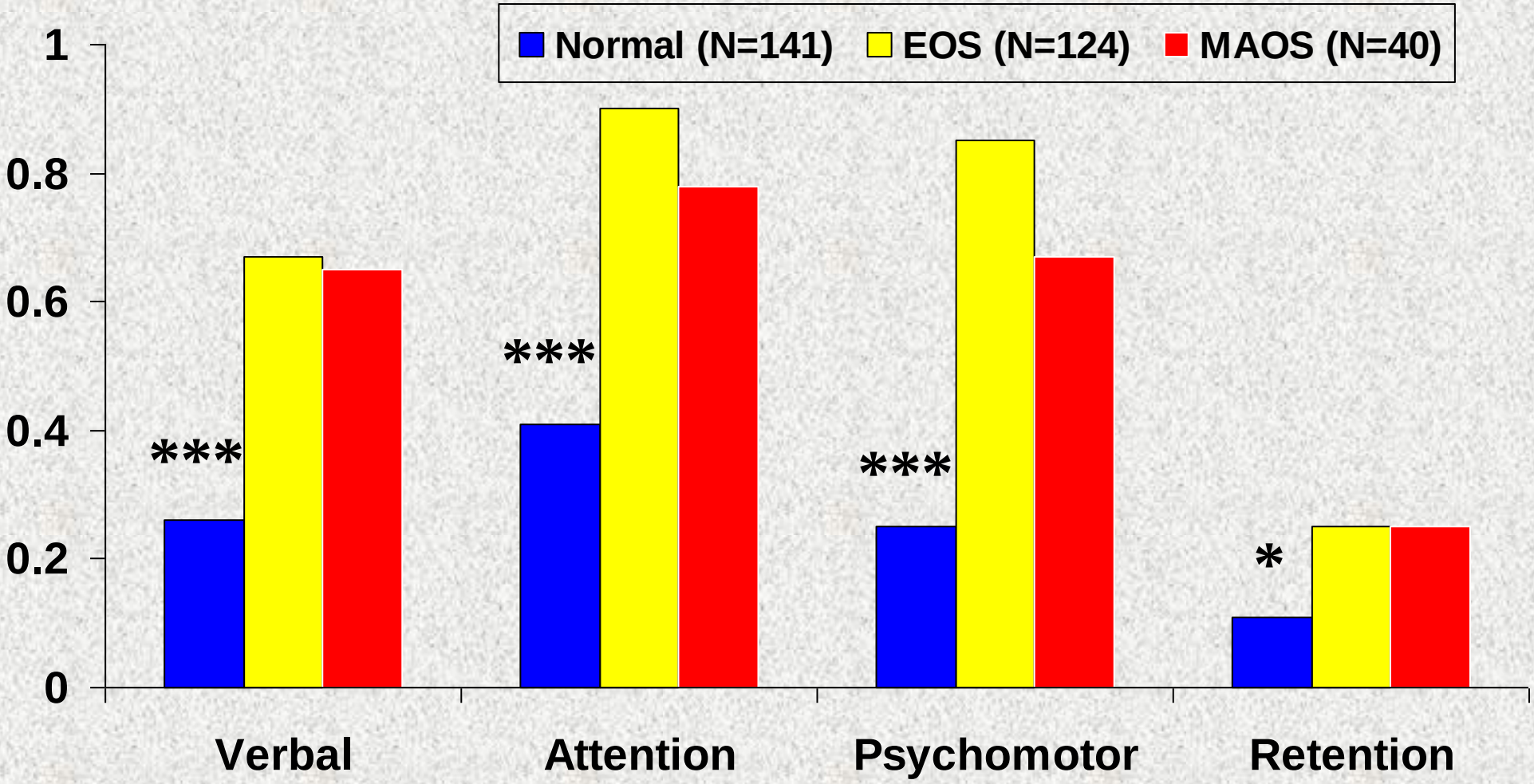
- **Expanded Halstead-Reitan battery, Age-, gender-, and education-corrected, T-, and deficit-scores for 7 ability areas:**

1) Verbal, 2) Attention, 3) Psychomotor,

4) Memory (retention), 5) Learning,

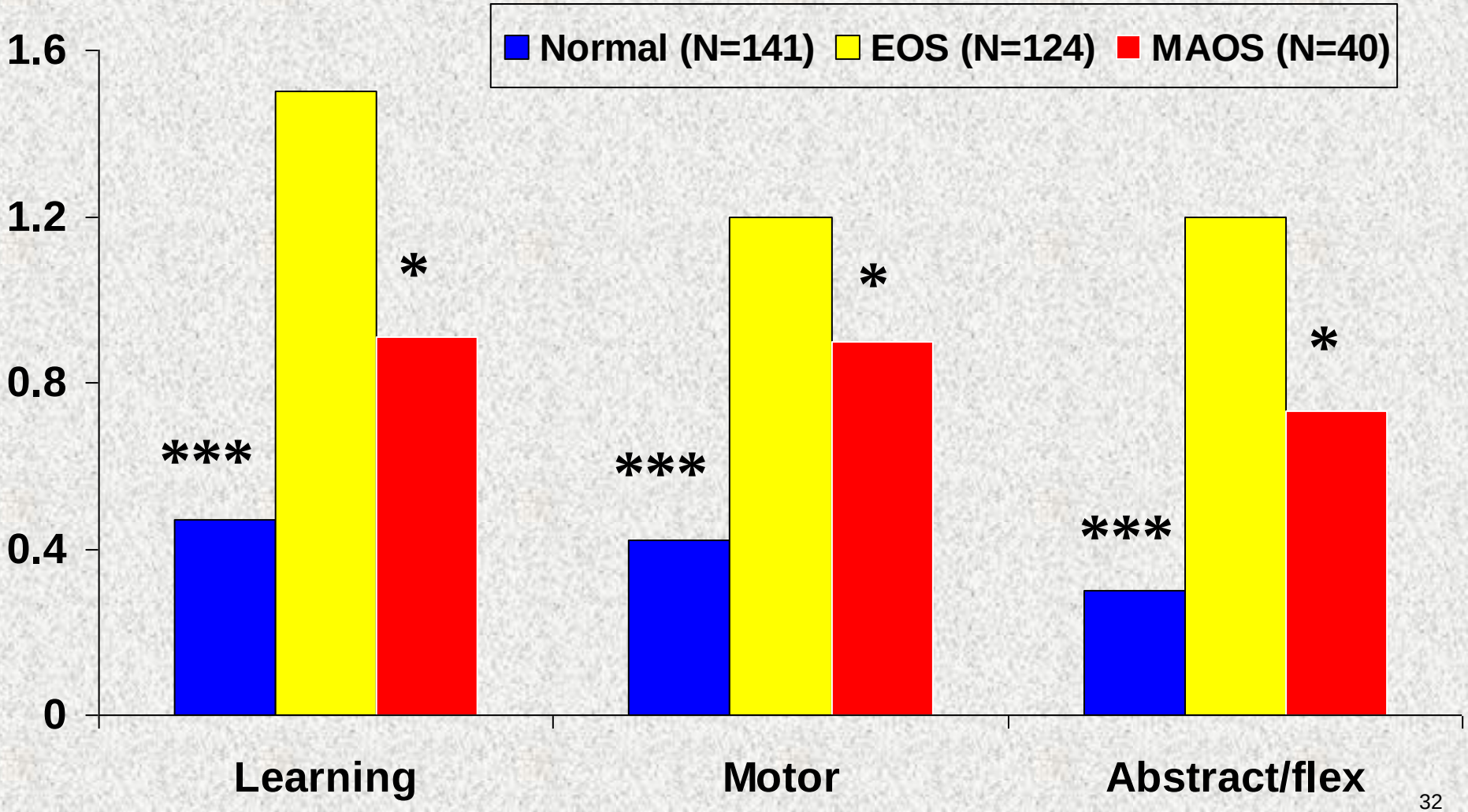
6) Motor, and 7) Abstraction.

Neuropsychological Deficit Scores



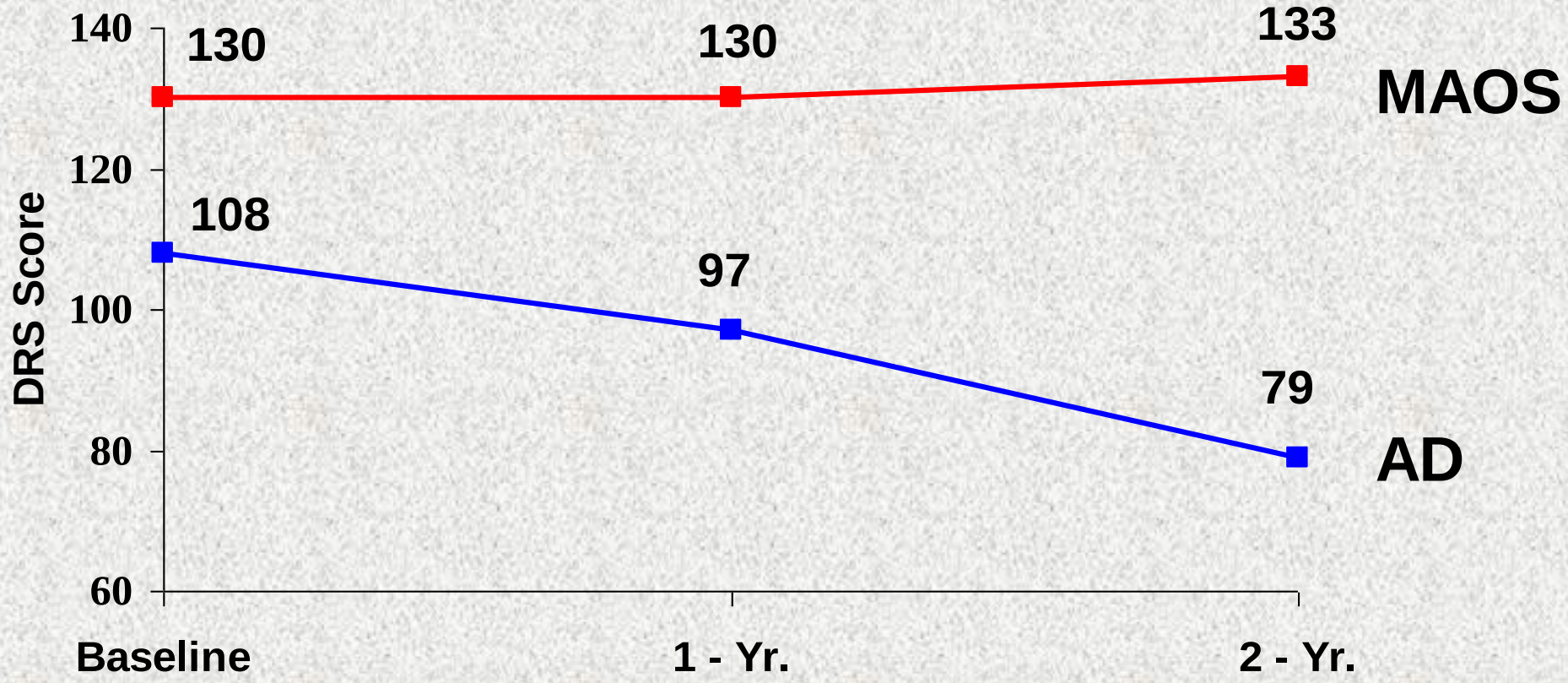
* p < .05; *** p < .0001(NC < MAOS, EOS)

Neuropsychological Deficit Scores



* p .05; *** p<.0001 (NC < MAOS < EOS)

MAOS (N=29) vs. Alzheimer Disease (N=61): Longitudinal Study of Mattis' Dementia Rating Scale (DRS)



MAOS: Similarities with EOS

(II) Neuropsychological

(1) Overall pattern of cognitive impairment

(III) MRI

(1) Nonspecific MRI abnormalities

(IV) Course & Treatment

(1) Chronic Course

(2) Qualitative response to neuroleptics

(3) Increased mortality

Jeste et al., Am J Psychiatry, 1995; Am J Geriatric Psychiatry, 1997

MAOS: Differences from EOS

(II) Neuropsychological

(1) Less severe impairment in learning and in abstraction

(III) MRI

(1) Larger thalamus?

(IV) Course & Treatment

(1) Need for lower doses of neuroleptics

Jeste et al., Am J Psychiatry, 1995; Am J Geriatric Psychiatry, 1997

Very Late-Onset Schizophrenia-like Psychosis

Heterogeneous group of disorders:

- **Psychosis of dementia**
- **Psychosis secondary to general medical conditions or substance use**
- **Mood disorder with psychotic features**
- **Delusional disorder**
- **Psychosis NOS**

Howard R et al., Am J Psychiatry, 2000

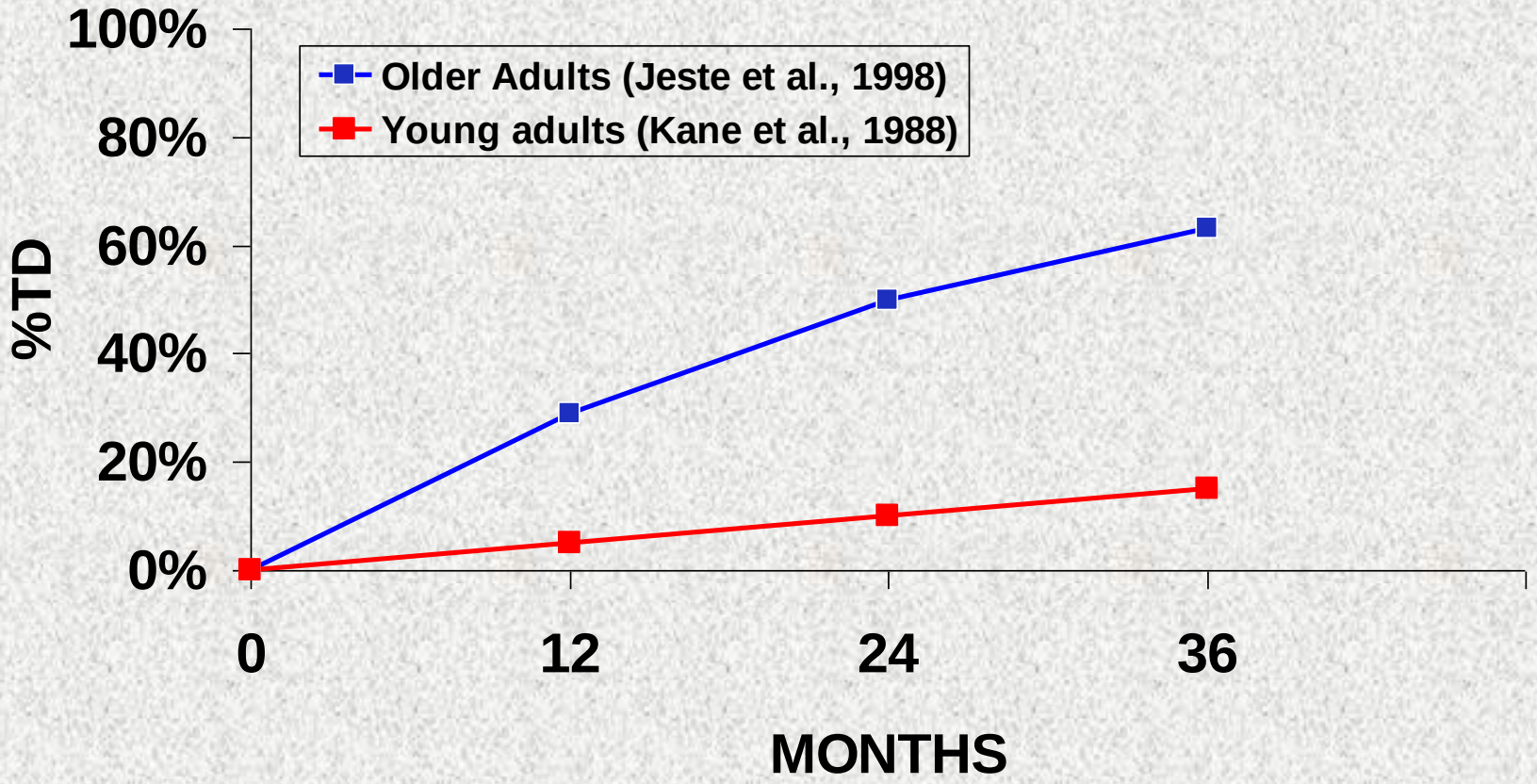
International Consensus Statement on Late-Onset Schizophrenia

In terms of epidemiology, symptomatology, and identified pathophysiology, LOS (onset after age 40) and very late-onset schizophrenia-like psychosis (onset after age 60) have face validity and clinical utility.

-Howard, Rabins, Seeman, Jeste, and International LOS Group (representatives from Australia, Brazil, Canada, Denmark, France, India, Japan, Spain, Switzerland, UK and USA)

American Journal of Psychiatry, 2000

Cumulative Incidence of TD with Conventional Antipsychotics



Kane et al., J Clin Psychopharm, 1988; Jeste et al., Am J Geriat Psychiatry, 1998

Risperidone vs Olanzapine in Elderly Schizophrenia Pts.

- International, double-blind, 8-week RCT*
- 176 patients, aged >60 years
- Schizophrenia or schizoaffective disorder
- Randomly assigned to flexible doses of Risperidone (1-3; median 2 mg/d) or Olanzapine (5-20; median 10 mg/d)

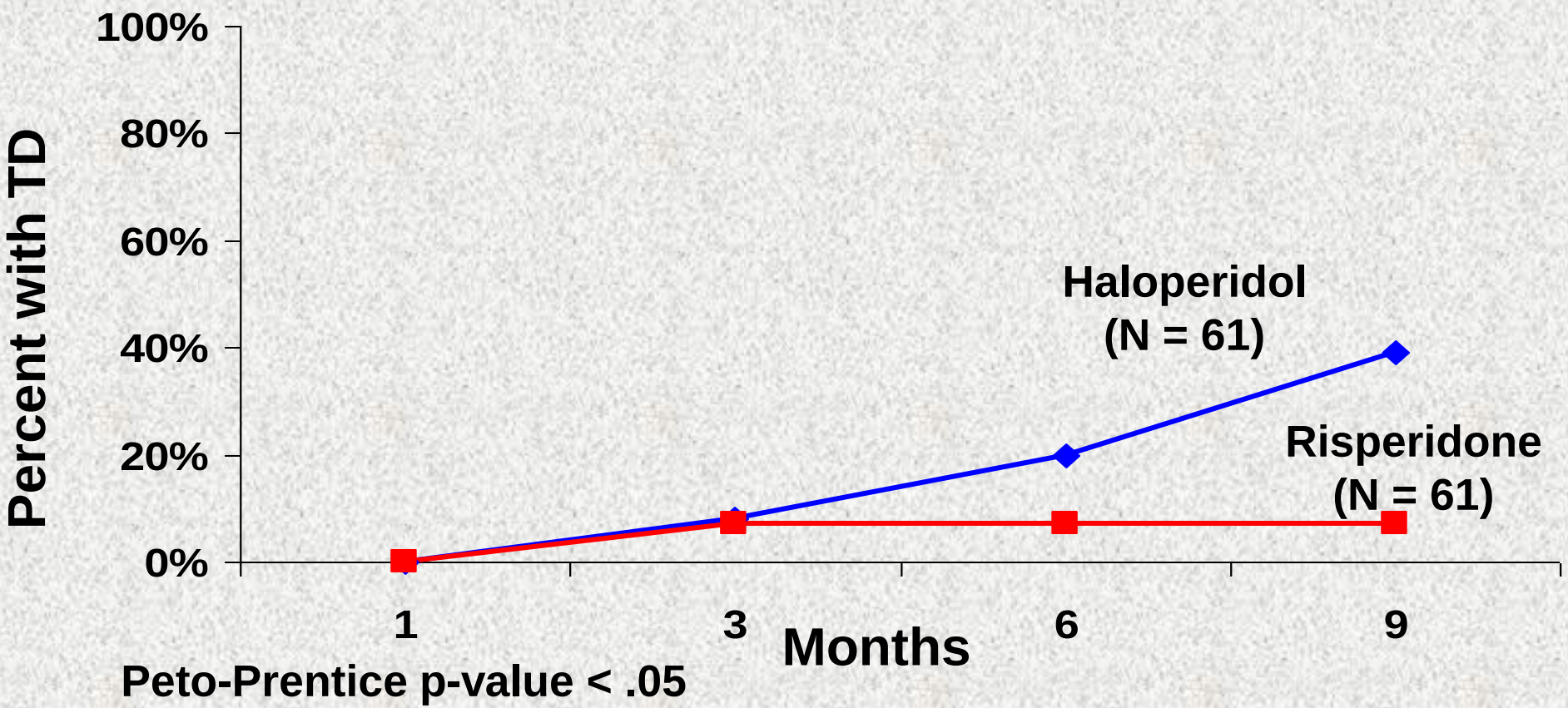
Jeste DV, et al., American Journal of Geriatric Psychiatry, 2003

Risperidone Vs. Olanzapine

- Both atypical antipsychotics produced significant improvement from baseline scores on PANSS
- No significant difference between the 2 drugs on Psychopathology, Cognitive function, QTc, or Reports of EPS or anticholinergic side effects
- Greater weight gain with olanzapine (p=.05)

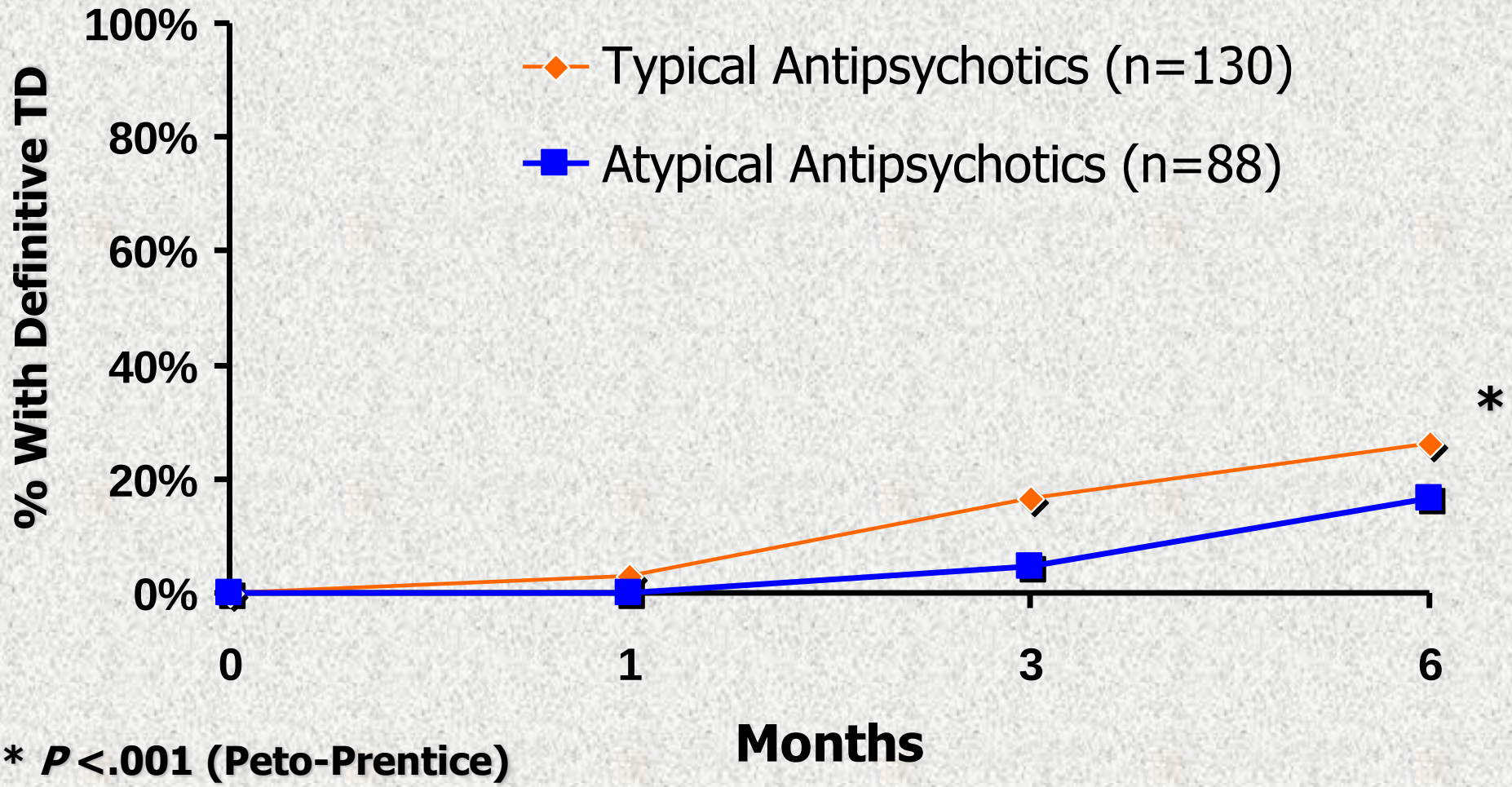
Jeste DV, et al., American Journal of Geriatric Psychiatry, 2003

TD Incidence in Older Patients: Haloperidol versus Risperidone (1mg/d)



Jeste, et al., JAGS, 1999

Cumulative Incidence of Definitive TD in Older Patients With Borderline Dyskinesia



* *P* <.001 (Peto-Prentice)

Dolder & Jeste. *Biol Psychiatry*. 2003, 53:1142-45

Atypical Antipsychotics: Possible Long-Term Side Effects

- Weight gain
- Type 2 diabetes mellitus
- Hyperlipidemia
- Hyperprolactinemia
- Cardiac conduction disorders
- Strokes?
- Increased mortality?

FDA Warnings About Antipsychotic Use

- In all age groups: Weight gain, Diabetes, Hyperlipidemia
- In dementia patients: Strokes, and Mortality

Caution in Interpreting Data on Strokes & Mortality with Antipsychotics

- **The patients in these trials were typically 80+ years old, and had multiple risk factors for strokes and mortality**
- **No cause- and-effect relationship between the antipsychotics and these adverse events in individual patients has so far been clearly established**
- **The exact underlying mechanisms are not yet known**

Recommended Dosages in Older Patients (mg/day)

Drug	Initial	Typical Range
Clozapine	6.25-12.5	50-150
Risperidone	0.25-0.5	1-3
Olanzapine	2.5-5	5-15
Quetiapine	12.5-25	75-200

Other Atypical Antipsychotics

- Ziprasidone
- Aripiprazole
- Others

Psychosocial Tx of Late-Life Schizophrenia

- **Cognitive Behavior Therapy**
- **Social Skills Training**
- **Functional Adaptation Skills Training**
- **Medication Adherence Therapy**
- **Vocational Rehabilitation**
- **Pedal for older Latino patients**

Cognitive Behavioral, Social Skills Training (CBSST)

Three modules, each with 4 weekly sessions, to be repeated, for a total of 24 group sessions

CBT – Thought challenging

SST – Asking for support

CBSST – Solving problems

Manualized treatment, with homework assignment after "classes"

Granholm E, et al., American Jr. of Psychiatry, 2005

Randomized Controlled Trial of CBSST

- 76 Patients with schizophrenia or schizoaffective disorder randomized to CBSST or Tx as usual
- Blind assessments on Independent Living Skills Survey, Beck's Cognitive Insight Scale, Comprehensive Module Test for CBSST skills, and Psychopathology (PANSS, HAM-D) at baseline, 3 months, & 6 months

Granholm E, et al., American Jr. of Psychiatry, 2005

CBSST Outcomes

- 86% Patients stayed in treatment
- No significant change in medication management
- Significant improvement at 3 & 6 months on:
  - Mastery of CBSST skills
  - Frequency of social activities
  - Cognitive insight
  - But not on psychopathology

Granholm E, et al., American Jr. of Psychiatry, 2005

Functional Adaptation Skills Training (FAST)

- **Teaching skills for: Communication, Transportation, Medication management, Social skills, Organization & planning,**

  Financial management
- **24 semi-weekly 2-hour group sessions**
- **FAST-treated patients showed significantly better everyday functioning than controls at end of Tx and 3 months later**

(Patterson T, et al., Schizophrenia Research 86:291-299, 2006)

Treatment - Summary

- Atypical antipsychotics have a considerably lower risk of EPS and TD than conventional neuroleptics, but they have other adverse effects
- Medications need to be supplemented by psychosocial therapies

Suggested Readings

- Jeste DV, Symonds LL, Harris MJ, et al.: Non-dementia non-praecox dementia praecox?: Late-onset schizophrenia. Am J Geriat Psychiatry 5:302-317, 1997
- Howard R, Rabins P, Seeman MV, et al.: Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: An international consensus. Am J Psychiatry,157:172-178, 2000
- Jeste DV, Twamley EW, Eyler Zorrilla LT, Golshan S, Patterson TL and Palmer BW: Aging and outcome in schizophrenia. Acta Psychiatrica Scandinavica 107: 336-343, 2003

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B. Remission of schizophrenia in late life appears independent of age or chronicity of illness

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Which of the following is true regarding treatment of late-onset schizophrenia?

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Self-Assessment Question 5

Which of the following are long-term adverse effects of atypical antipsychotics?

A. Weight gain
B. Type 2 diabetes mellitus
C. Dyslipidemia
D. Increase in strokes and mortality in dementia patients
E. Any of the above

Answers to Self-Assessment Questions

1) E
2) B
3) D
4) E
4) E