Psychosis and Agitation in Dementia

Dilip V. Jeste, MD
Estelle & Edgar Levi Chair in Aging,
Director, Stein Institute for Research on Aging,
Distinguished Professor of Psychiatry & Neurosciences,
University of California, San Diego
VA San Diego Healthcare System

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. Psychosis and agitation are uncommon symptoms in demented patients.

B. Psychosis, in Alzheimer disease patients, is associated with increased functional impairment.

C. Male gender and higher educational level are associated with increased risk of psychotic symptoms in Alzheimer disease.

D. All of the above

E. None of the above

Self-Assessment Question 2

Psychosis in AD is associated with which of the following?

A. Frontal lobe neurobehavioral dysfunction
B. Apathy
C. Disinhibition
D. All of the above
E. None of the above

Self-Assessment Question 3

Which of the following statements is true?

A. Atypical antipsychotics are FDA-approved for treatment of psychosis in Alzheimer disease.

B. Off-label, evidence-based use of medications is legal, and should be accompanied by appropriate disclosure and discussion of rationale, risks, and benefits

C. Atypical antipsychotics are associated with greater mortality risk than conventional antipsychotics.

D. All of the above

E. None of the above

Self-Assessment Question 4
Adverse effects associated with use of atypical antipsychotic medications in dementia patients with psychosis include which of the following?

A. Sedation/somnolence
B. Postural hypotension
C. Cerebrovascular accidents
D. Increased mortality
E. All of the above

Self-Assessment Question 5

Which of the following medications has been approved for treating agitation or psychosis in dementia patients?

A. Citalopram
B. Divalproex sodium
C. Carbamazepine
D. Cholinesterase inhibitors
E. None of the above

Major Points

- Psychosis and/or agitation are frequent concomitants of dementia
- Psychosis in AD is associated with frontal neurobehavioral dysfunction
- No drug is FDA-approved for treatment of psychosis or agitation in dementia
- Off-label use of antipsychotics, especially the atypicals, is common, but these drugs FDA's carry black-box warnings regarding increased mortality in dementia patients
- Antidepressants, anticonvulsants, benzodiazepines, and cognitive enhancers have been used for psychosis or agitation in demented patients, but with inconsistent results
- Psychosocial treatments have a valid role in treatment
- Shared decision making is recommended

Prevalence of Behavioral Disturbances in Alzheimer Disease

- Psychosis: 40% - 60%
- Depression: 20% - 40%
- Agitation: 70% - 90%

Wragg and Jeste, Am J Psychiatry, 1988;
Ropacki and Jeste, Am J Psychiatry, 2005

Psychosis of Alzheimer Disease: Diagnostic Criteria

- Primary diagnosis is Alzheimer disease
- Characteristic psychotic symptoms: delusions or auditory/visual hallucinations
- Dementia onset precedes psychotic symptoms
- Duration >1 month
- Functional disruption
- Exclusion of delirium, schizophrenia, other causes of psychosis

Jeste DV and Finkel SI. *Am J Geriatr Psychiatry.* 2000;8:29-34

Psychosis of AD: Associated Features

1) Agitation

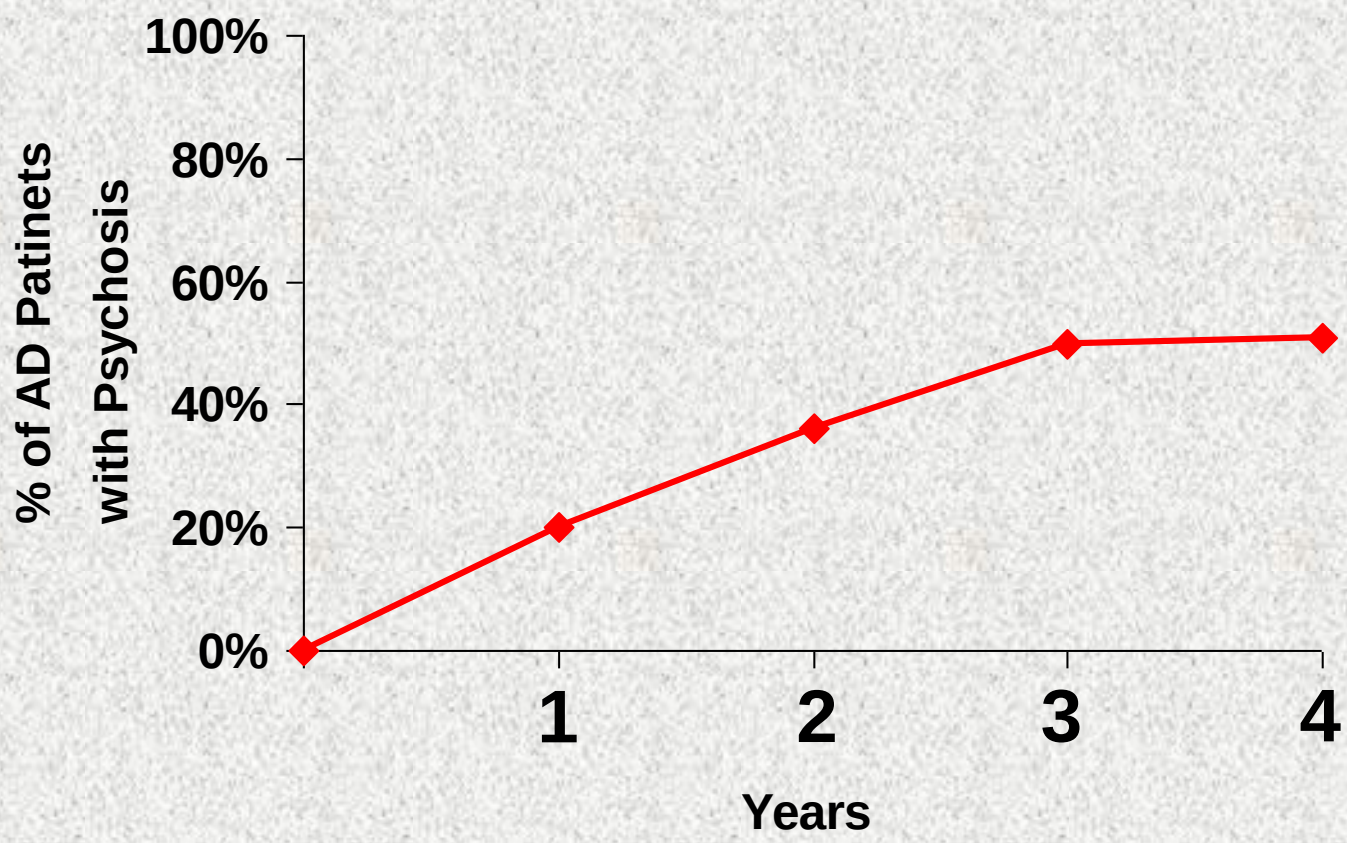
2) Negative symptoms

3) Depression

Psychosis of AD: Public Health Importance

1) High incidence and prevalence
2) Chronic or recurrent
3) Commonly produces functional disruption
4) May require prolonged treatment

Cumulative Incidence of Psychosis of Alzheimer Disease (N = 329)



Paulsen JS et al. *Neurology.* 2000;54:1965-1971

Psychosis of AD: Recent Studies

- **55 studies, published between 1990 and 2003, with a total N of 9,749**
- **Mean prevalence of psychosis 41% (delusions 36%, hallucinations 18%)**
- **Sx last for several months, but become less prominent after 1 year**
- **Significant association: More severe, & more rapidly progressive cognitive decline**

(Ropacki SA & Jeste DV: Am J Psychiatry, 2005)

Predictors of Development of Psychosis in AD Patients

Predictors:

1) Parkinsonian gait
2) Bradyphrenia
3) Global cognitive decline
4) Semantic memory decline

Non-predictors:

1) Age
2) Gender
3) Education

Paulsen JS et al., Neurology, 2000

Frontal Neurobehavioral Dysfunction in Psychosis of AD

- **FLOPS (Frontal Lobe Personality Scale) given to 20 AD + Psychosis pts & 20 AD – Psychosis pts matched on age, gender, education, & dementia severity**
- **AD + Psychosis pts had greater frontal neurobehavioral dysfunction, especially disinhibition and apathy**

Paulsen et al., J Int'l Neuropsychol Soc 6: 815-820, 2000

Treatment Modalities

- Nonpharmacologic approaches
- Typical (conventional) antipsychotics
- Atypical antipsychotics
- Other psychotropics

Review of Psychosocial Interventions

- Sensory, social contact, behavior therapy, staff training, structured activities, environmental, medical / nursing care, combination therapies
- Variably positive results, but with methodological limitations
- Psychosocial treatments have a valid role to play in treatment of most dementia patients

Cohen-Mansfield J. *Am J Geriatr Psychiatry*. 2001;9:361-381

Caveat in Using Drugs in Older Patients with Psychotic Disorders

- **Currently no drug (antipsychotic or other) has been approved for treatment of psychosis of Alzheimer disease**
- **Atypical antipsychotics have been approved by the FDA only for treatment of schizophrenia and bipolar disorder**
- **Off-label use of drugs is not illegal and is common in practice, but requires clear justification in individual patients**

Conventional (Typical) Neuroleptics in Patients with Dementia

- **Effective in <60% of cases[1]**
- **Improvement rate only 18% greater than with placebo[2]**
- **Modest clinical effects**
- **Effective doses often produce EPS, sedation, & other side effects**

1. Wragg and Jeste. *Psychiatr Clin North Am*. 1988;11:195.
2. Schneider et al. *J Am Geriatr Soc*. 1990;38:53.

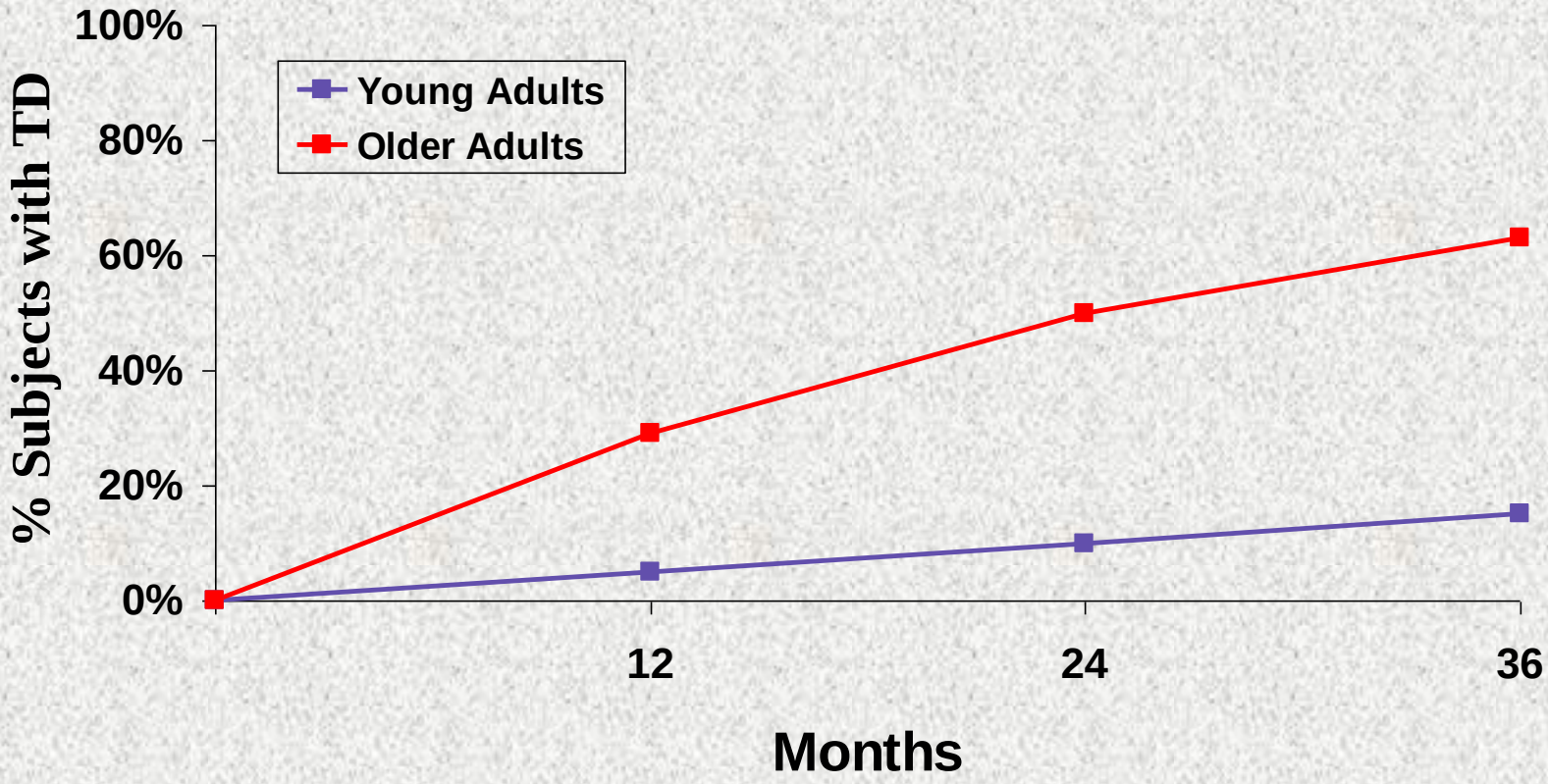
Adverse Effects of "Typical" Antipsychotics in Older Patients

- Anticholinergic toxicity
- Postural hypotension
- Extrapyramidal symptoms
- Tardive dyskinesia
- Other

Antipsychotic-Induced Tardive Dyskinesia

- Potentially persistent
- Associated with adverse consequences
- Often refractory to treatment
- Has medicolegal implications
- Much more common in older patients

Cumulative Incidence of Tardive Dyskinesia with Typical Neuroleptics

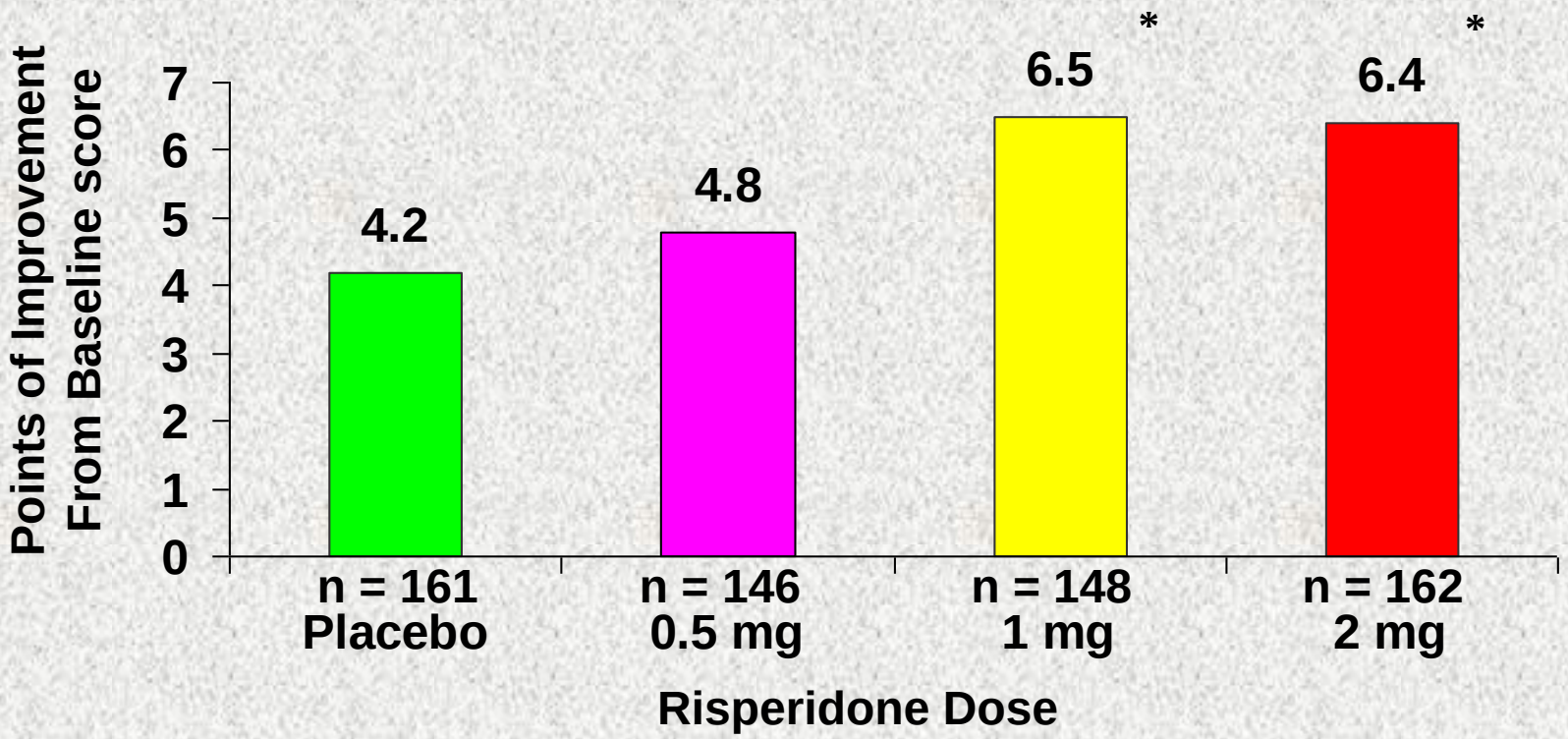


Jeste DV et al. Arch Gen Psychiatry 52:756-765, 1995; Kane JM et al. J Clin Psychopharmacol 1988;8(suppl):52S-56S

Clozapine in Elderly Patients

- Use restricted because of side effects (sedation, hypotension, anticholinergic toxicity) and weekly blood draws (agranulocytosis)
- Indication: psychosis in Parkinson's disease
- Lower dosages than in younger adults

Risperidone in Dementia: Total BEHAVE-AD Scores

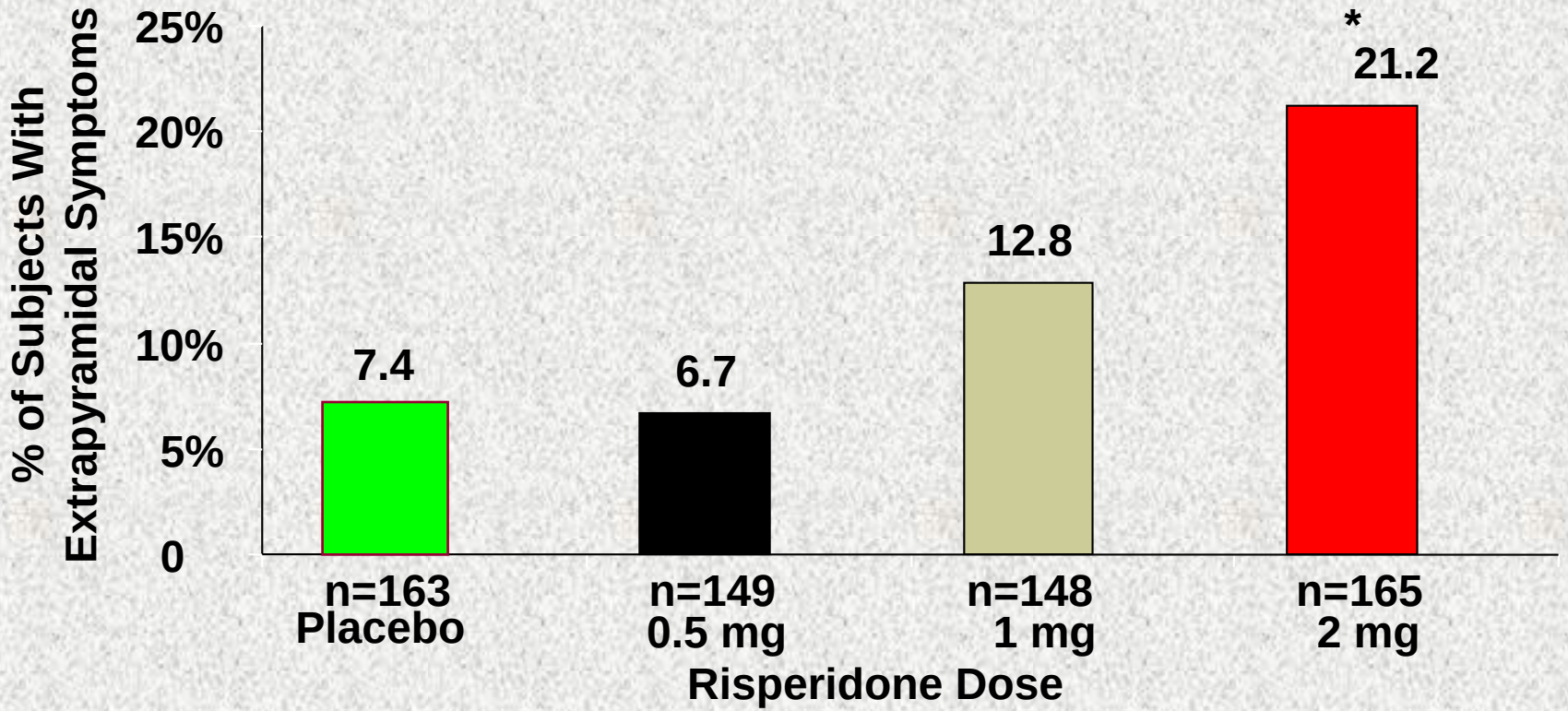


***P < 0.005 vs placebo.**

BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease

Katz IR et al. *J Clin Psychiatry.* 1999;60:107-115

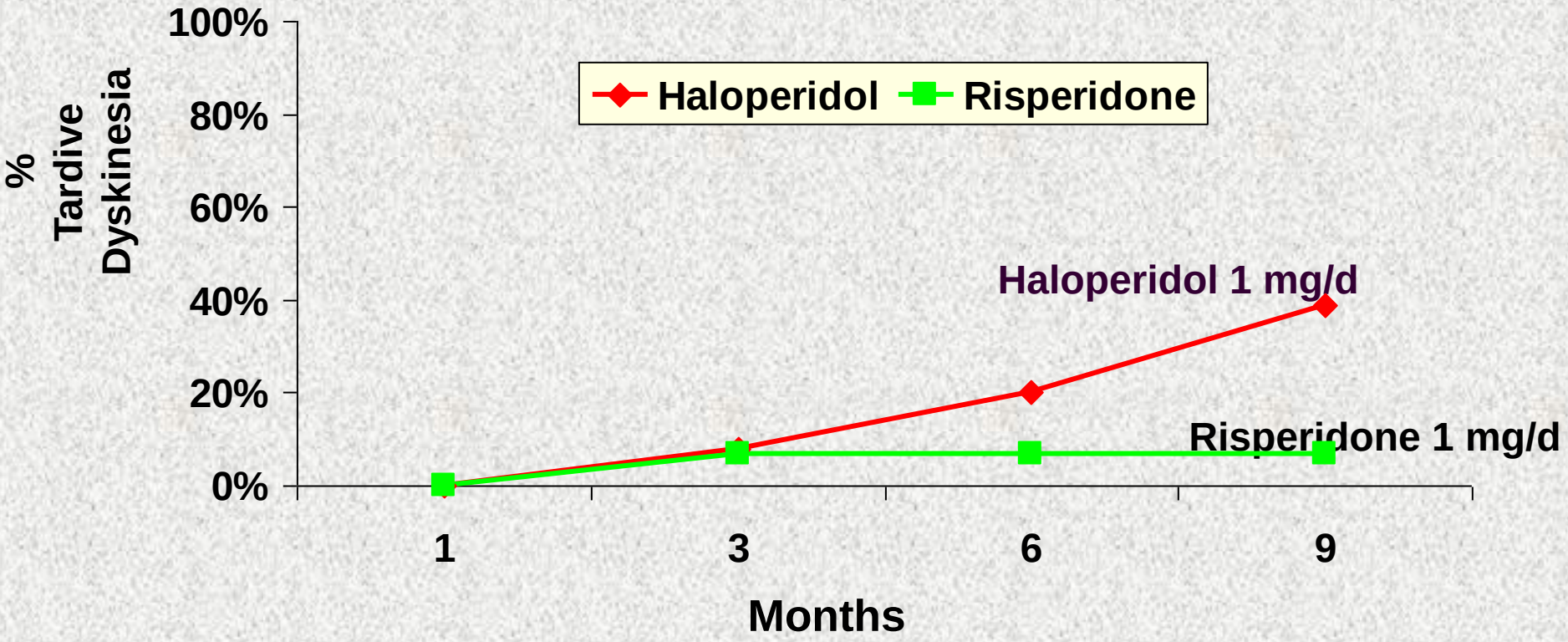
Risperidone in Dementia (N = 625): Incidence of EPS



******P* **≤ 0.05.**

Katz IR et al. ***J Clin Psychiatry.*** **1999;60:107-115.**

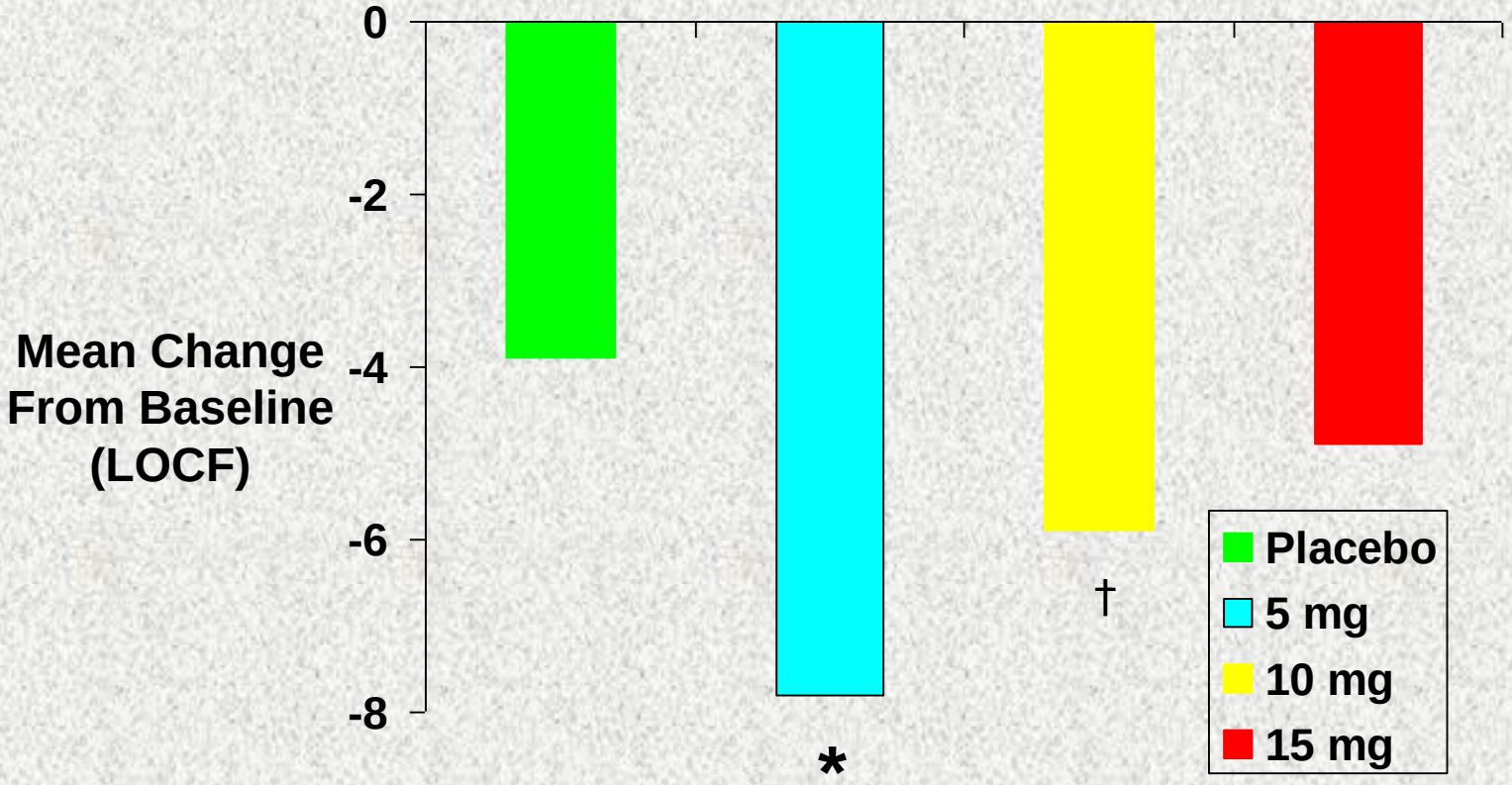
Tardive Dyskinesia in Older Patients: Haloperidol (N = 61) vs Risperidone (N = 61)



Peto-Prentice *P* value < 0.05.

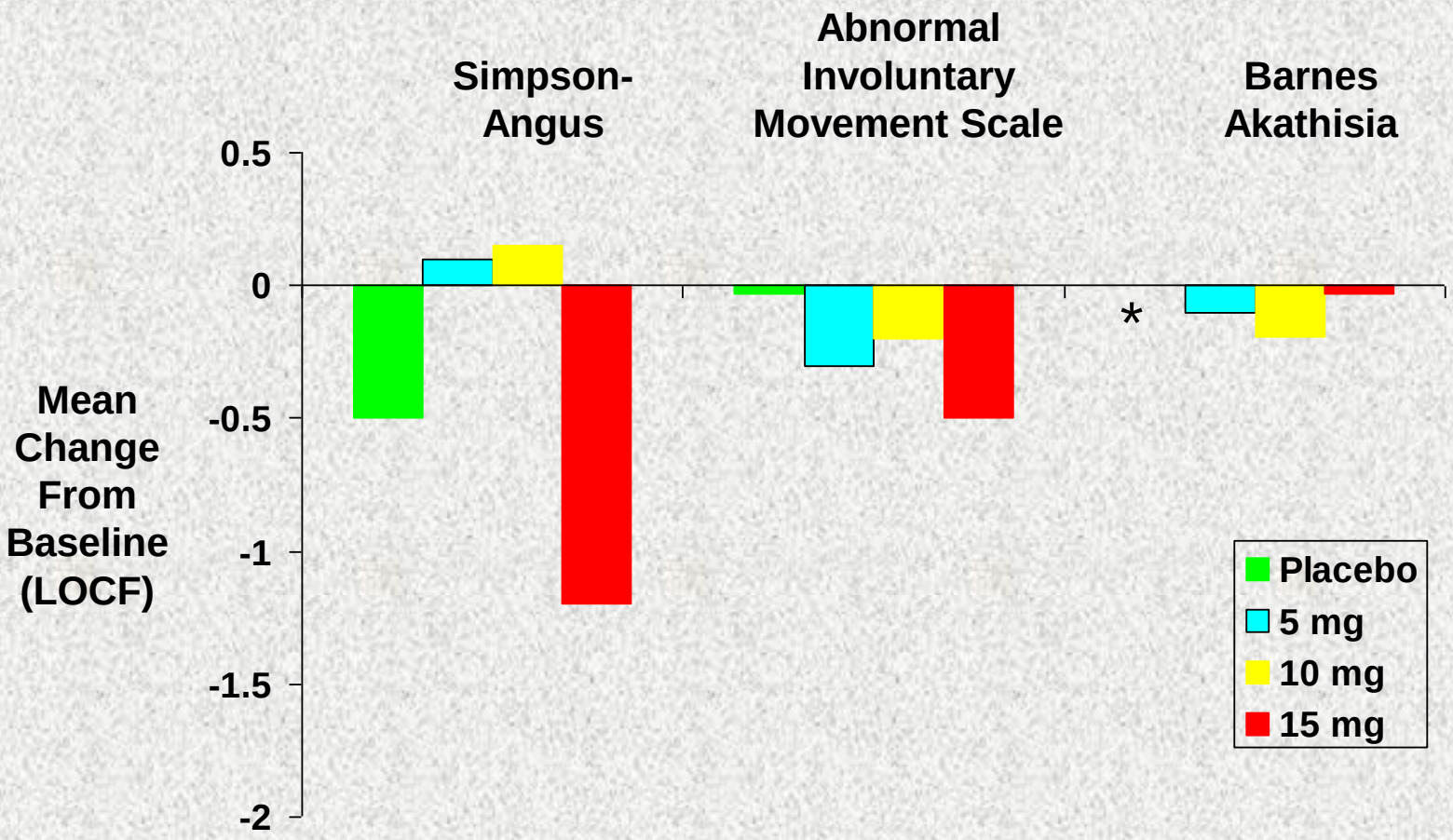
Jeste DV et al. *J Am Geriatr Soc*. 1999;47:716-719

Olanzapine in Dementia: NPI-NH Core Total (N = 206)



*P < 0.001, †P < 0.01 vs placebo.
LOCF = last observation carried forward.
NPI-NH = Neuropsychiatric Inventory–Nursing Home version.
Street JS et al. *Arch Gen Psychiatry*. 2000;57:968-976.

Olanzapine in Dementia (N = 206): Incidence of Movement Disorders



*No change.

LOCF = last observation carried forward.

Street JS et al. *Arch Gen Psychiatry.* 2000;57:968-976

Double-Blind Trial of Quetiapine in AD Patients With Psychosis

- Quetiapine compared with haloperidol and placebo for improving psychotic symptoms in patients with AD (n=284)
- Ten-week, randomized trial followed by a two-week washout period
- Flexible dosing adjusted to patient response and tolerability

Tariot PN et al. Abstract, *Am J Geriatr* Psychiatry 2002;10(2), Supplement:93.

Quetiapine in AD Patients With Psychosis: Results

- All treatment groups improved psychotic symptoms, but no difference among the 3 groups (Quetapine, Haloperidol, Placebo)
- Quetiapine and Haloperidol improved agitation more than Placebo
- Quetiapine showed better tolerability than Haloperidol, & similar EPS and anticholinergic effects as Placebo

Tariot PN et al. Abstract, *Am J Geriatr* Psychiatry 2002;10(2), Supplement:93.

Aripiprazole for Psychosis of AD: 10-Week Double-Blind, Placebo-Controlled Trial (N = 208)

- Outpatient study in Europe
  - Flexible dosage
  - Dose range 2-15 mg once per day
  - Mean dose at end point 10 mg/d
- Efficacy measures
  - NPI psychosis [hallucinations and delusions]
  - BPRS psychosis [hallucinatory behavior and unusual thought content]

DeDeyn, Jeste et al., J Clinical Psychopharmacology, 2005

Aripiprazole vs Placebo for Psychosis of AD: Summary

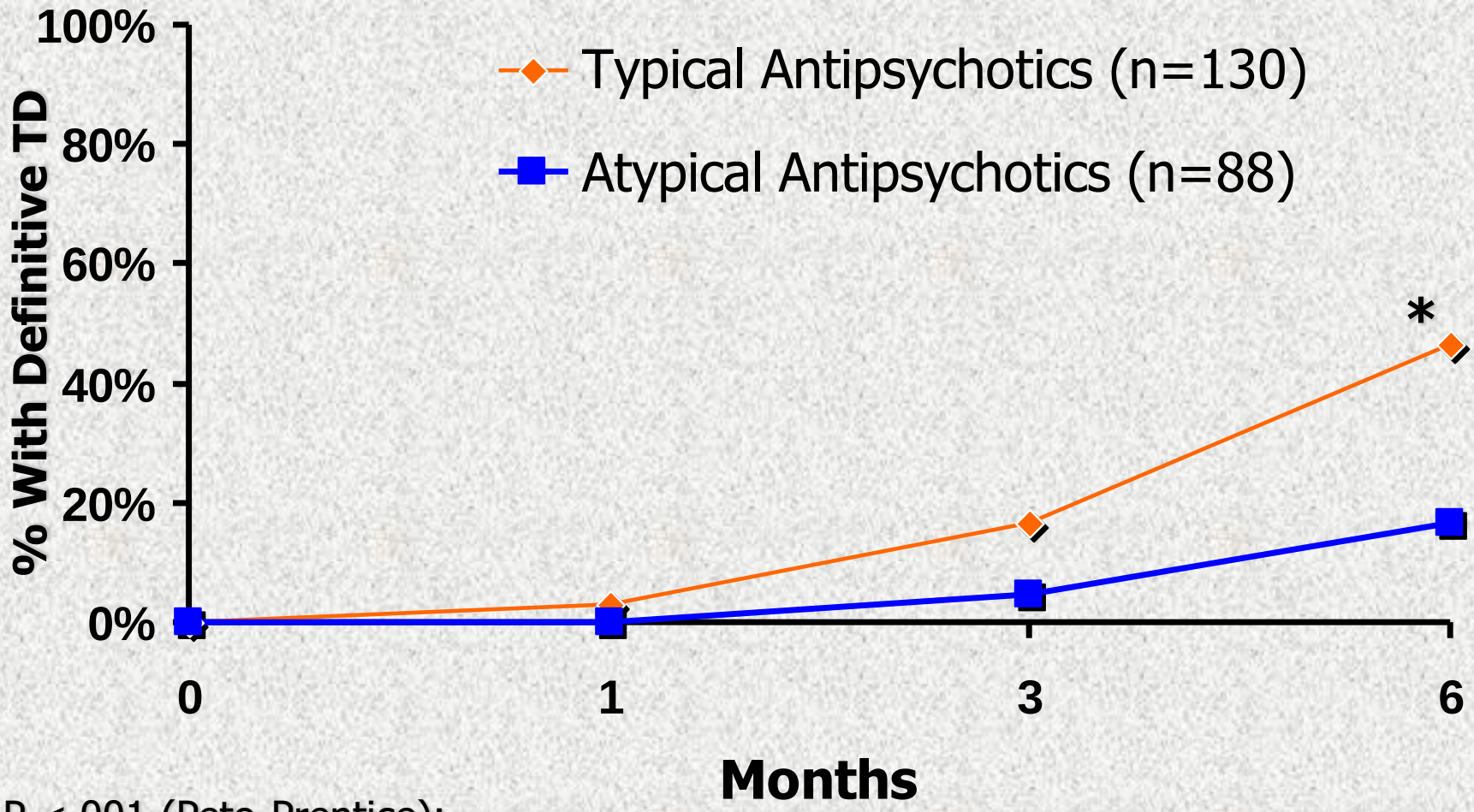
- Efficacy
  - Significant reduction in BPRS core and psychosis scores, but not in NPI psychosis score at end point (the primary outcome measure)
- Safety and tolerability
  - No drug-placebo differences in incidence of EPS-related AE or orthostatic events
  - Low rate of discontinuation due to AEs
  - Somnolence was mild and not associated with falls

DeDeyn, Jeste et al., J Clinical Psychopharmacology, 2005

Ziprasidone

- Efficacious in patients with schizophrenia
- Low risk of sedation
- Low risk of extrapyramidal symptoms
- Low risk of weight gain
- Possible issue: QTc prolongation
- No controlled data in dementia patients

Cumulative Incidence of Definitive TD in Older Patients With Borderline Dyskinesia



* P <.001 (Peto-Prentice);

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

Efficacy of Atypical Antipsychotics in AD

- **Atypical antipsychotics generally better than placebo for agitation, aggression, and overall behavioral problems in patients with psychosis of AD**
- **Efficacy for specific psychotic symptoms in AD patients less certain**
- **High placebo response rate in psychosis of AD**
- **Useful dose ranges tend to be restricted**
- **Use of antipsychotics in dementia patients is off-label**

Short-Term Side Effects of Atypical Antipsychotics in Elderly Patients

- More common
  - Sedation/somnolence
  - Postural hypotension and falls
  - Extrapyramidal symptoms and gait abnormality
- Increased risk with higher doses
- Some selectivity for different drugs

Long-Term Side Effects

- Weight gain
- Type 2 diabetes mellitus
- Hyperprolactinemia
- Cardiac conduction disorders
- Cerebrovascular accidents
- Increased mortality

FDA Warnings About Antipsychotic Use

- In all patients: Weight gain, Diabetes, Dyslipidemia
- In dementia patients:
  - Increased incidence of strokes with risperidone, olanzapine, and aripiprazole
  - Increased overall mortality with all atypical antipsychotics as a class

New FDA Public Health Advisory on Antipsychotics for Elderly patients with Behavioral Disturbances

- Data pooled from 17 placebo-controlled trials in dementia patients with behavioral disorders
- Mortality with antipsychotics was 1.6 to 1.7 times greater than with placebo
- 15/17 Studies showed numerically higher mortality; the most common causes were cardiac (heart failure) and infectious (pneumonia)
- Limited available data suggest that first-generation antipsychotics are associated with comparable increase in 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 relationships between the antipsychotics and these adverse events in individual patients have so far been clearly established
- However, the possibility of a causal relationship cannot be excluded
- Must keep in mind FDA's black-box warnings in dementia patients

CATIE – AD Trial: Rates of Discontinuation of Tx

- **Primary outcome measure: Discontinuation due to any reason**
- **Median time to discontinuation:**

  Olanzapine (8.1 wks); Risperidone (7.4 wks); Quetiapine (5.3 wks); Placebo (8.0 wks)
- **No significant group differences**

(Schneider et al., NEJM, 355:1525-1538, 2006)

Recommended Dose Ranges in Patients with Psychosis of AD

Drug	Initial (mg/d)	Typical Range (mg/d)
Risperidone	0.25-0.5	0.5-1.5
Olanzapine	2.5-5	5-10
Quetiapine	12.5-25	50-200
Aripiprazole	2-5	7-12

Alternative Psychotropics

- Citalopram
- Divalproex sodium
- Carbamazepine
- Benzodiazepines (e.g. lorazepam)
- Trazodone
- Cognitive enhancers

Other Psychotropics for Treatment of Psychosis and Agitation in Dementia Patients

Limitations of the published reports

1. **Few large-scale double-blind randomized controlled trials in dementia patients with behavioral problems**
2. **Known adverse effects with each drug**
3. **Limited long-term safety data in these patients**

Shared Decision Making

- **Discussing with patients and caregivers (as appropriate) benefits & risks of different Tx options**
- **Giving an informed opinion with rationale**
- **The final decision made by the “consumer/s”**
- **Issues of Proxy consent, Assent, Advance directive**
- **“Enhancing” the informed consent process**
- **Documenting the discussion**

Clinical Recommendations for Treatment of Dementia Patients

- **General therapeutic considerations**
- **Shared decision making**
- **Choice of pharmacotherapy and dosages**
- **Monitoring efficacy and safety**
- **Role of psychosocial interventions**
- **Switching or discontinuing pharmacotherapy**
- **Coordinating overall patient care**

(Jeste et al.: ACNP White Paper: Update on Antipsychotics in Older Patients, Neuropsychopharmacology, 2007, July 18, e-pub)

Suggested Readings

- Teri L. Logsdon RG. McCurry SM. Nonpharmacologic treatment of behavioral disturbance in dementia. Medical Clinics of North America. 86:641-56, 2002

- Lawlor B. Bhriain SN. Psychosis and behavioural symptoms of dementia: defining the role of neuroleptic interventions. International Journal of Geriatric Psychiatry. 16 Suppl 1:S2-6, 2001

- Jeste DV and Finkel SI: Psychosis of Alzheimer s disease and related dementias: Diagnostic criteria for a distinct syndrome. American Journal of Geriatric Psychiatry 8: 29-34, 2000

Suggested Readings

- **Jeste DV, Blazer D, Casey DE, Meeks T, Salzman C, Schneider L, Tariot P and Yaffe K: ACNP White Paper: Update on the use of antipsychotic drugs in elderly persons with dementia. Neuropsychopharmacology (in press, 2007; July 18, e-pub)**

- **Ropacki S and Jeste DV: Epidemiology of and risk factors for psychosis of Alzheimer Disease: A review of 55 studies published from 1990 to 2003. American Journal of Psychiatry, 2005**

- **Sweet RA, Nimgaonkar VL, Devlin B and Jeste DV: Psychotic symptoms in Alzheimer Disease: Evidence for a distinct phenotype. Molecular Psychiatry 8:383-392, 2003**

Self-Assessment Question 1

Which of the following statements is true?

A. Psychosis and agitation are uncommon symptoms in demented patients.

B. Psychosis, in Alzheimer disease patients, is associated with increased functional impairment.

C. Male gender and higher educational level are associated with increased risk of psychotic symptoms in Alzheimer disease.

D. All of the above

E. None of the above

Self-Assessment Question 2

Psychosis in AD is associated with which of the following?

A. Frontal lobe neurobehavioral dysfunction
B. Apathy
C. Disinhibition
D. All of the above
E. None of the above

Self-Assessment Question 3

Which of the following statements is true?

A. Atypical antipsychotics are FDA-approved for treatment of psychosis in Alzheimer disease.

B. Off-label, evidence-based use of medications is legal, and should be accompanied by appropriate disclosure and discussion of rationale, risks, and benefits

C. Atypical antipsychotics are associated with greater mortality risk than conventional antipsychotics.

D. All of the above

E. None of the above

Self-Assessment Question 4
Adverse effects associated with use of atypical antipsychotic medications in dementia patients with psychosis include which of the following?

A. Sedation/somnolence
B. Postural hypotension
C. Cerebrovascular accidents
D. Increased mortality
E. All of the above

Self-Assessment Question 5

Which of the following medications has been approved for treating agitation or psychosis in dementia patients?

A. Citalopram
B. Divalproex sodium
C. Carbamazepine
D. Cholinesterase inhibitors
E. None of the above

Answers to Self-Assessment Questions

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