

# The Impact of Treatment on Quality of Life

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# What is our Goal?

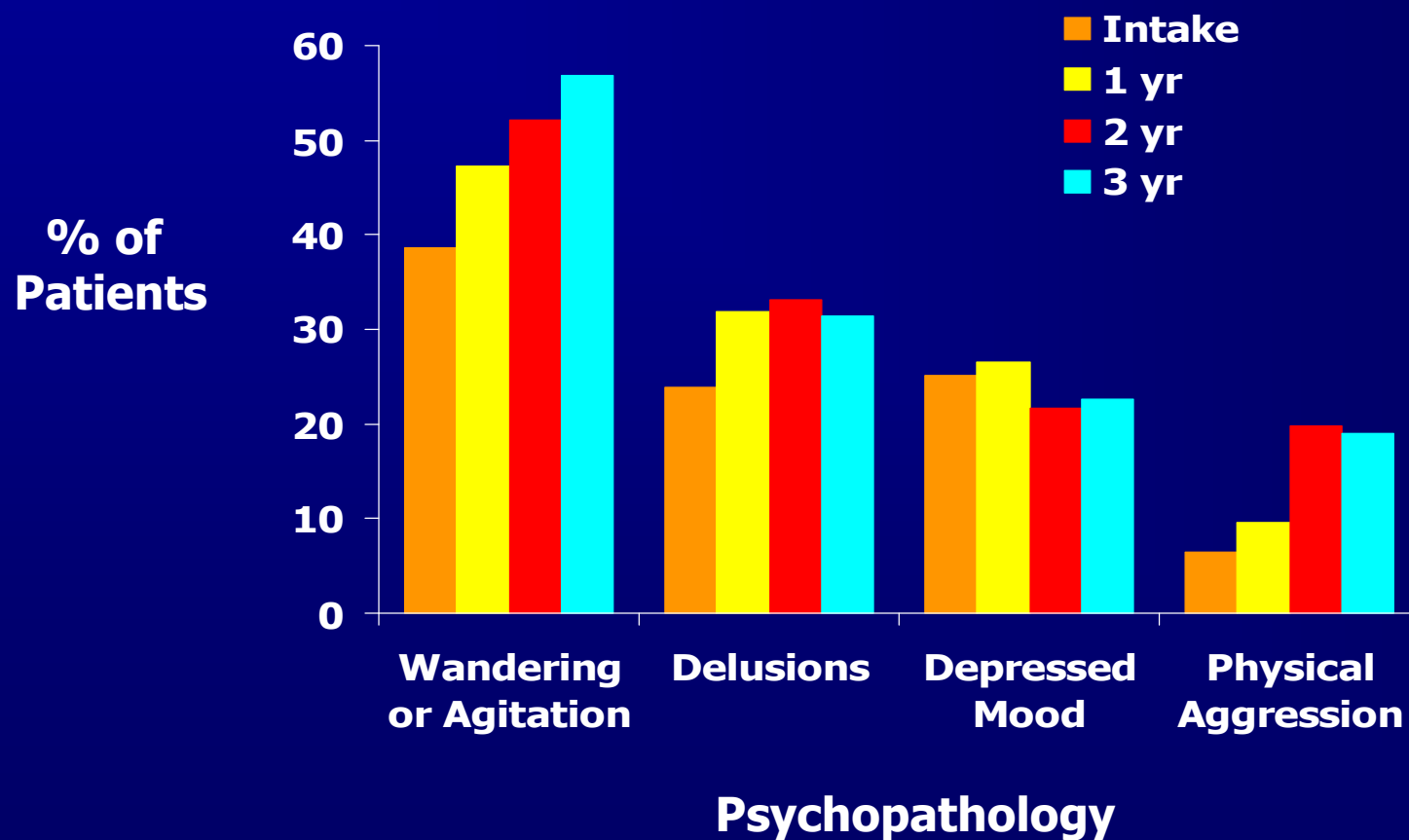
## Improved Quality of Life

- Efficacy with minimal side effects - OBRA
- Optimal functional level
- Minimal effect on cognition
- Peace & comfort
- Improved socialization
- Without adversely affecting co-morbidities

# Behavioral Problems in Nursing Home Residents

- Restlessness 38%
- Passive aggression 38%
- Active aggression 26%
- Verbal aggression 26%
- Wandering 24%

# Alzheimer's Disease-Related Disorders During 3-Year Follow-Up



Devanand DP et al, *Arch Gen Psychiatry* 1997;54:257-263

# Behaviors Unlikely to Respond to Medication

- Wandering, pacing, exit seeking
- Screaming, inappropriate verbalizing, using foul language
- Resistance with toileting
- Inappropriate voiding, defecation, or spitting
- Inappropriate sexual behaviors, public masturbation, disrobing

# When Drug Therapy Is Needed

- What do we know about efficacy of antipsychotic agents?

# Efficacy of Conventional Antipsychotics in Dementia

- As of 1990, 33 clinical trials in dementia patients
- Of the 17 placebo-controlled trials:
  - Only 13 used parallel-group design
  - Only 8 used randomized treatment assignment
  - Only 9 contained >78% dementia patients
- Therefore, only 7 used double-blind, placebo-controlled, parallel-group design to assess dementia patients

# Conventional Antipsychotics for Dementia: Efficacy

- Improvement rate 18% greater than placebo
- Type doesn't matter
- Modest effects
- Low doses usually work
- Use side effect profiles as guidelines

Wragg RE, Jeste DV, *Psychiatr Clin North Am* 1988;11:195-213  
Schneider LS et al, *J Am Geriatr Soc* 1990;38:553-563

# Withdrawal of Haloperidol, Thioridazine, and Lorazepam in the Nursing Home

- *Archives of Internal Med*  
Aug 9/23, 1999  
Cohen-Mansfield
- Double-blind, controlled
- Result - no difference drug  
vs placebo on Cohen-  
Mansfield Agitation  
Inventory or Brief  
Psychiatric Rating Scale  
scores

# Looking at the Results

- 22 weeks later
  - Only 1/3 remained free of medications
  - 20% had drugs restarted
  - 67% received a different psychoactive
  - 16% received a combination of original and another

# What about the Newer Atypical Agents?

- Are they more effective?
- Are they safer?
- Are there any differences between agents?

# Atypical Advantages in the Elderly

- Equivalent efficacy for positive symptoms
- Acts on negative symptoms
- Lower incidence of EPS and less TD
- Lower central anticholinergic activity
- Favorable safety profile
- Fewer potential drug interactions
- Lower risk of liver dysfunction
- Less or no induction of prolactin
- Better compliance, less relapse

# Risperdal in Dementia: Landmark Study

- Multicenter, fixed dose double-blind
  - N=625 nursing home resident
  - Placebo, 0.5mg, 1, 2, mg/d x 12 weeks
  - Decreases behave-AD total, psychosis, aggression scores
  - Decreased CMAI verbal/physical aggression scores
    - $p < 0.05$  vs placebo for 1, 2 mg/d
  - Well tolerated
    - EPS increased at 2 mg/d
    - Some sedation

# Risperdal Response Rate by Dose

- Patient characteristics:
  - 95% agitated
  - 56.4% delusions, 23.3% hallucinations
  - 57.9% mixed
- Response rate (similar to conventionals)
  - Placebo - 52%
  - 0.5 mg/d - 53%
  - 1mg/d - 60%\* target dose
  - 2mg/d - 65%

# Olanzapine Study

- Preliminary study in outpatients
- N=238 pts w/dementia & psychosis
- Starting dose 2.5mg/d
  - Doses 1-8 mg/d - slow titration
  - Well tolerated
  - No drug-placebo difference: ? Dose too low; patients heterogeneous

# Olanzapine in Dementia: Follow-up Study

- N=206 LTC pts
- Washout, placebo-lead-in (3-4 days)
- 6 wks, double-blind
  - Placebo, 5mg/d, 10mg/d, 15mg/d
- Results - Neuropsychiatric Inventory Nursing Home Scale
  - Placebo -4
  - 5mg/d -8
  - 10mg/d -6.5
  - 15mg -6
  - Same with BPRS - U shaped curve

# Olanzapine Adverse Events

- Somnolence
  - Placebo 6.4
  - 5mg - 25
  - 10mg - 26
  - 15mg - 35.8
- Abnormal gait (Parkinson's & Lewy Body)
  - Placebo 2.1
  - 5mg - 19.6
  - 10mg - 14
  - 15mg - 17
- Weight gain & control of DM

# Quetiapine

- Open trial in pts with dementia, psychosis (n=106); n=78 with other psychosis
- Mean age=77
- Doses 25-800mg (target dose 200mg)
- Mean total BPRS at 12 wks: 7.5 (p<.0001)
  - 55% had >20% improvement
  - Both positive & negative symptom clusters
- Mean improvement in CGI sx: 0.3 (p<.05)

# Quetiapine Side Effects and Efficacy

- Somnolence 20% in early phase of treatment
  - Not dose related
- Orthostatic hypotension
  - Early in treatment but not common
- Dizziness
  - Early in trial but not later
- No change in EPS over time, no TD, no EKG changes or vital sign changes
- Agitation improved over time with a marked fall after 70 days, CGI & BPRS improved
- **Open trial not double-blind**

# CATIE in Progress

- National Institute of Public Health - large study - Schizophrenia and another in Alzheimer's Disease
- Head to head study with many facets

# Side Effect Risk

- DO NO HARM
- Risk vs. Benefit Ratio
- Abdication of responsibility to psychiatrist & comorbidities

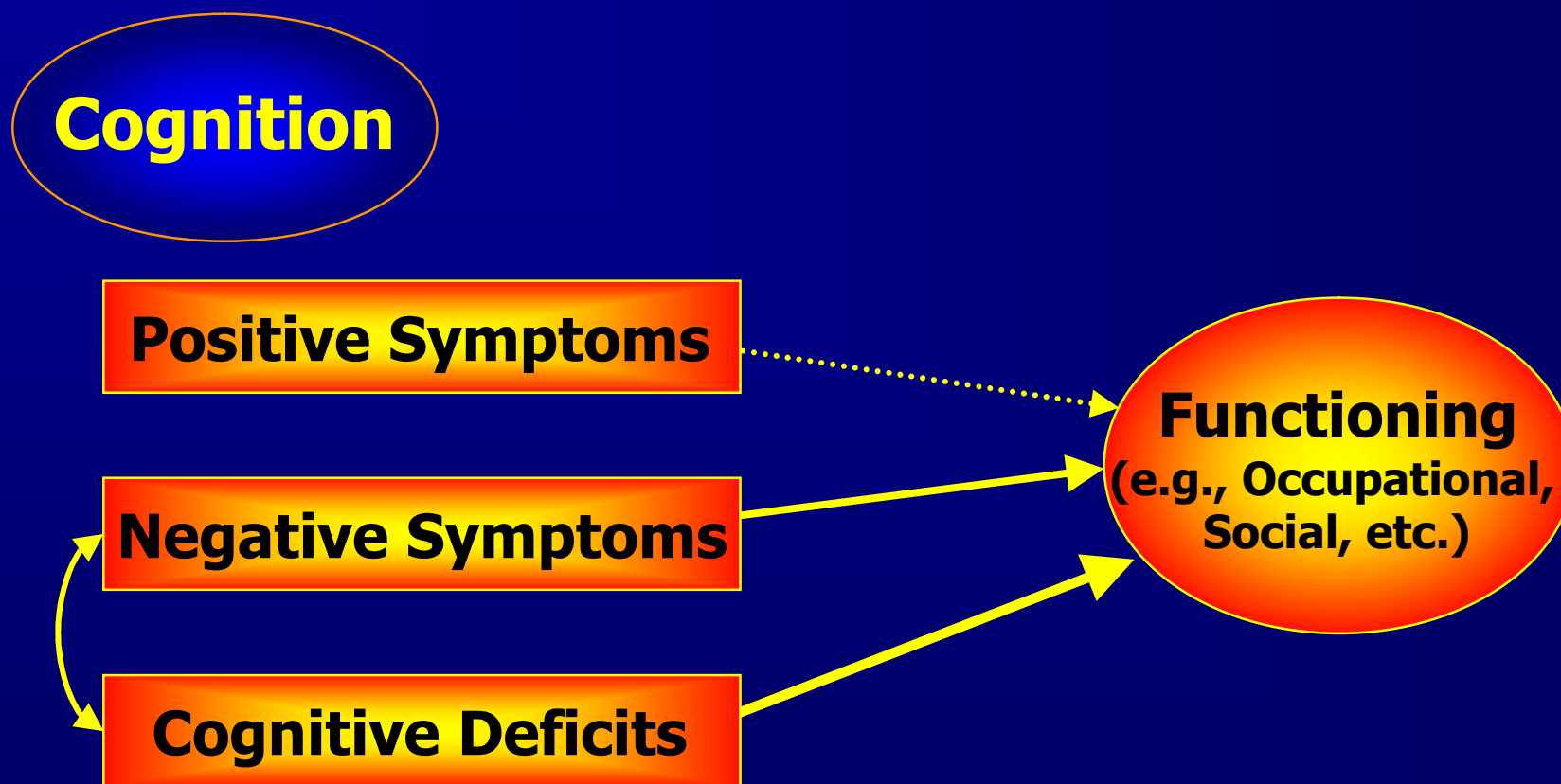
# Adverse Events Associated With Conventional Antipsychotics in Dementia

- Extrapyrarnidal reactions
  - Neuroleptic-induced Parkinsonism
    - Bradykinesia
    - Decreased postural reflexes
    - Rigidity
    - Masked faces
    - Tremor
    - Drooling
    - Gait
  - Acute dystonic reaction
  - Akathisia
  - Tardive dyskinesia
- Other neurological effects
  - Catatonia syndrome
  - Seizures
  - Neuroleptic malignant syndrome
  - Hypo- or hyperthermia

# Adverse Events Associated With Conventional Antipsychotics

- Anticholinergic effects
  - Confusion, memory loss
- Cardiovascular
  - Orthostatic hypotension
  - Tachycardia
  - Conduction delays
- Sedation
- Falls/fractures
- Miscellaneous
  - Agranulocytosis
  - Weight gain
  - Rashes and dermatological effects
  - SIADH (syndrome of inappropriate antidiuretic hormone secretion)

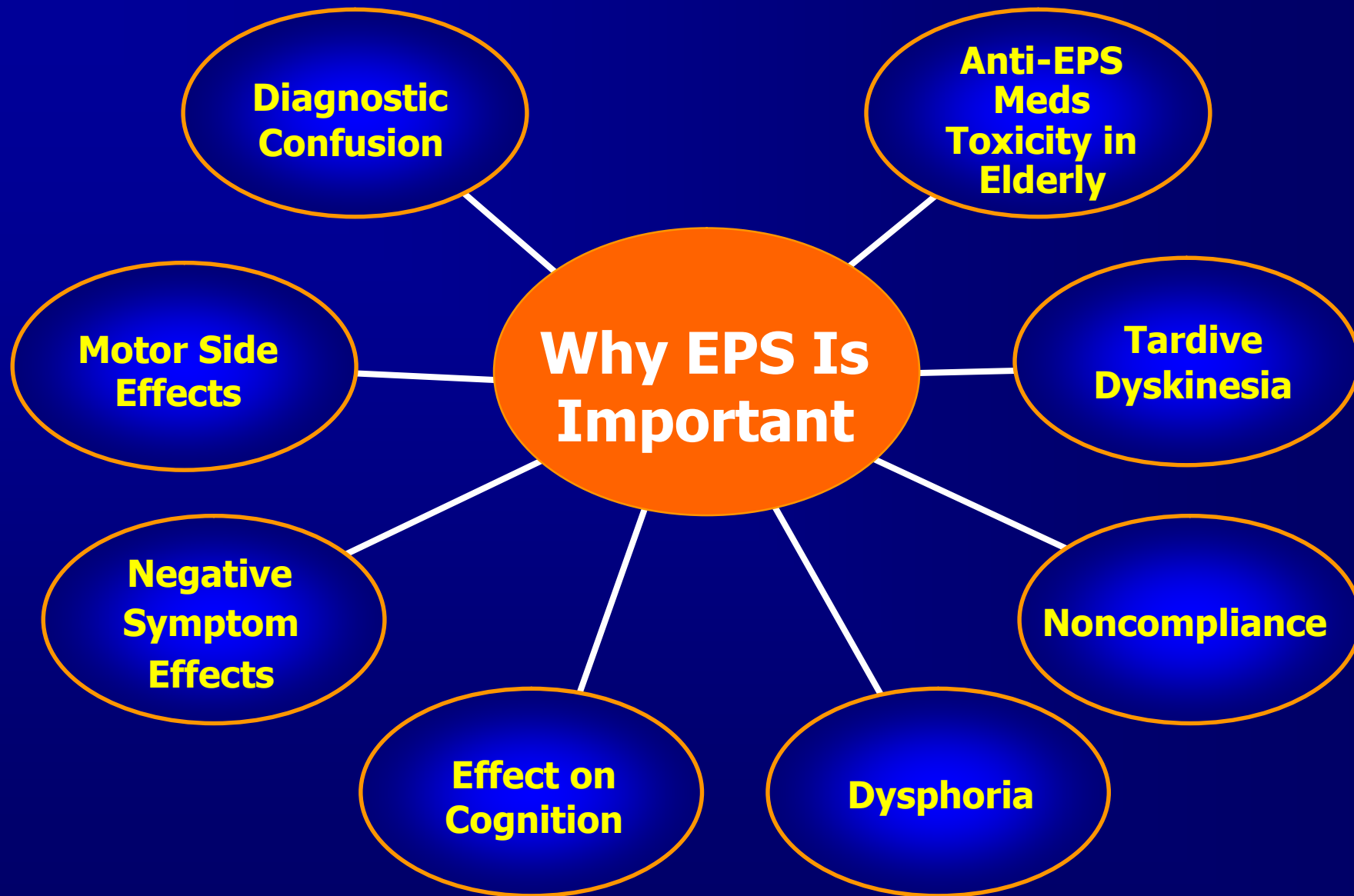
# Relationships Between Positive, Negative Symptoms, Cognition and Functioning



Green, *Am J Psychiatry* 1996;153:321-330  
Velligan et al, *Schizophr Res* 1997;25:21-31

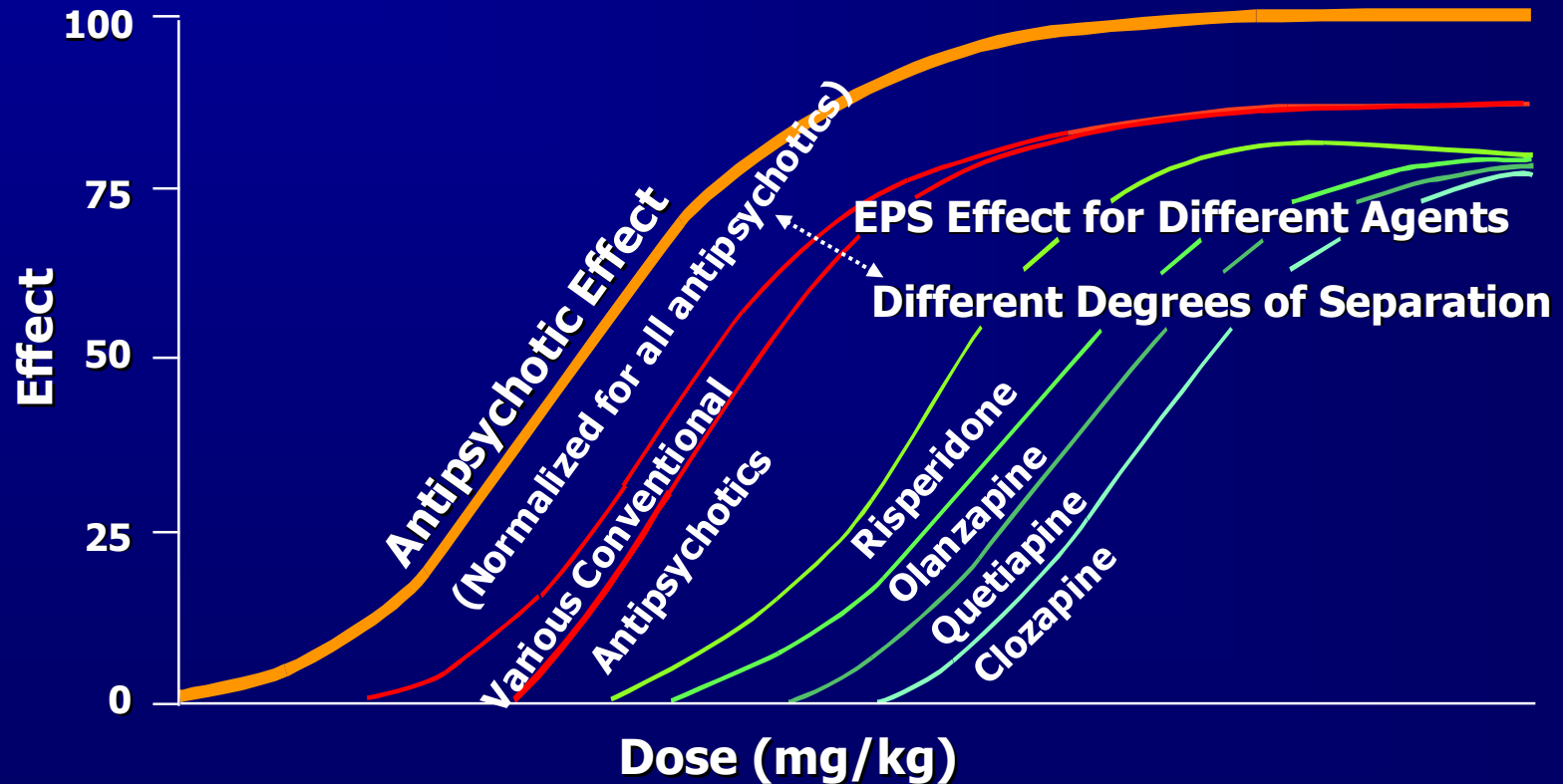
# Antipsychotic Seizure Risk

- Pre-marketing incidence of seizures
  - Risperidone 0.3%
  - Olanzapine 0.9%
  - Quetiapine 0.8% (placebo 0.5%)

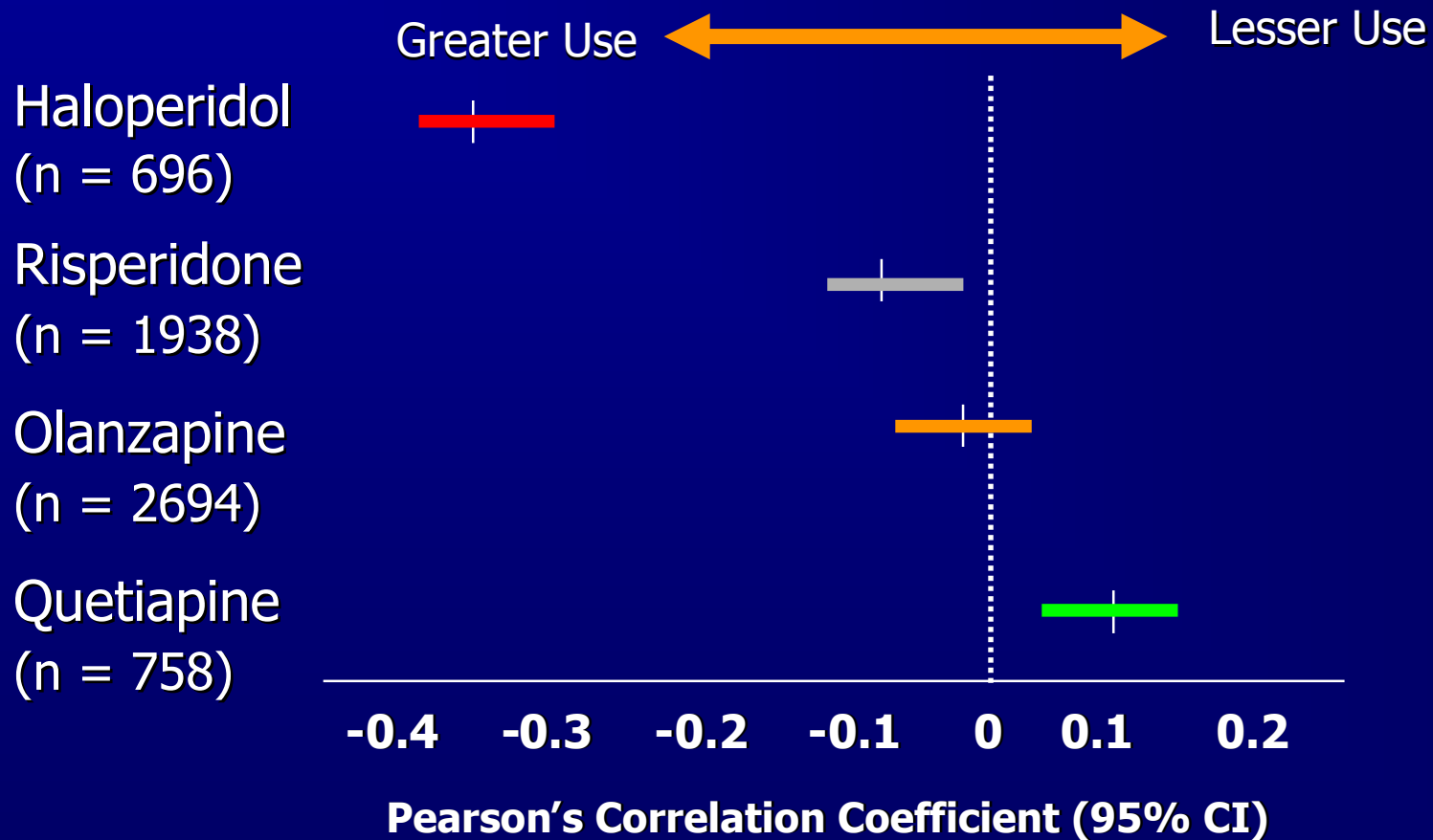


Adapted from Jibson and Tandon, 1998

# Dose-Response Curve: Antipsychotic Effects vs. EPS

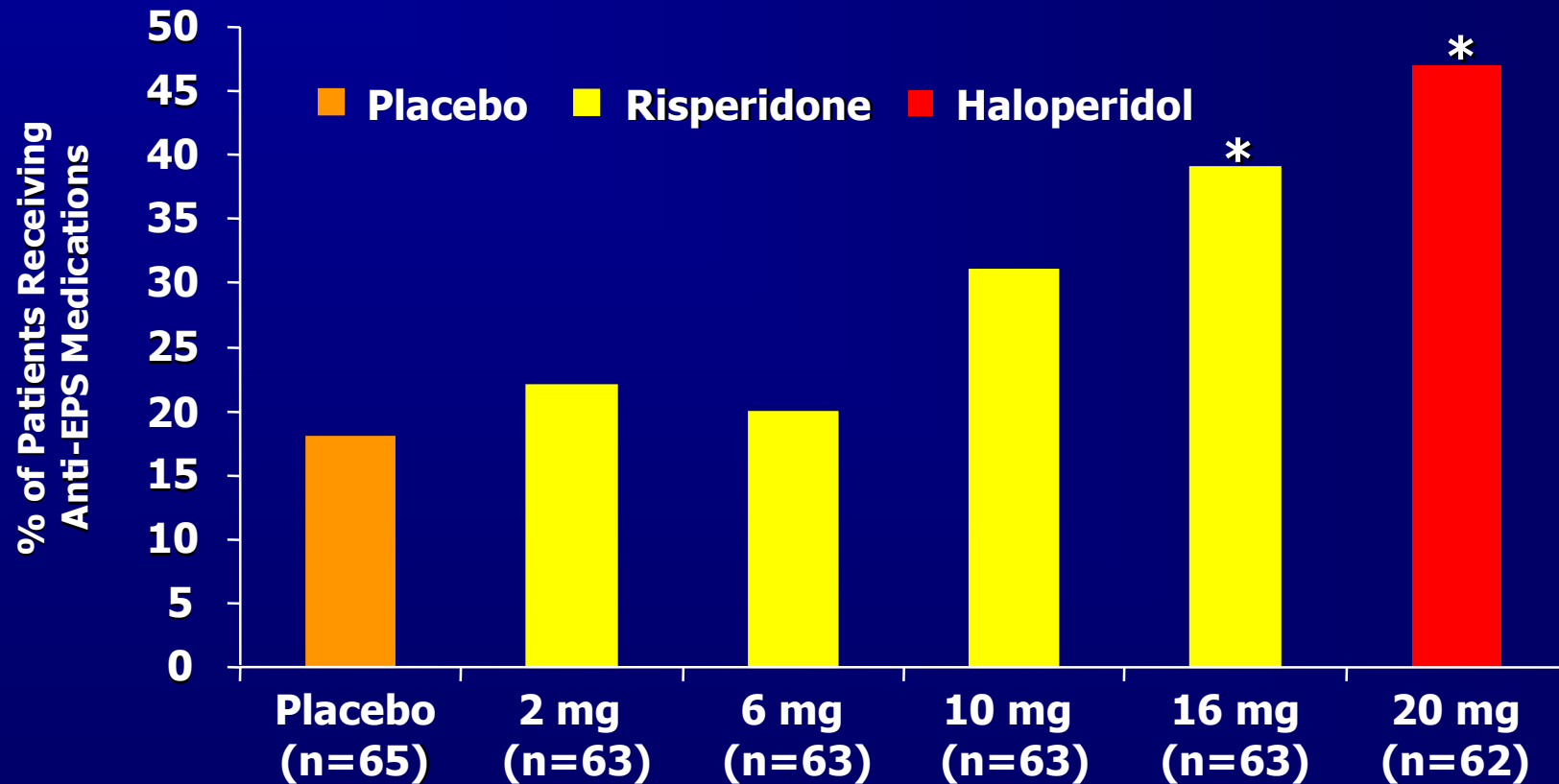


# Use of Anticholinergic Medications: Atypical Antipsychotics vs. Placebo



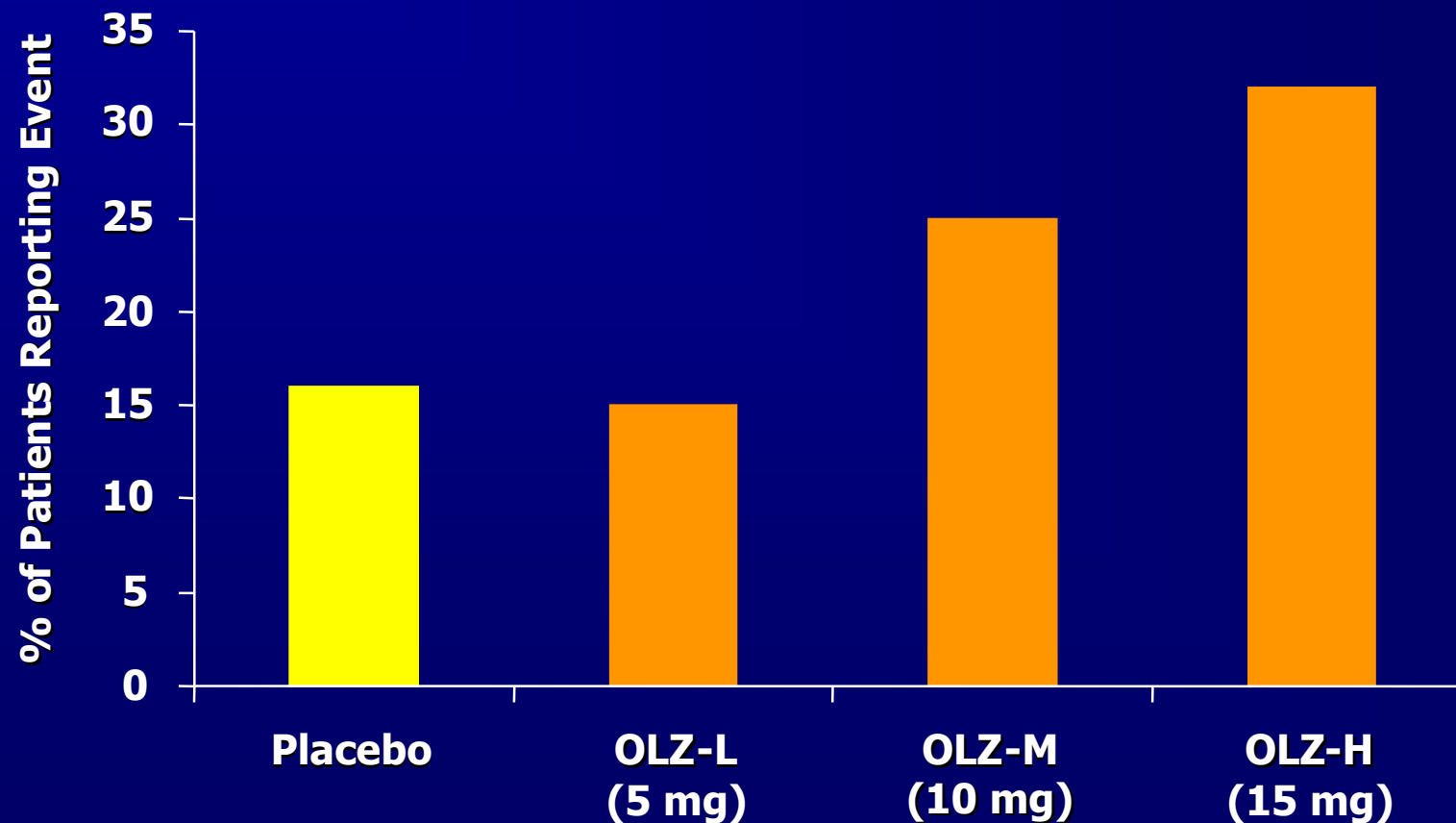
From Leucht et al, *Schizophr Res* 1999;35:51-68

# Use of Antiparkinsonian Medications in a Risperidone Fixed-Dose Study



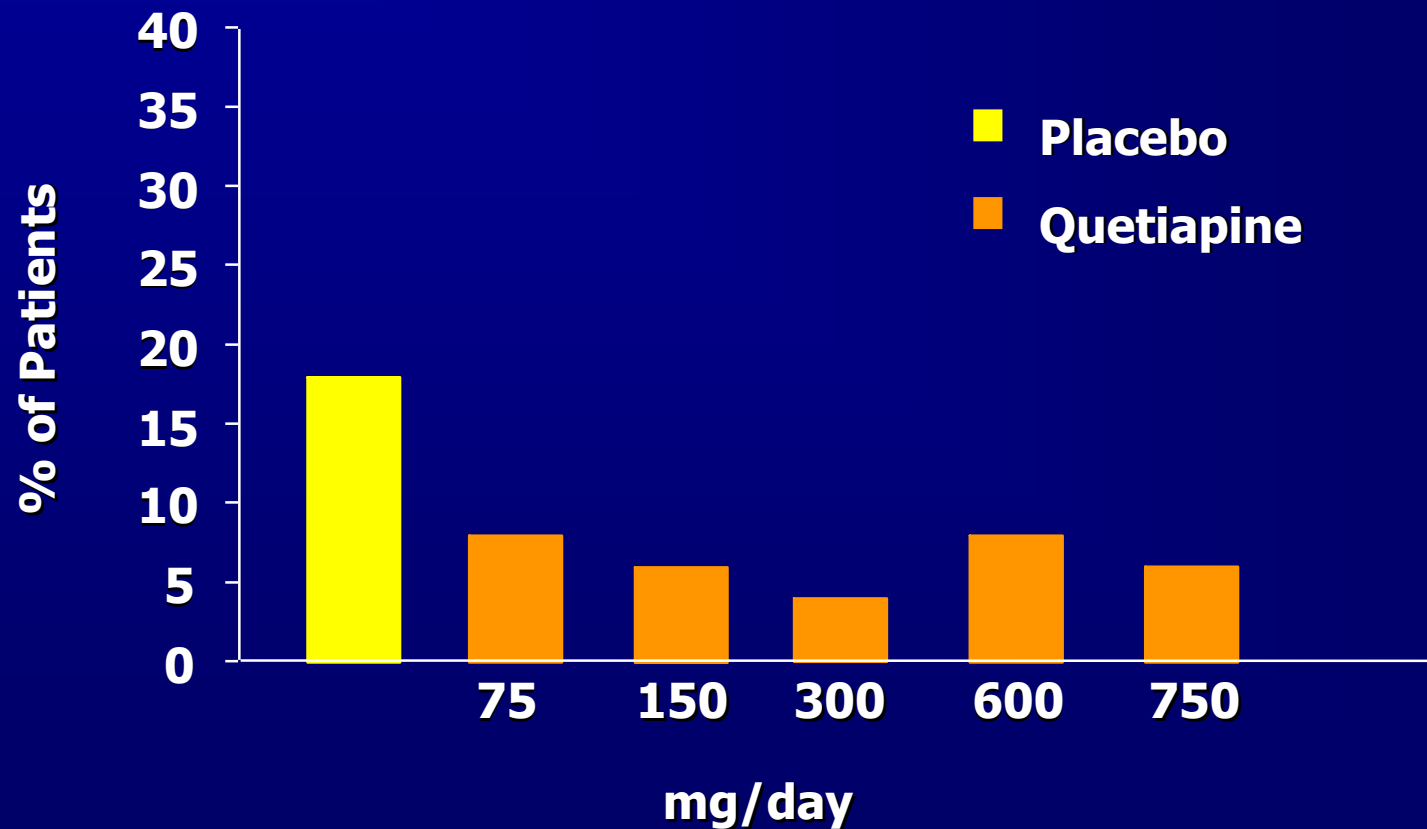
\*  $p < 0.01$

# Treatment-Emergent EPS: Olanzapine (Low, Medium, High-Dose) vs. Placebo



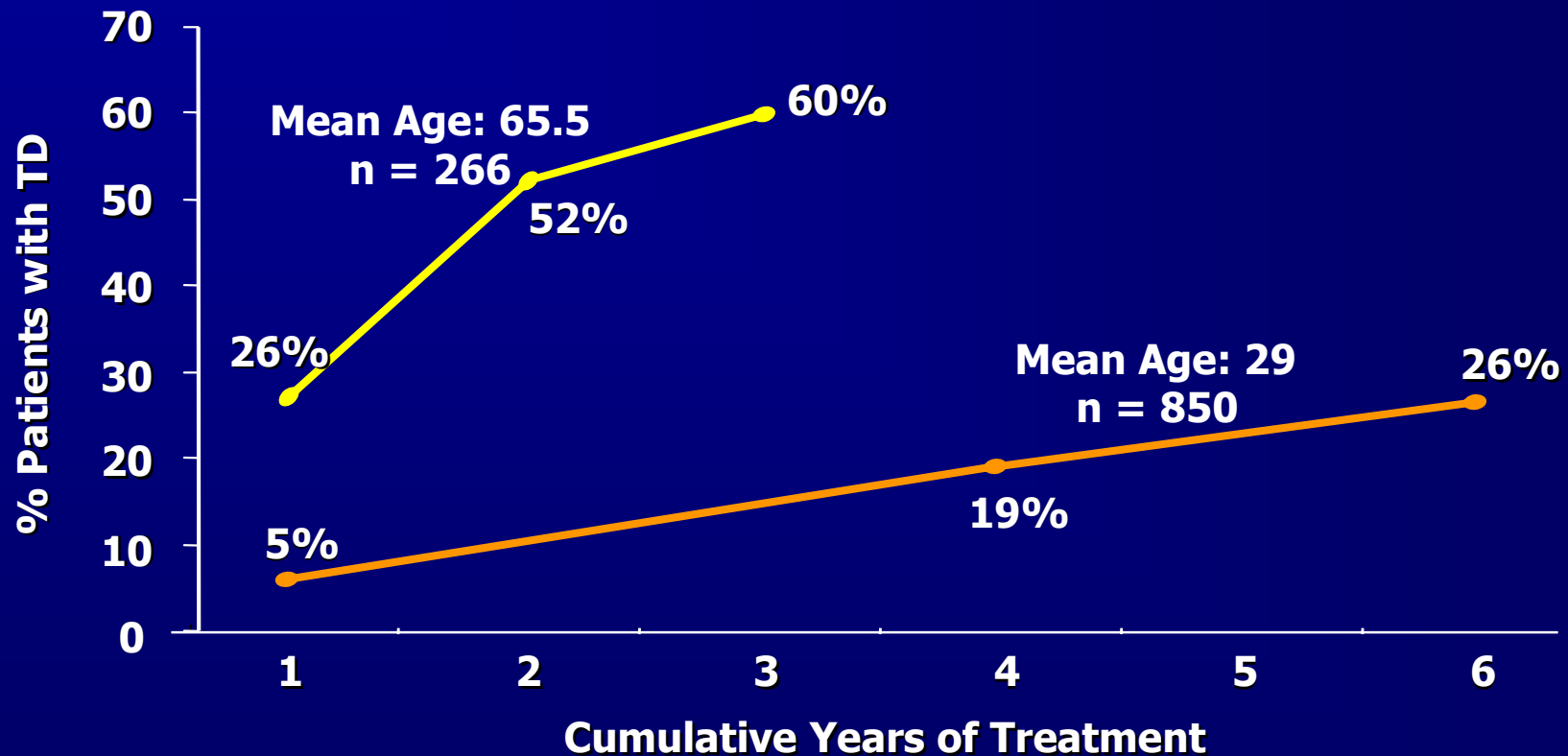
From Physicians Desk Reference, 1999

# EPS in Quetiapine Fixed-Dose Trial: Simpson-Angus Scores



From Arvanitis et al, *Biol Psychiatry* 1997;42:233-246

# Incidence of Tardive Dyskinesia in Older and Younger Patients (Conventional Antipsychotics)



■ Jeste et al, *Arch Gen Psychiatry* 1995;52:756-765

■ Kane JM, *Psychopharmacology: The Fourth Generation of Progress*, Raven Press Ltd, 1995;1485-1495

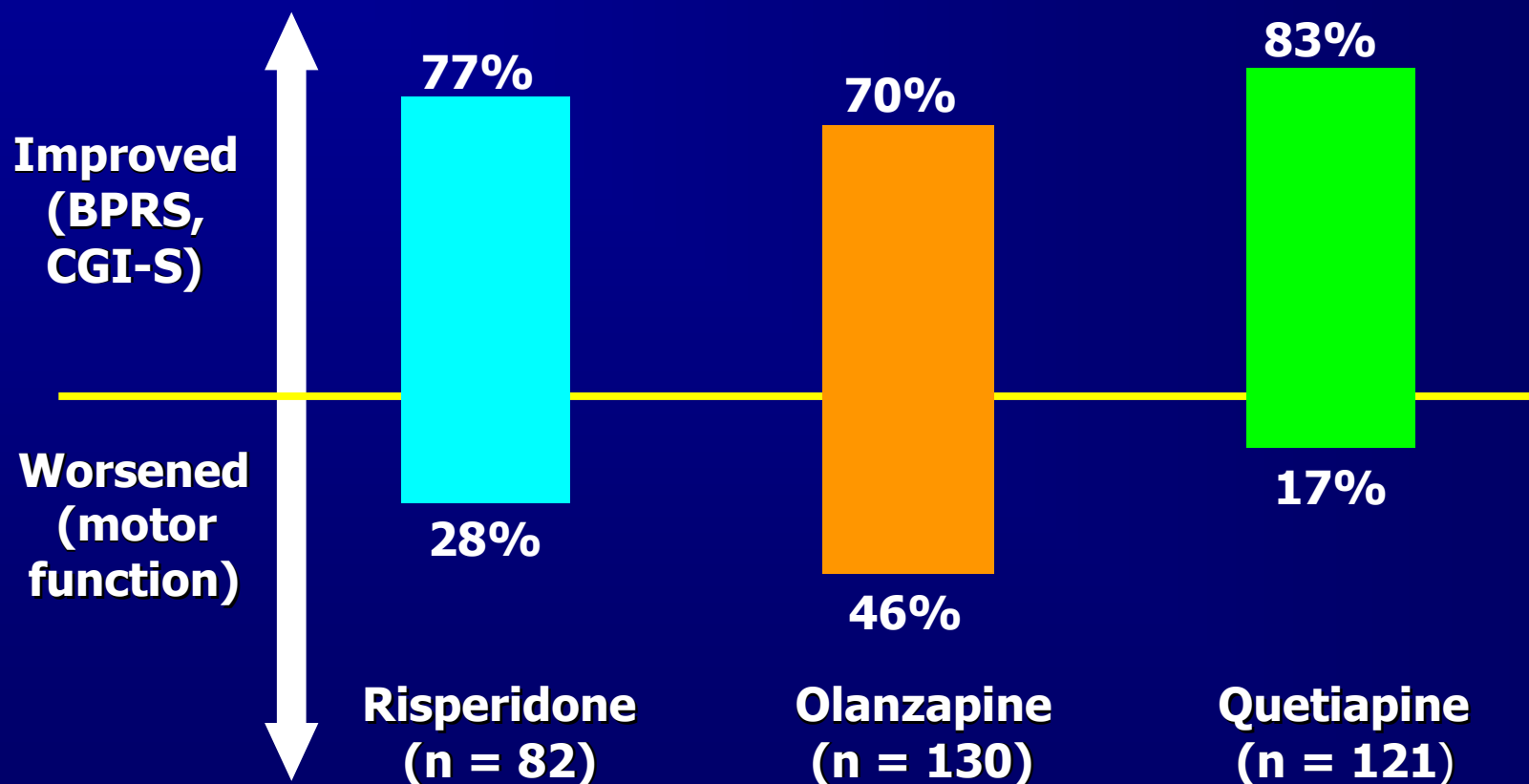
# New HCFA Guidelines for Upper Daily Dose Range in Long-Term Care Facilities\*

Conventional Agents	mg	Atypical Agents	mg
Chlorpromazine	75	Clozapine	50
Pormazine	150	Risperidone	2
Haloperidol	4	Olanzapine	10
Thioridazine	75	Quetiapine	200

\* Not all agents are listed here. Amounts shown are not necessarily equivalent doses or maximum doses, but are levels at which higher doses should be justified by specific clinical circumstances, according to HCFA

From the 1999 Health Care Financing Administration's State Operations Manual

# Atypical Antipsychotics in Parkinson's Disease: Summary



From Factor, 1999 (presentation)

# Mood Stabilizer: Lithium

- Actions
  - Changing neuron architecture (Neuroprotective)
- Relationship to serum sodium
- Side effects
  - Psoriasis
  - Electrolyte imbalance
  - Polydypsia
  - Hypothyroidism

# Mood Stabilizers

- Carbamazepine
- Effectiveness
- Risks
  - Blood dyscrasias
  - Rash: Stevens-Johnson
  - Drug interactions
- Gabapentin
- Indication - Literature
- Serum levels
- Side effects
- Dosing

# Divalproex: Theoretically Attractive for Behavioral Disturbance in Dementia

- FDA-approved for treatment of acute mania in bipolar disorder
- Effective in a broad range of psychiatric conditions characterized by agitation
- Used successfully to treat agitation associated with dementia
- Changing neuron architecture (neuroprotective)
- Relatively benign side-effect profile\*\*\*
- Few drug–drug interactions

# Summary of Efficacy in Agitation and Aggression

Data From Trials Using Sodium Valproate  
or Divalproex Sodium

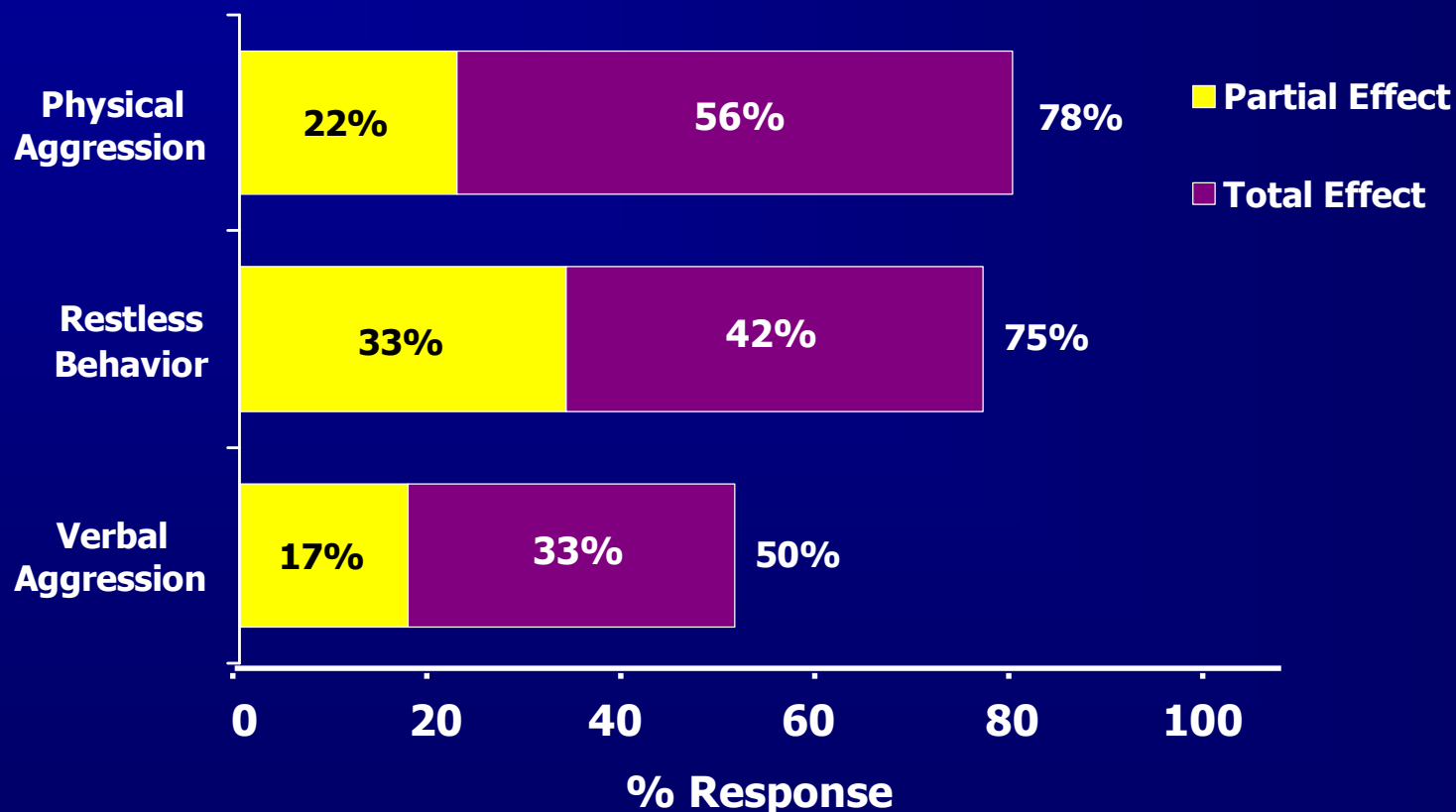
	<b>N</b>	<b>Design</b>	<b>Outcome (N)</b>
Mellow et al, 1993	4	Open	↓ agitation (3)
Sival et al, 1994	23	Chart review	↓ aggression (6)
Lott et al, 1995	10	Open	↓ agitation (9)
Horne & Lindley, 1995	1	Open	↓ agitation (1)
Sandborn et al, 1995	4	Open	↓ partial agitation (4)
Narayan et al, 1997	25	Chart Review	↓ agitation (13)
Porsteinsson et al, 1997	12	Open	↓ aggression (10)

# Summary of Efficacy in Agitation and Aggression

## Data From Trials Using Valproate

	<b>N</b>	<b>Design</b>	<b>Outcome (N)</b>
Haas et al, 1997	12	Open	↓ aggression (12)
Kaskow et al, 1997	10	Open	↓ agitation (5)
Kunik et al, 1998	13	Chart Review	↓ agitation (9)
Herrmann et al, 1998	16	Open	↓ agitation (11)
Gardner et al, 1998	13	Open	↓ aggression (8)
Gupta et al, 1998	4	Chart review	↓ agitation (4)
Goldberg, 1999	22	Chart review	↓ agitation (16)
Porsteinsson et al , 1999	56	Placebo-controlled	↓ agitation (38)

# Valproate in Dementia With Behavioral Disturbance, Open Trial



N=23 (14M, 9F); mean age=79M, 82F

Benzodiazepine and antipsychotic refractory; Dose=481±248 mg/day

Sival RC et al, *J Am Geriatr Soc* 1994;42:906-907

Thank You !