Psychosis in Dementia

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Potential Conflicts of Interest

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

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

Psychotic symptoms are common in which of the following dementias?

A. Alzheimer disease
B. Lewy body dementia
C. Fronto-temporal dementia
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 Alzheimer disease (AD) and other dementias
- 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 strongly recommended

Prevalence of Behavioral Disturbances in Alzheimer Disease

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

Wragg RE and Jeste DV, Am J Psychiatry, 146:5:577-587, 1989
Ropacki SA and Jeste DV, Am J Psychiatry, 162:2022-2030, 2005

Psychosis of Alzheimer Disease: Diagnostic Criteria

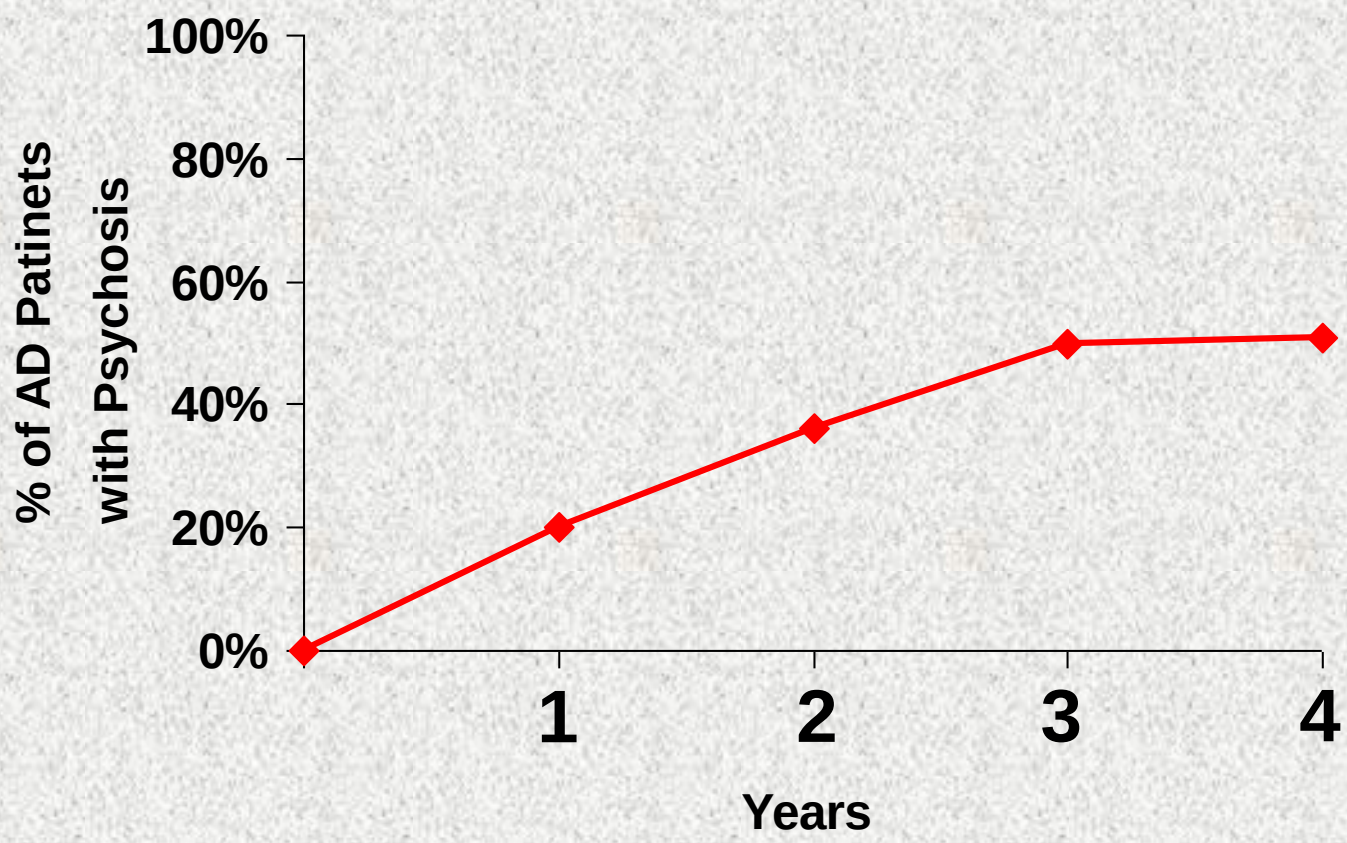
- Primary diagnosis is Alzheimer disease
- Characteristic psychotic symptoms: delusions or auditory/visual hallucinations
- Dementia onset precedes psychotic symptoms
- Duration >1 month
- Functional disruption
- Exclusion of delirium, schizophrenia, other causes of psychosis

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

Psychosis of AD: Public Health Significance

1) High incidence and prevalence
2) Chronic or recurrent
3) More agitation, aggression
4) More rapid cognitive decline, and possibly death
5) Greater caregiver distress
6) Earlier institutionalization
7) Higher cost of care

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*, 2005,162:2022-2030)

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, 54:1965-1971

Neurobiology of Psychosis of AD

- Clinical, neuropsychological, electrophysiological, brain imaging, and neuropathology studies
- Predominantly fronto-temporal pathology
- Involvement of DA, NA, and 5-HT systems
- Some similarities with but also several differences from “functional” psychoses such as schizophrenia

Psychosis in Other Dementias

1) Common in Lewy Body Dementia; high sensitivity to medications
2) Psychosis in Parkinson disease with dementia: Different causes; Commonly due to dopaminergic drugs; Unique treatment considerations (e.g., usually reduction in dopaminergic drugs)
3) Non-psychotic behavioral symptoms more common in fronto-temporal dementia and vascular dementia

Treatment Modalities

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

Review of Psychosocial Interventions for Behavioral Disturbances in Dementia

(Behaviors That May Accompany Psychosis)

- **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;

Teri L, et al. *Med Clin North America 2002;* 162:2022-2030

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 RE and Jeste DV. *Psychiatr Clin North Am*. 1988;11:195.
2. Schneider LS, et al. *J Am Geriatr Soc*. 1990;38:53.

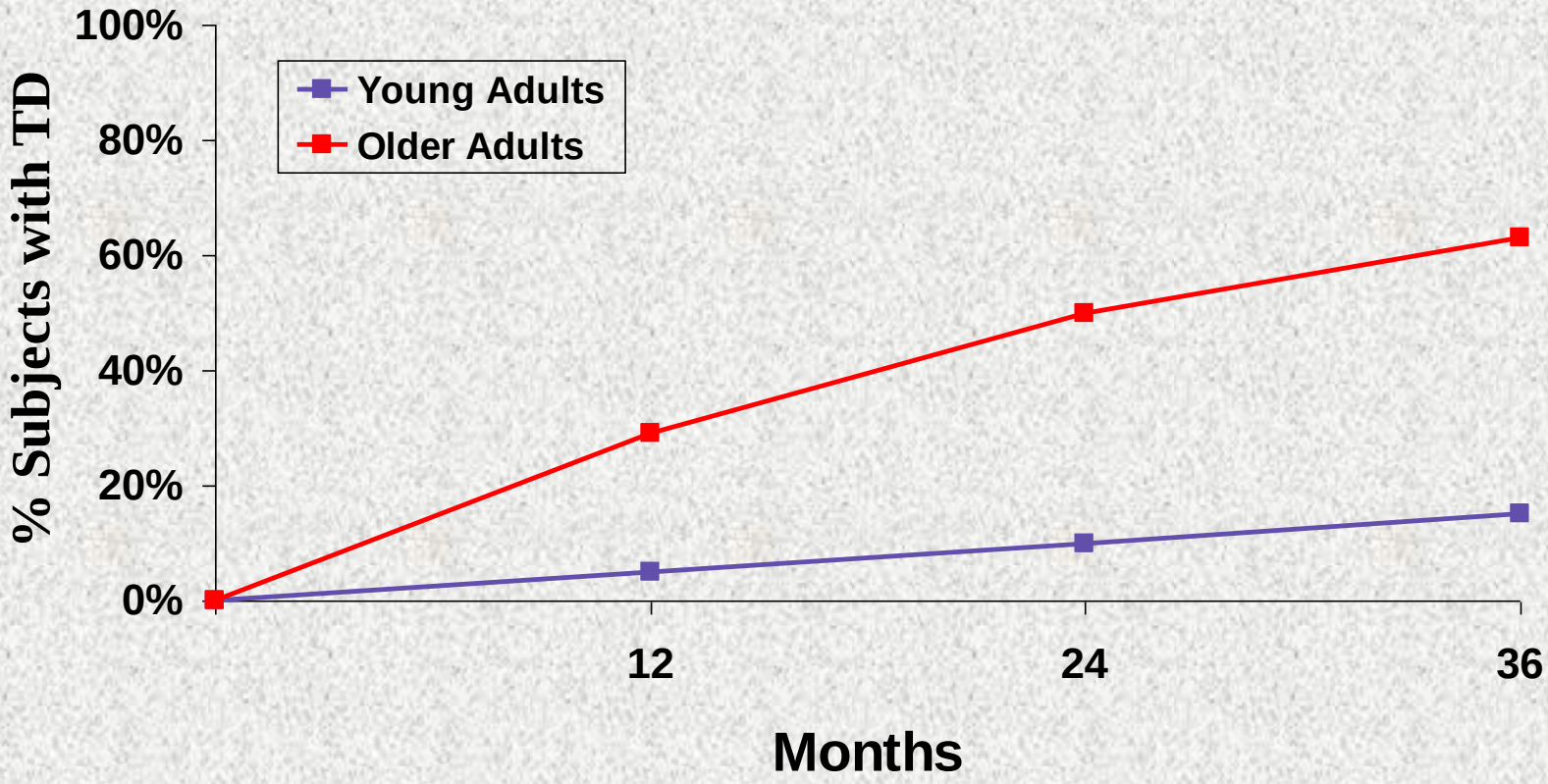
Adverse Effects of "Typical" Antipsychotics in Older Patients

- 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

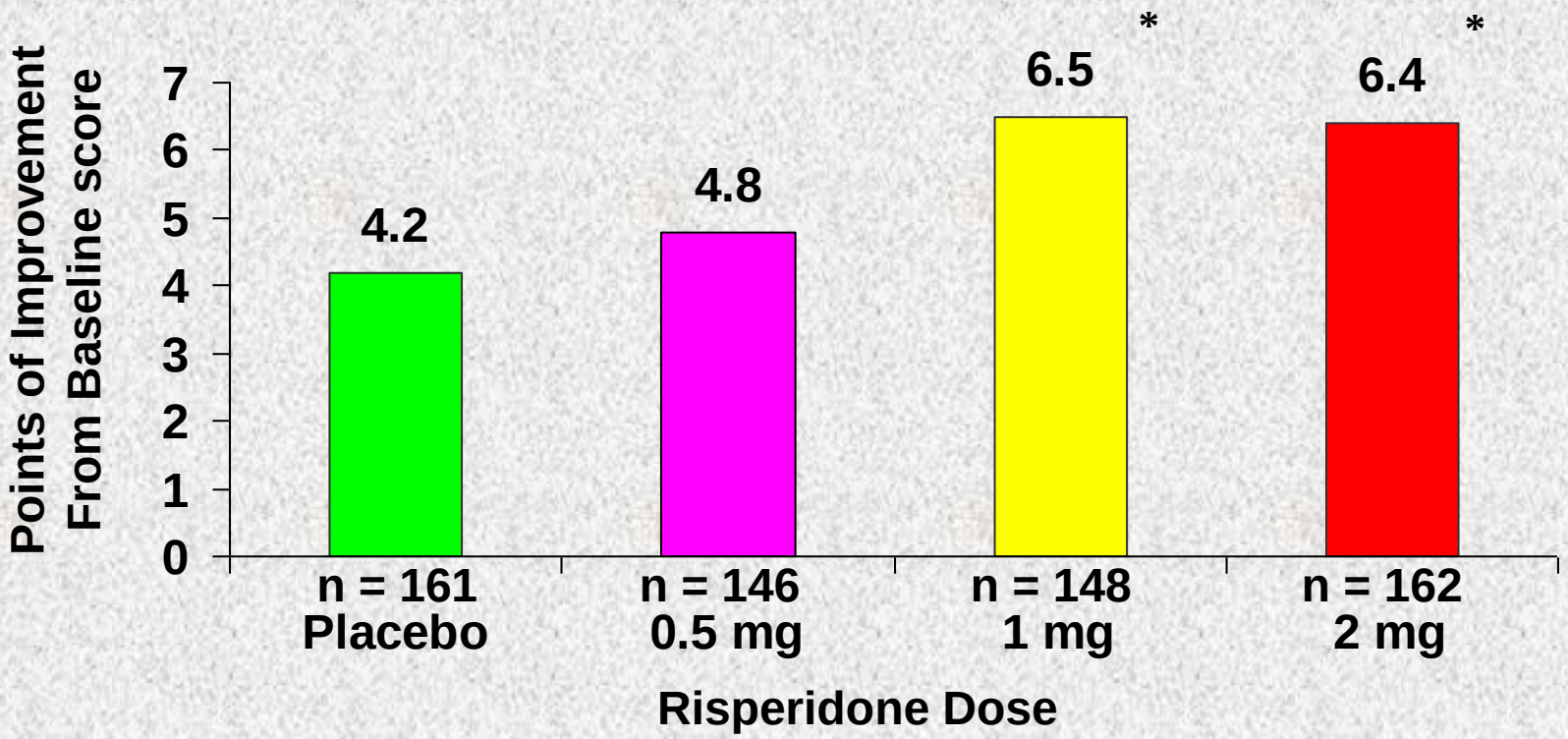


Jeste DV et al. Arch Gen Psychiatry 52:756-765, 1995; Kane JM et al. J Clin Psychopharmacol 1988;8(suppl):52S-56S

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

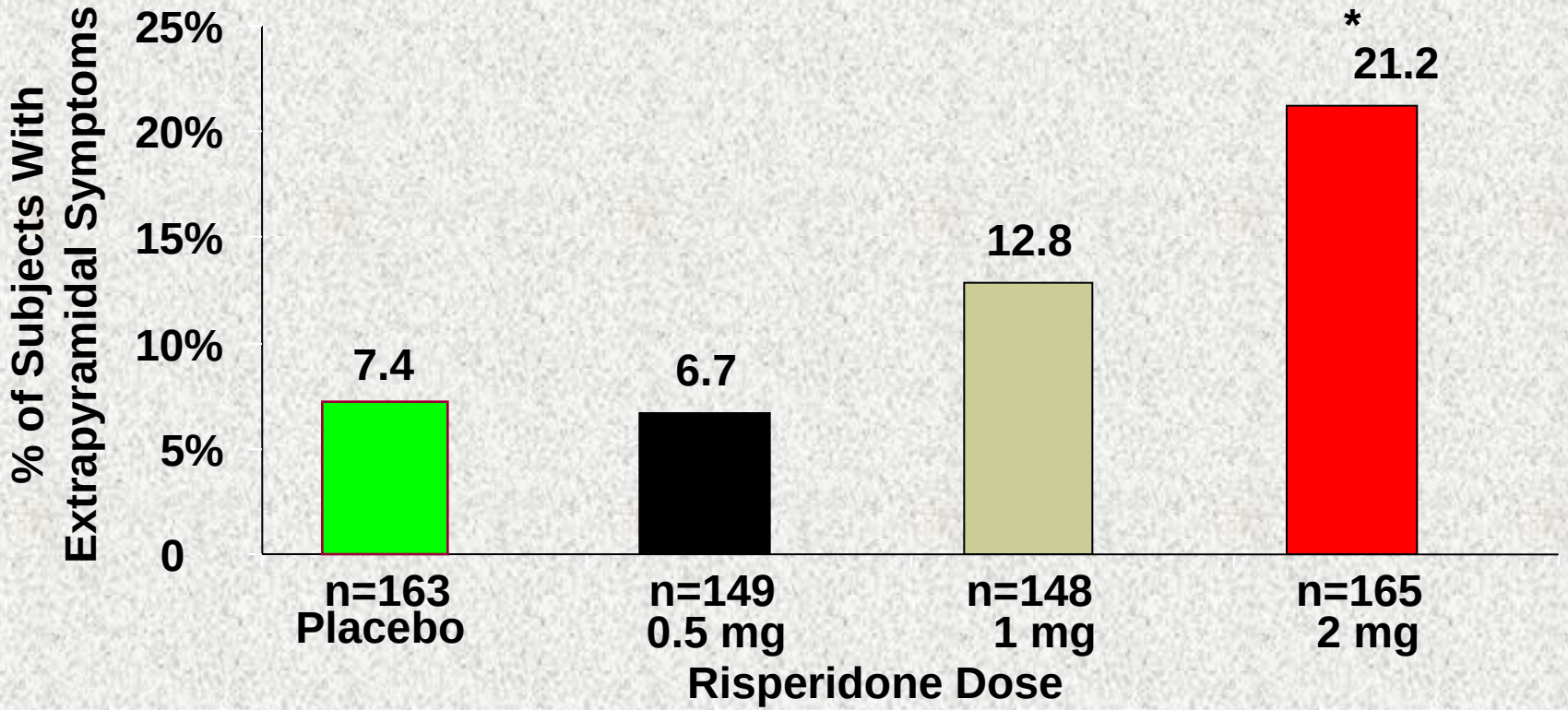


****P* < 0.005 vs placebo.**

BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease

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

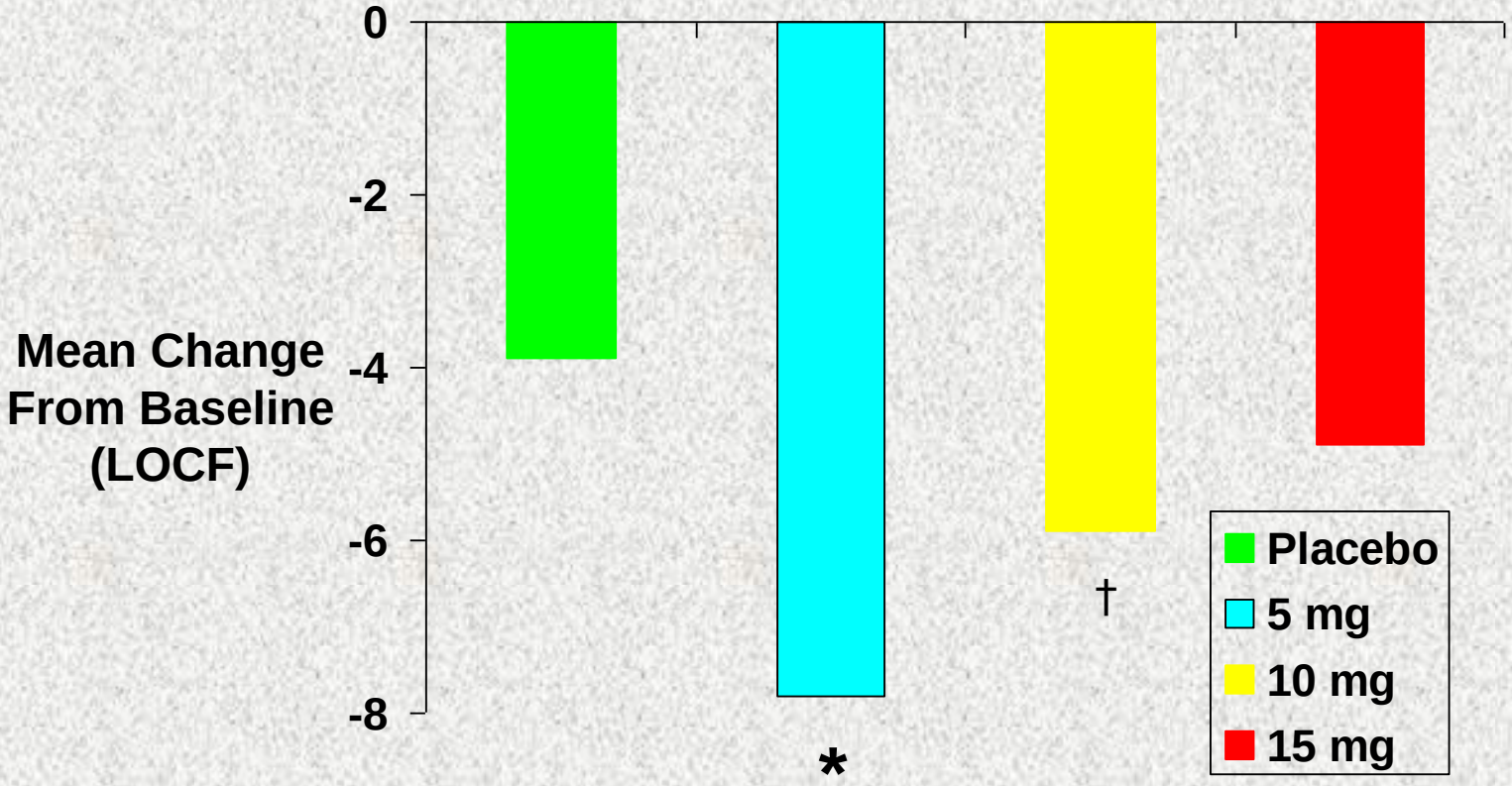
Risperidone in Dementia (N = 625): Incidence of EPS



******P* **≤ 0.05.**

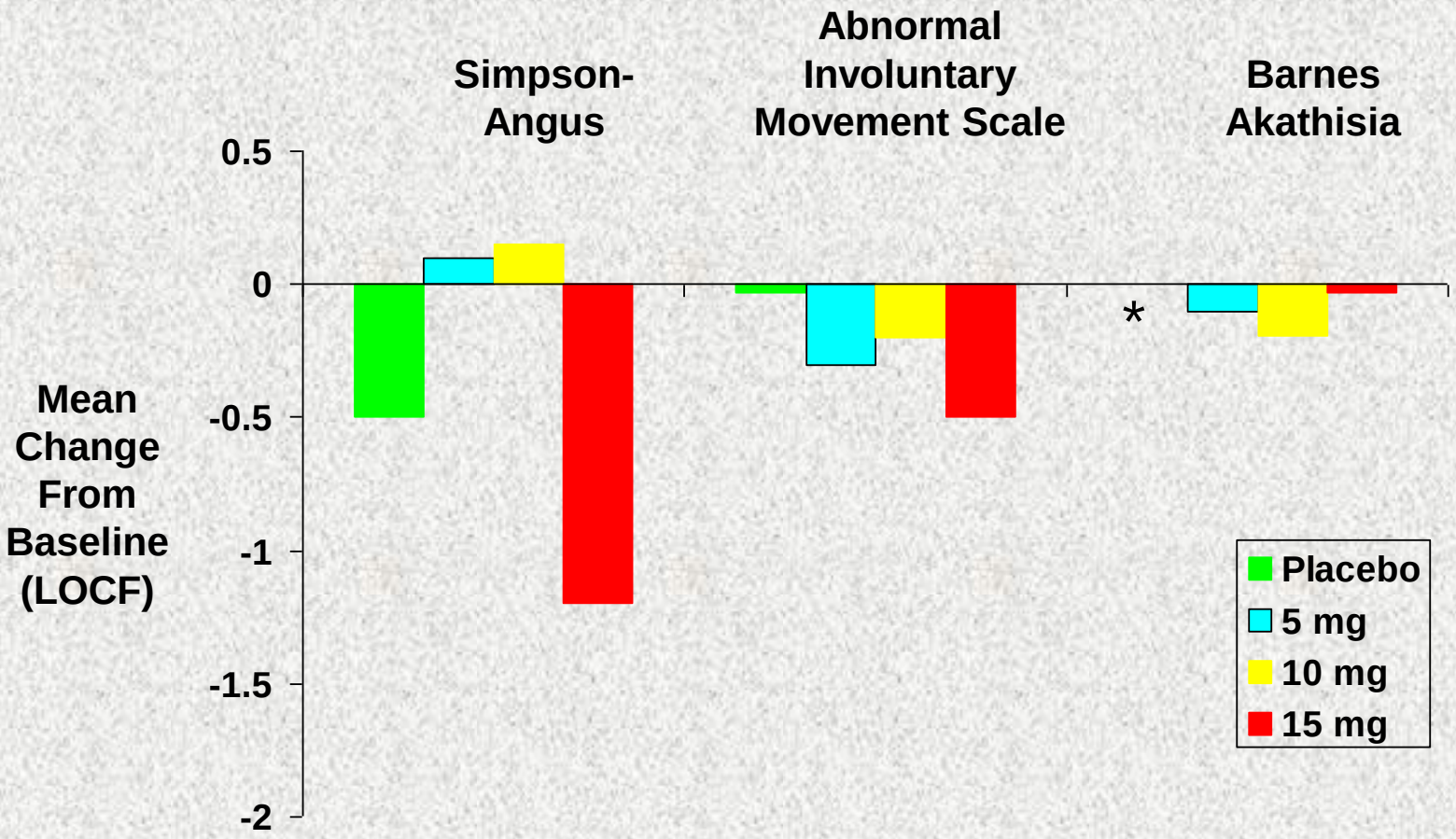
Katz IR et al. ***J Clin Psychiatry.*** **1999;60:107-115.**

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. *Am J Geriatr Psychiatry* 2006; 14: 767-776

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. *Am J Geriatr Psychiatry* 2006; 14: 767-776

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 P, *J Clin Psychopharmacol*, 2005; 25: 463-467

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 P, et al., *J Clin Psychopharmacol*, 2005; 25: 463-467

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

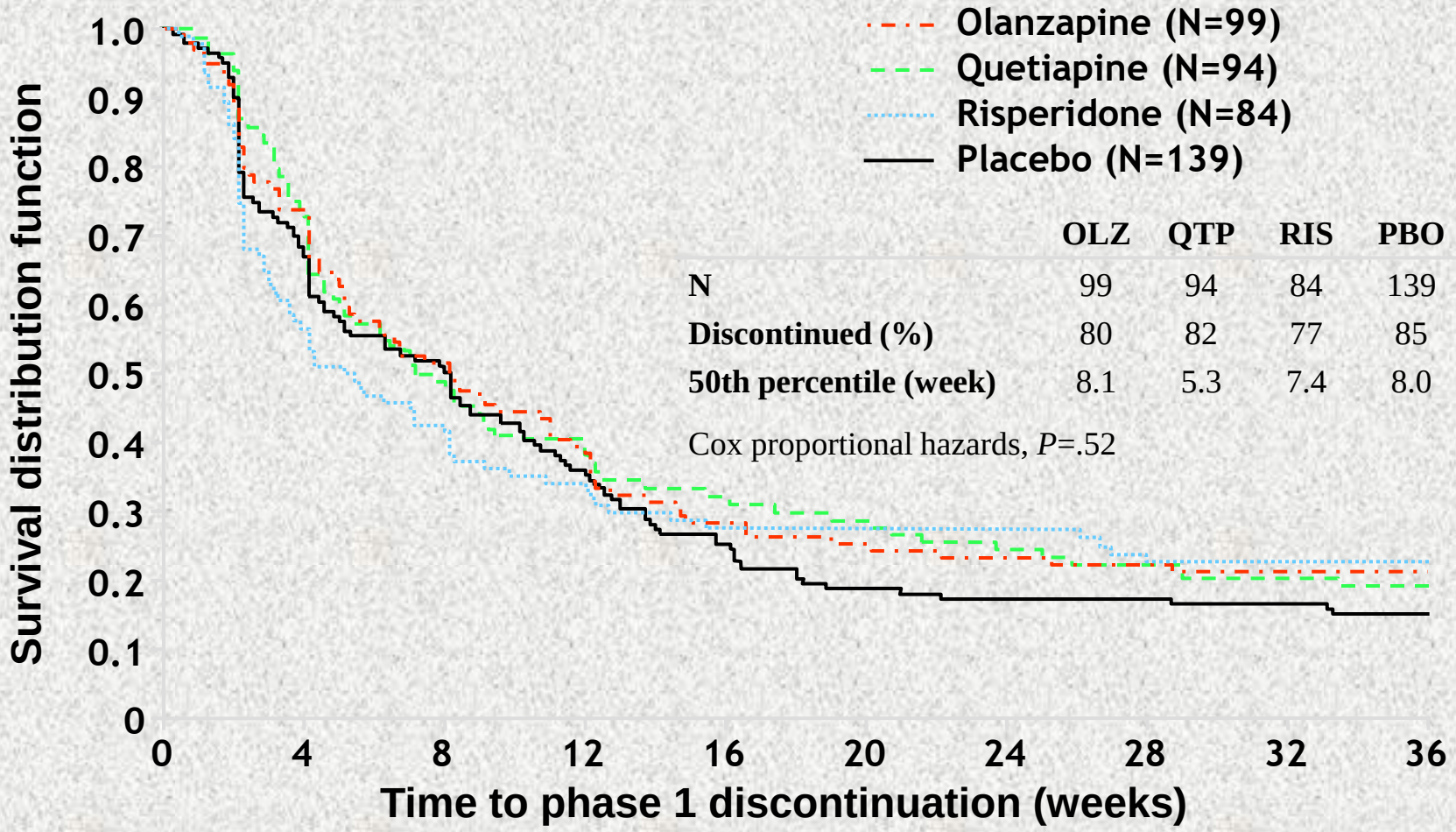
CATIE – AD Trial: Rates of Discontinuation of Drug

- **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 LS, et al., NEJM, 355:1525-1538, 2006

CATIE-AD: All-cause Discontinuation (Phase 1, Intent To Treat)



	OLZ	QTP	RIS	PBO
N	99	94	84	139
Discontinued (%)	80	82	77	85
50th percentile (week)	8.1	5.3	7.4	8.0

Cox proportional hazards, *P*=.52

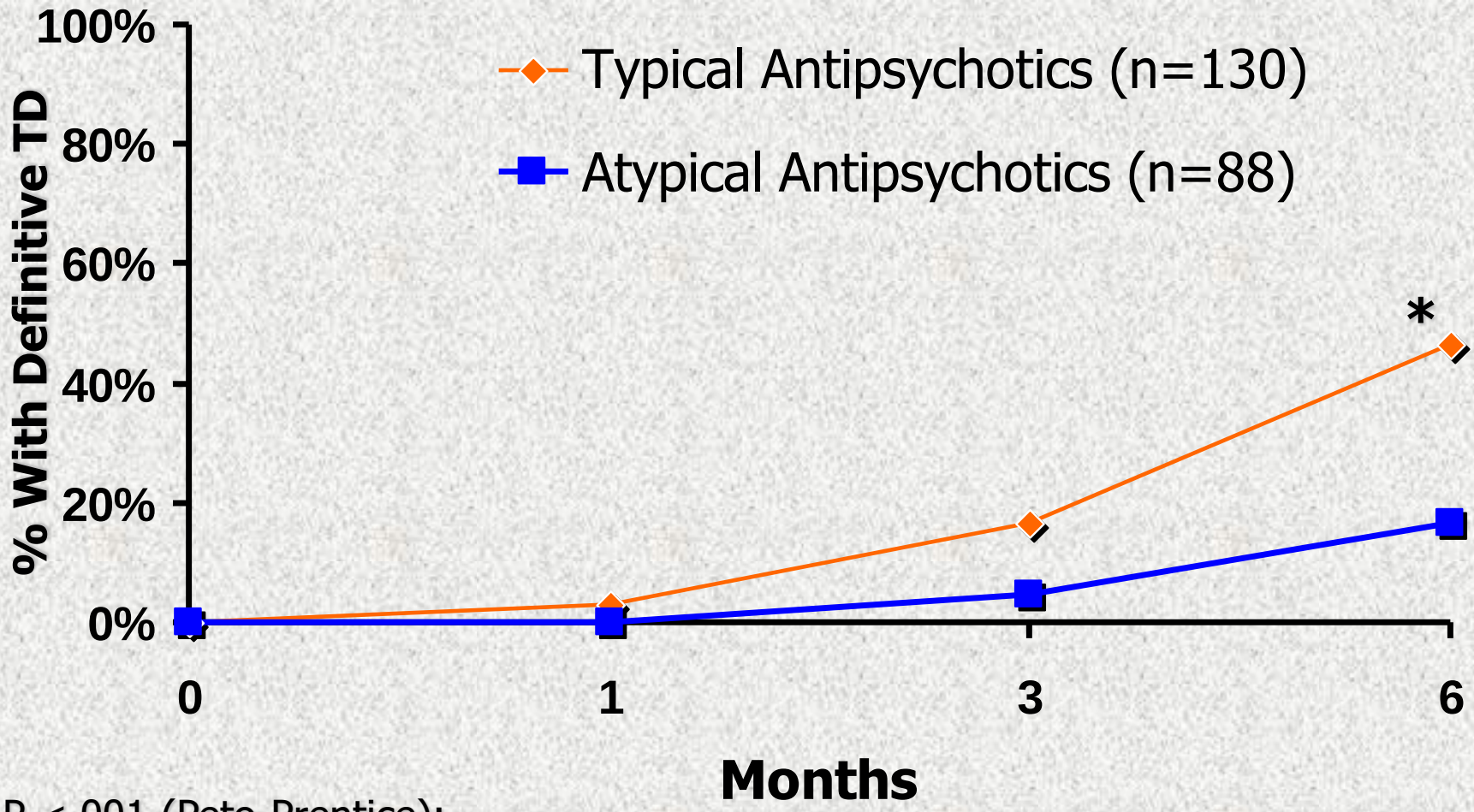
Efficacy of Atypical Antipsychotics in AD

- 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

Cumulative Incidence of Definitive TD in Older Patients With Borderline Dyskinesia



* P <.001 (Peto-Prentice);

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

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

FDA Black-Box Warning Re. Strokes with Atypical Antipsychotics in Dementia Pts.

- A double-blind placebo-controlled trial of risperidone in elderly patients with dementia (Brodaty et al., 2003) indicated a higher risk of strokes with risperidone compared to placebo
- The FDA analyzed data from all the placebo-controlled trials in dementia patients, & found a significantly higher risk of strokes with several atypical antipsychotics than with placebo
- This led to black-box warnings re. increased risk of strokes with risperidone, olanzapine, & aripiprazole in dementia patients

FDA Black Box Warning Re Mortality with Antipsychotic Use in Elderly Dementia Patients

- 17 Placebo-controlled trials of atypical antipsychotics in dementia patients with behavioral disorders
- Mortality with atypical antipsychotics 1.6 to 1.7 times greater than with placebo
- Common causes were cardiac (heart failure) or infectious (pneumonia)
- June 2008: Warning extended to conventional neuroleptics

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
(primarily investigated in treating agitation in dementia)

- Citalopram (or possibly other SSRI's)
- 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**

Step-wise Treatment of Psychosis of AD

- Treat underlying causes, if possible
- Environmental and behavioral measures
- Antipsychotics
- Benzodiazepines
- Other drugs

(Rabins PV, et al., APA Practice Guidelines, 2007)

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 Tx Recommendations

- Share decision making with patients & caregivers
- Use appropriate psychosocial interventions
- Coordinate overall patient care
- Individualize pharmacotherapy and dosages
- Monitor efficacy and safety
- Risk:benefit ratio varies by diagnosis, age, gender, ethnicity, medication
- Limit duration of pharmacotherapy

(Jeste DV, et al.: ACNP White Paper: Update on antipsychotics in older patients, *Neuropsychopharmacol*, 2008; 33:957-970)

Suggested Readings

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

- **Rabins PV, Blacker D, Rovner BW, Rummans T, Schneider LS, Tariot PN: Practice Guidelines for the Treatment of Patients with Alzheimer's Disease and Other Dementias, Second edition, American Psychiatric Press, Inc., Washington, DC, 2007**

- **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**

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- 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 33:957-970, 2008

- 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, 162:2022-2030, 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

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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