Psychosis and Agitation in Dementia

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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-indicated for treatment of psychosis in Alzheimer disease.

B. Off-label, evidence-based use of medications is legal and common, 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 psychotic, demented patients have included which of the following?

A. Sedation/somnolence
B. Weight gain
C. Type 2 diabetes mellitus
D. Cerebrovascular/cardiovascular mortality
E. All of the above

Self-Assessment Question 5

Which of the following medications may be alternatives to antipsychotics in treating agitation or psychosis in demented patients?

A. Citalopram
B. Divalproex sodium
C. Carbamazepine
D. Cholinesterase inhibitors
E. Any of the above

Major Points

- Psychosis and/or agitation are frequent concomitants of dementia
- Psychosis in AD is associated with frontal neurobehavioral dysfunction, especially disinhibition and apathy
- Although no drug is FDA-indicated for treatment of psychosis in dementia, data support the use (with caution regarding adverse effects) of antipsychotics, especially the atypicals.
- Limited data support alternative roles for antidepressants, anticonvulsants, benzodiazepines, or cholinesterase inhibitors in treating psychosis or agitation in demented patients.

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

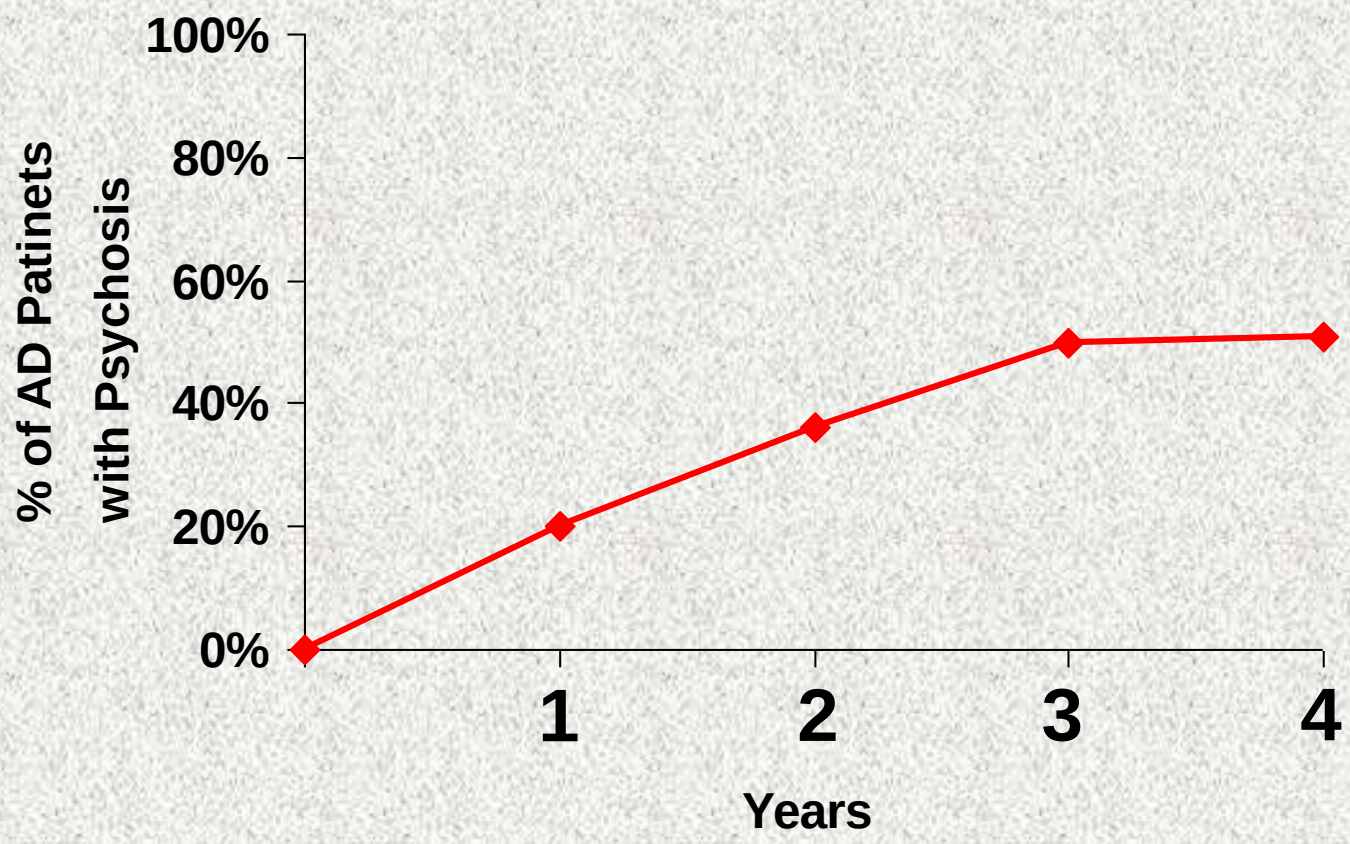
2) Negative symptoms

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

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

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

Caveat in Using Drugs in Patients with Psychosis of Dementia

- No drug (antipsychotic or other) has yet been approved for the treatment of psychosis of Alzheimer disease or other dementias.
- Atypical antipsychotics have been approved by the FDA only for the treatment of schizophrenia or bipolar disorder.
- Evidence-based off-label use of medications may be appropriate, is not illegal, and is common in practice.

Adverse Effects of "Typical" Antipsychotics in Older Patients

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

Functional Implications of Movement Disorders

- Higher EPS score associated with greater impairment in everyday functioning
- Higher AIMS score associated with worse quality of well-being
- Will EPS increase risk of non-adherence?

Patterson TL et al. Psychiatry Res 1998;80:41–52
Patterson TL et al. Psychiatry Res 1996;63:169–81

EPS with Typical Neuroleptics in AD Patients

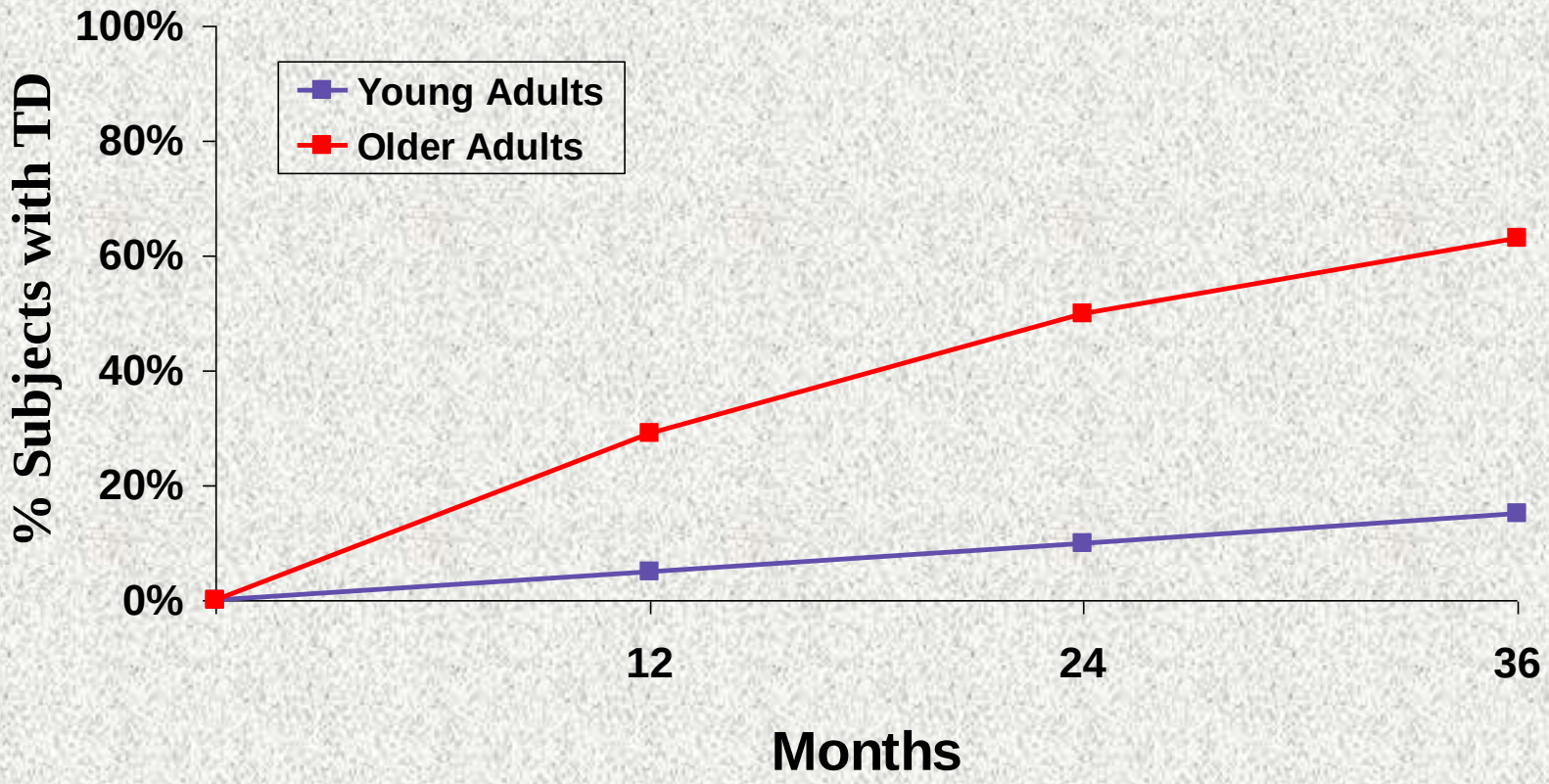
- Mean dose: 26mg (±18) CPZ/day
- 67% patients developed Parkinsonism within 9 months
- Risk factor: pretreatment bradykinesia on instrumental assessment

Caligiuri MP et al. Am J Geriatr Psychiatry 1998;6:75–82

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

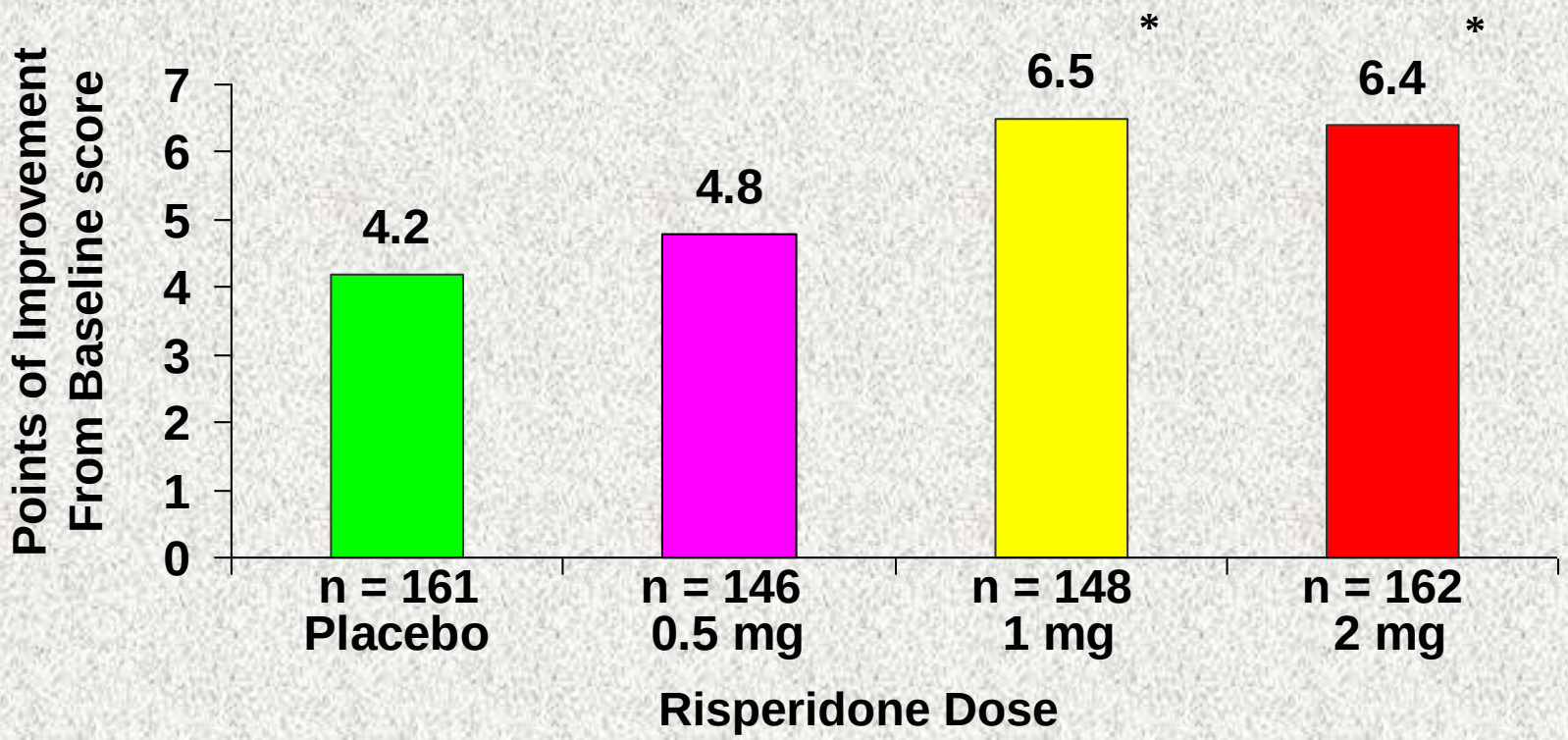


Jeste DV et al. Arch Gen Psychiatry 52:756-765, 1995; Kane JM et al. J Clin Psychopharmacol 1988;8(suppl):52S-56S

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

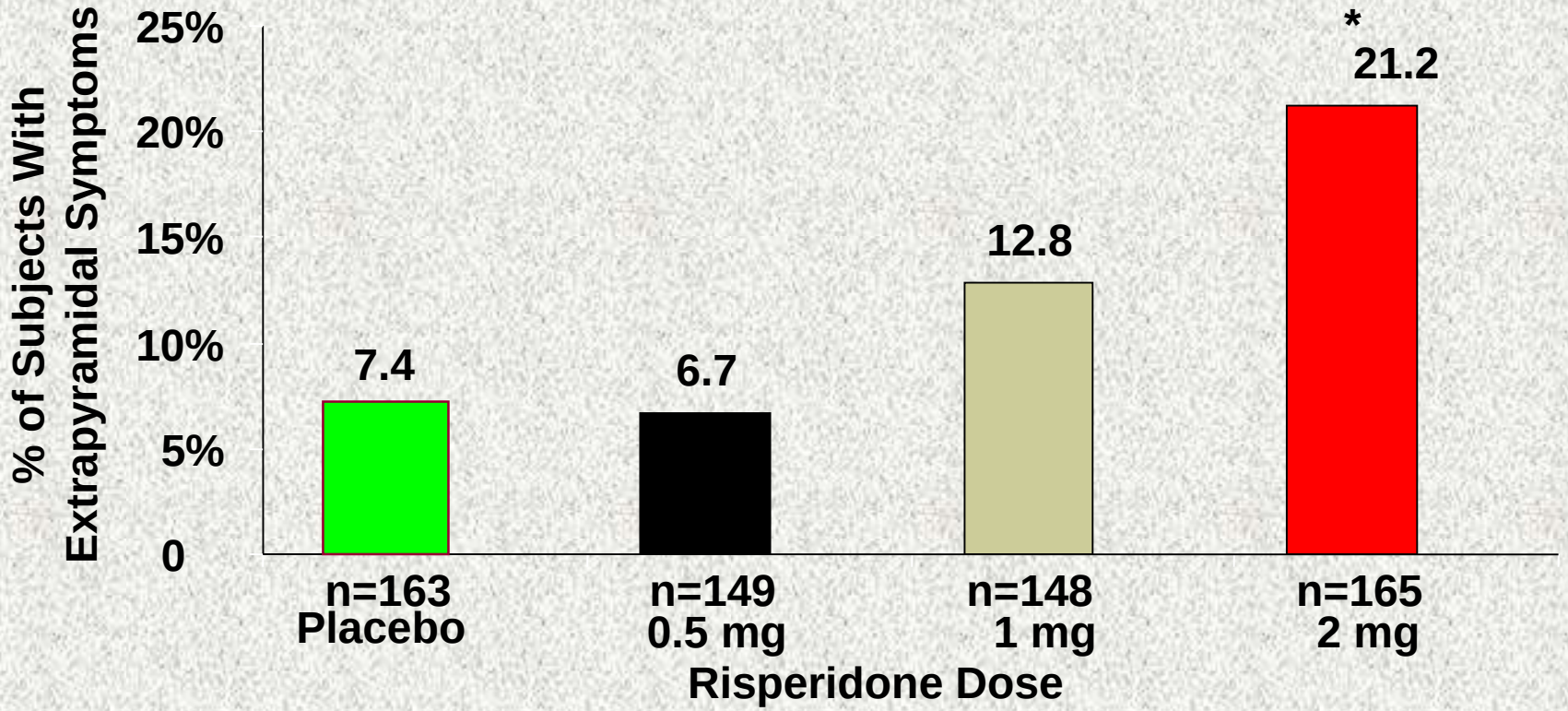


****P* < 0.005 vs placebo.**

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.**

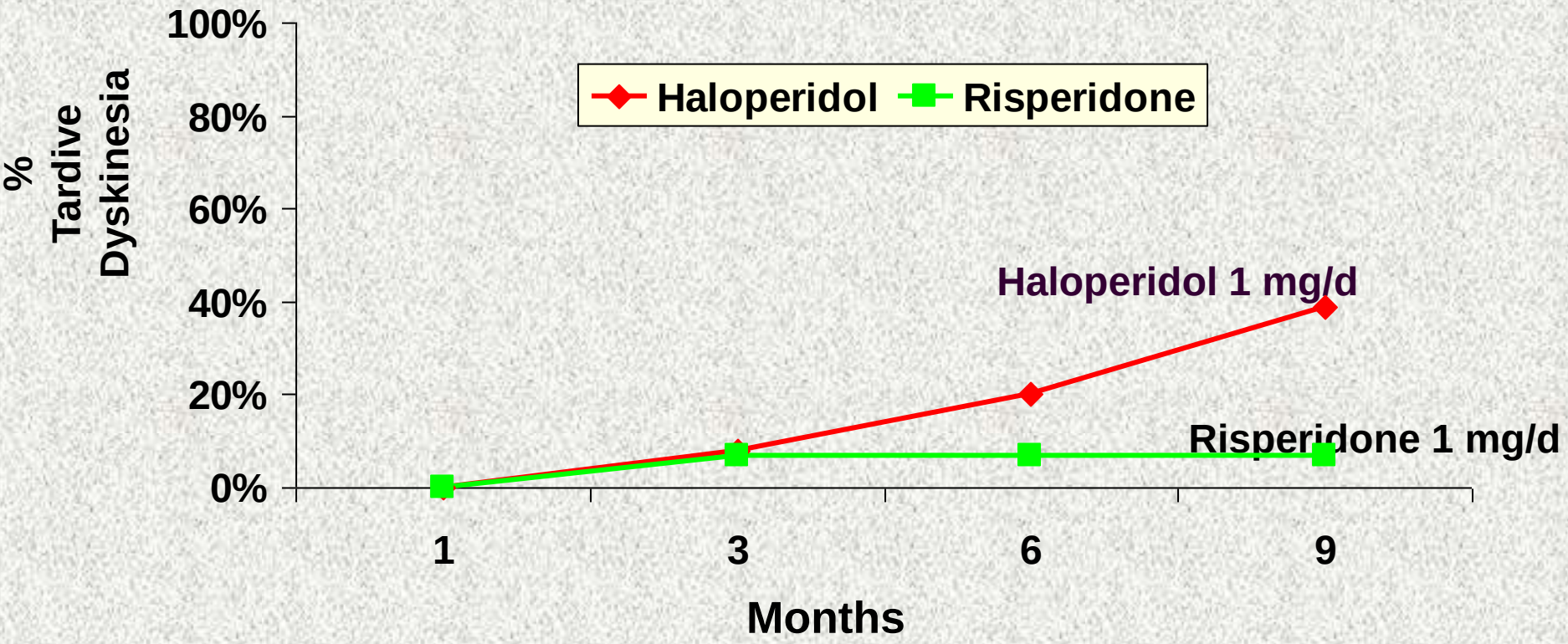
Katz IR et al. ***J Clin Psychiatry.*** **1999;60:107-115.**

Risperidone in Dementia: Australian Study

- 301 elderly nursing home patients with dementia and aggression randomized to risperidone or placebo
- 12-Week double-blind trial
- Significant improvement with risperidone in physical, verbal and total aggression on Cohen-Mansfield Agitation Inventory

Brodaty et al., J Clin Psychiatry, 2003

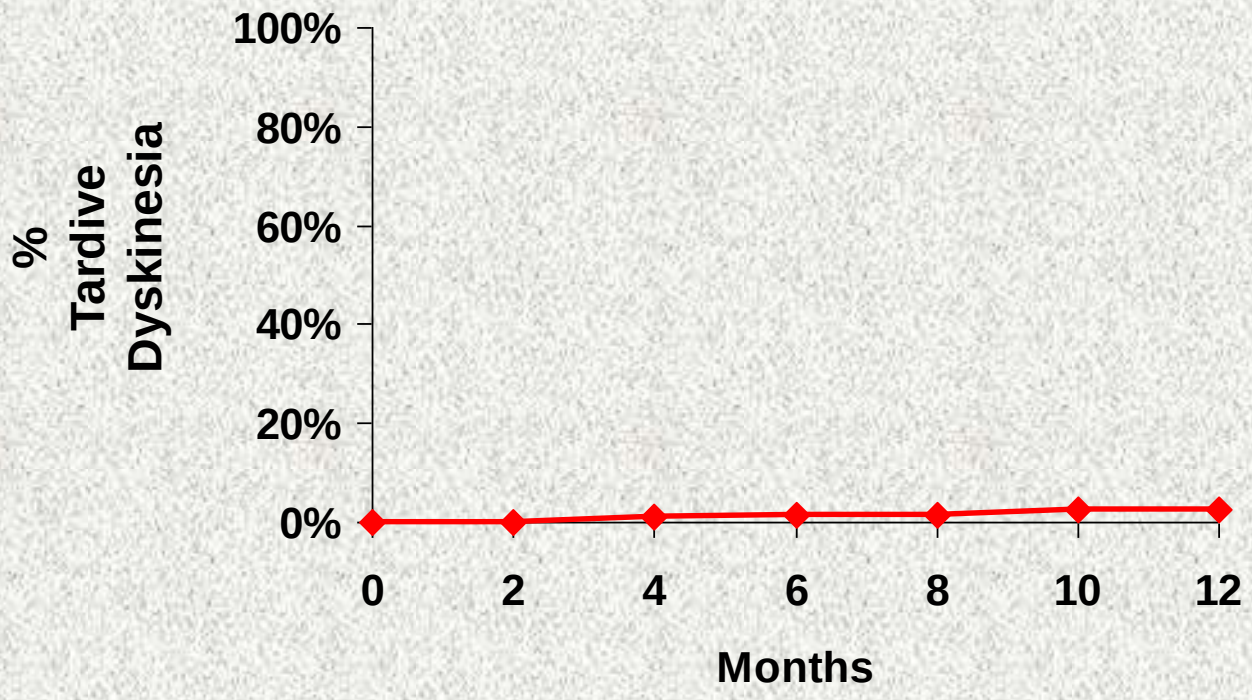
Tardive Dyskinesia in Older Patients: Haloperidol (N = 61) vs Risperidone (N = 61)



Peto-Prentice *P* value < 0.05.

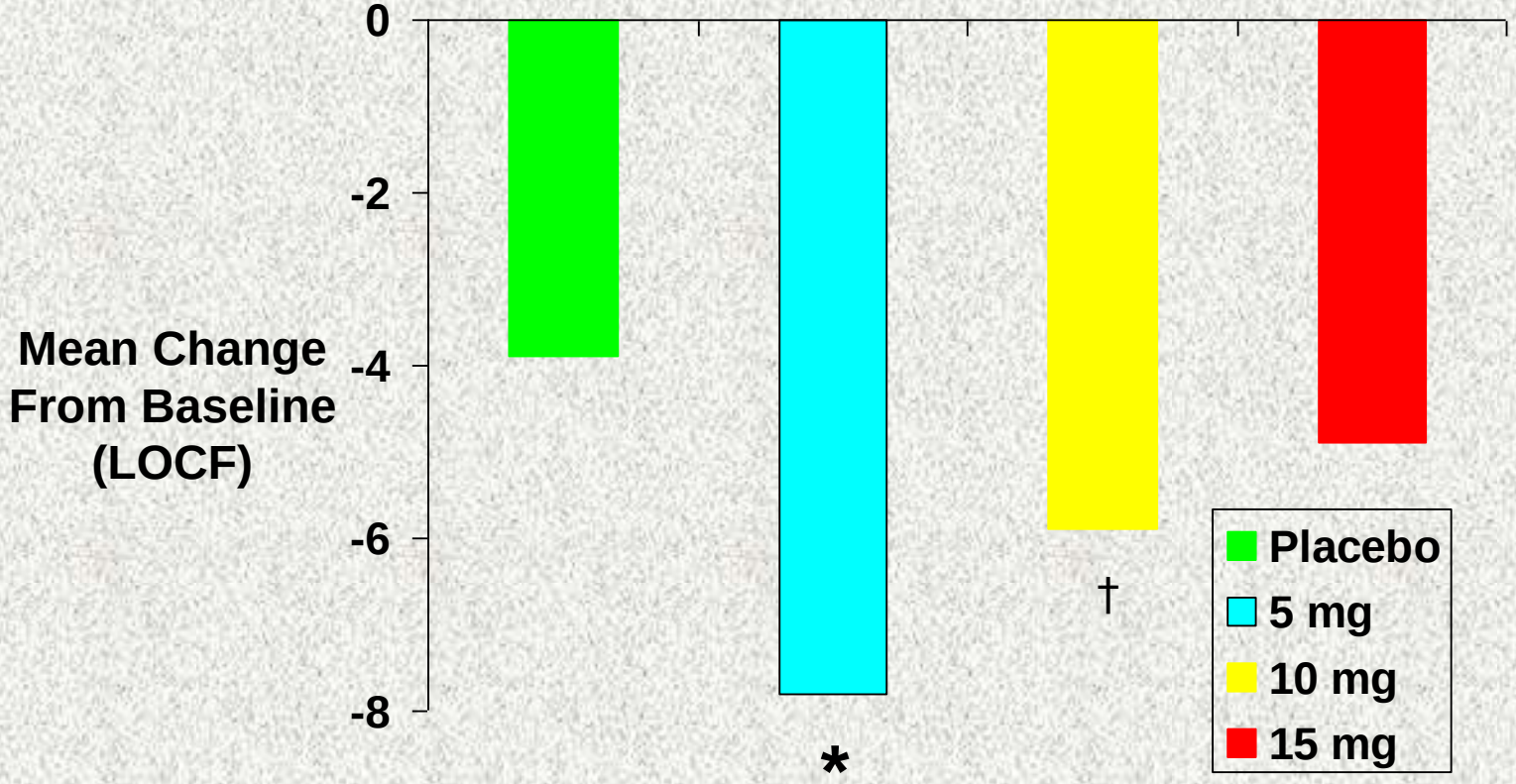
Jeste DV et al. *J Am Geriatr Soc*. 1999;47:716-719

Cumulative Incidence of Persistent TD With Risperidone (Mean = 1 mg/d) in Dementia Patients (N = 330)



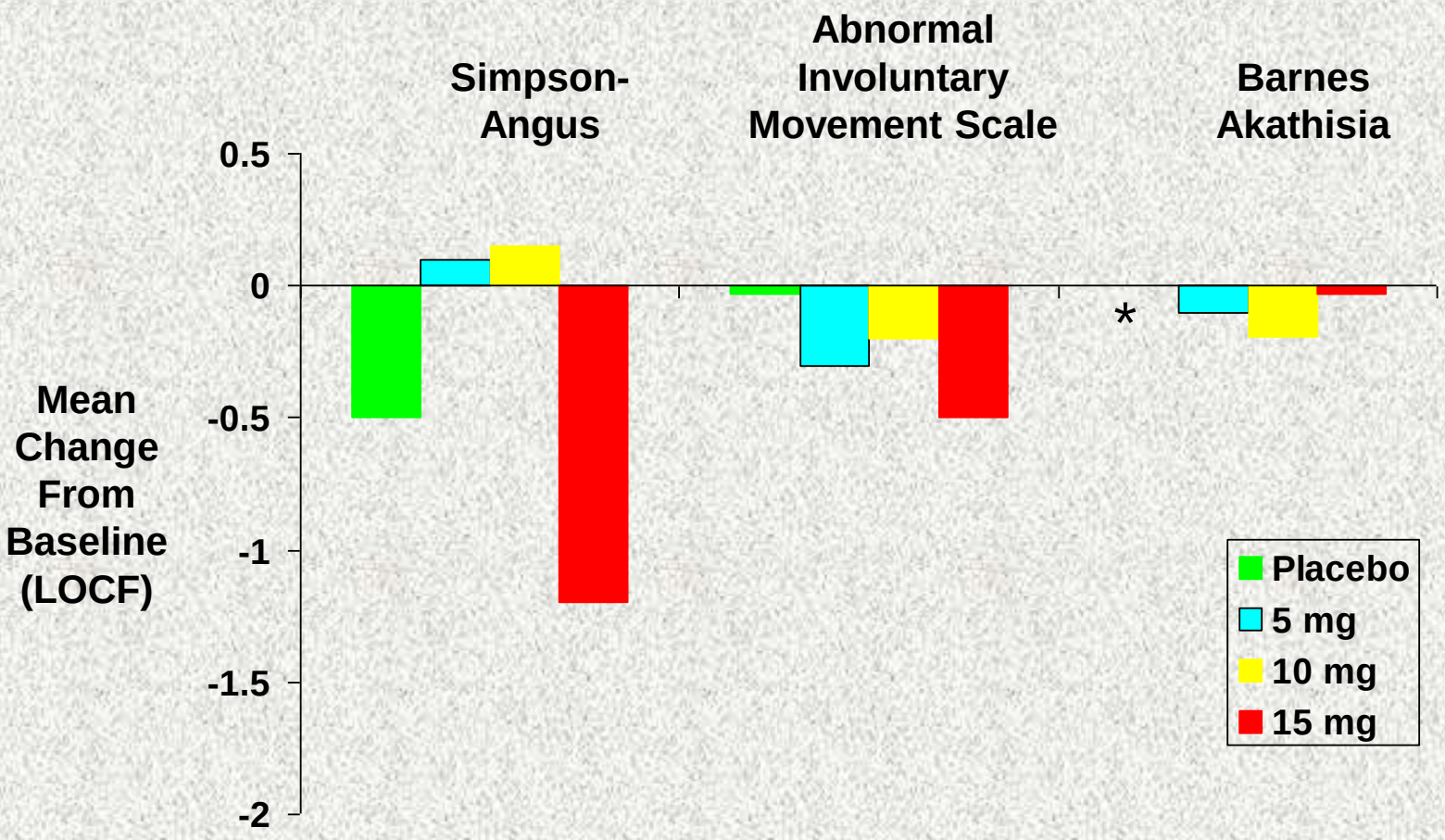
Jeste DV et al. *Am J Psychiatry.* 2000;157:1150-1155

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

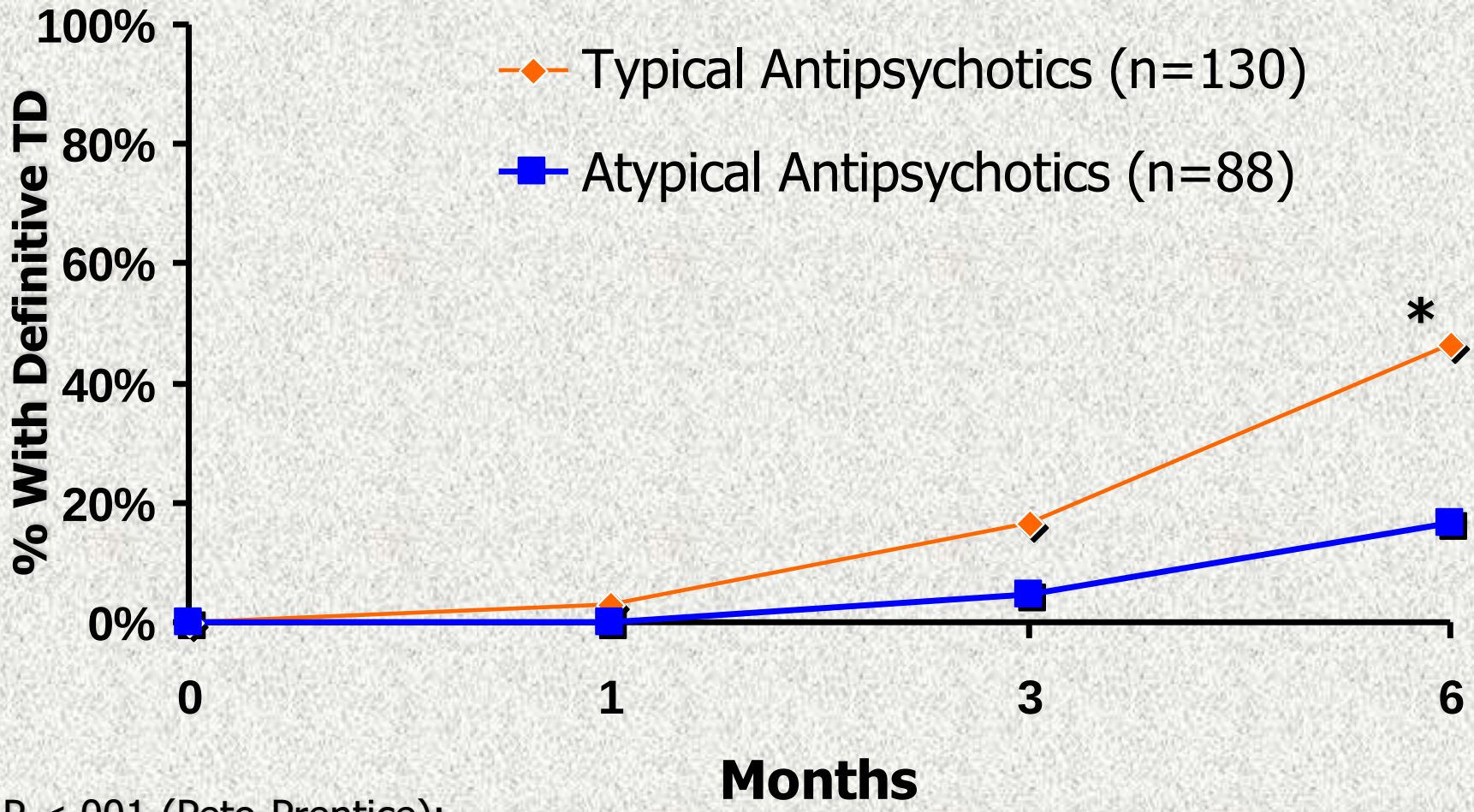
- Efficacy
  - Significant reduction in BPRS core and psychosis scores, but not in NPI psychosis score at end point
- Safety and tolerability
  - No drug-placebo differences in incidence of EPS-related AE or orthostatic events
  - Low rate of discontinuation due to AEs
  - Somnolence was mild and not 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?
- Limited 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

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

Possible 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 age groups: Weight gain, diabetes, hyperlipidemia
- In dementia patients:
  - Increased incidence of strokes
  - Increased overall mortality

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
- The exact underlying mechanisms are not yet known

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
Ziprasidone	10-20	60-80
Aripiprazole	2-4	8-12

Alternative Psychotropics and their Suggested Dosages

- Citalopram (10-40 mg/d)
- Divalproex sodium (125-1000 mg/d)
- Carbamazepine (100-400 mg/d)
- Benzodiazepines
  e.g. lorazepam 0.5-3 mg/d
- Trazodone (50-200 mg/d)
- Cholinesterase Inhibitors ?

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 patients with dementia**
2. **Known adverse effects with each drug**
3. **Limited long-term safety data in patients with dementia**

Management of Older Dementia Patients With Psychosis

- Dementia patients need/tolerate lower doses than in younger adults
- Atypical antipsychotics safer than typical ones but have some limitations, and need to be used in low dosages
- Pharmacotherapy should be combined with supportive therapy, behavior modification, & caregiver education

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

- Kindermann SS. Dolder CR. Bailey A. Katz IR. Jeste DV. Pharmacological treatment of psychosis and agitation in elderly patients with dementia: four decades of experience. Drugs & Aging. 19:257-76, 2002

- 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

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C. Carbamazepine
D. Cholinesterase inhibitors
E. Any of the above

Answers to Self-Assessment Questions

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