

Evaluation and Management of Behavioral Disturbances and Psychosis in Dementia

Brent Forester, MD
Medical Director,
Geriatric Neuropsychiatry Unit
McLean Hospital

Lesley Adkison, MSN, RN
Nurse Director,
Geriatric Neuropsychiatry Unit
McLean Hospital

Outline

- **Define behavioral disturbances in dementia**
- **Review diagnostic assessment and formulation of treatment plan**
- **Discuss behavioral and other non-pharmacological approaches to treatment of behavioral disturbances in dementia**
- **Review an evidenced based approach to pharmacological management of the behavioral and psychiatric symptoms of dementia**
- **Questions**

BPSD Definitions

- **The Psychosis of AD (Jeste and Finkel)**
- **Neuropsychiatric Symptoms of AD**
- **BPSD (Behavioral and Psychological Symptoms of Dementia)**
- **Includes:**
 - **agitation, aggression, wandering, delusions, hallucinations, repetitive vocalizations, mood disturbances.**

Behavioral Disturbances ...

- **Leading reasons for admission into nursing facilities**
- **Increase stress between patients and caregivers**
- **Create more intensive and costly levels of treatment**
- **Increase morbidity and mortality of dementia patients**
- **Lead to public health problems that contribute to the enormous cost of treating dementia**
- **No FDA-approved drug therapy for agitation**

Paradigm for Comprehensive Assessment

- Environment/stressors
- **Dementia**
- **Delirium**
- **Medical problems**
- **Psychotic disorder**
- **Affective disorder**
- **Anxiety disorder**
- **Personality disorder**

Non-Pharmacologic Interventions to Behavioral Disturbances in Patients With Dementia

Outline

- **Definitions**
- **Types of Interventions**
- **Case studies**

Definitions of a behavioral disturbance:

- **a behavior that puts the patient or others at risk.**
- **a behavior that makes keeping the patient in the milieu difficult for either staff or other patients.**

Examples -- Behavioral Disturbances

- **Hitting/ Kicking**
- **Screaming/ Incessant calling out**
- **Sexual disinhibition (verbal or physical)**
- **Perseveration on bathroom activities**
- **Aggression during daily care**
- **Attention seeking behaviors**

Begin at the beginning...

- What is the problem?
- Whose problem is it?
- Specificity is important!



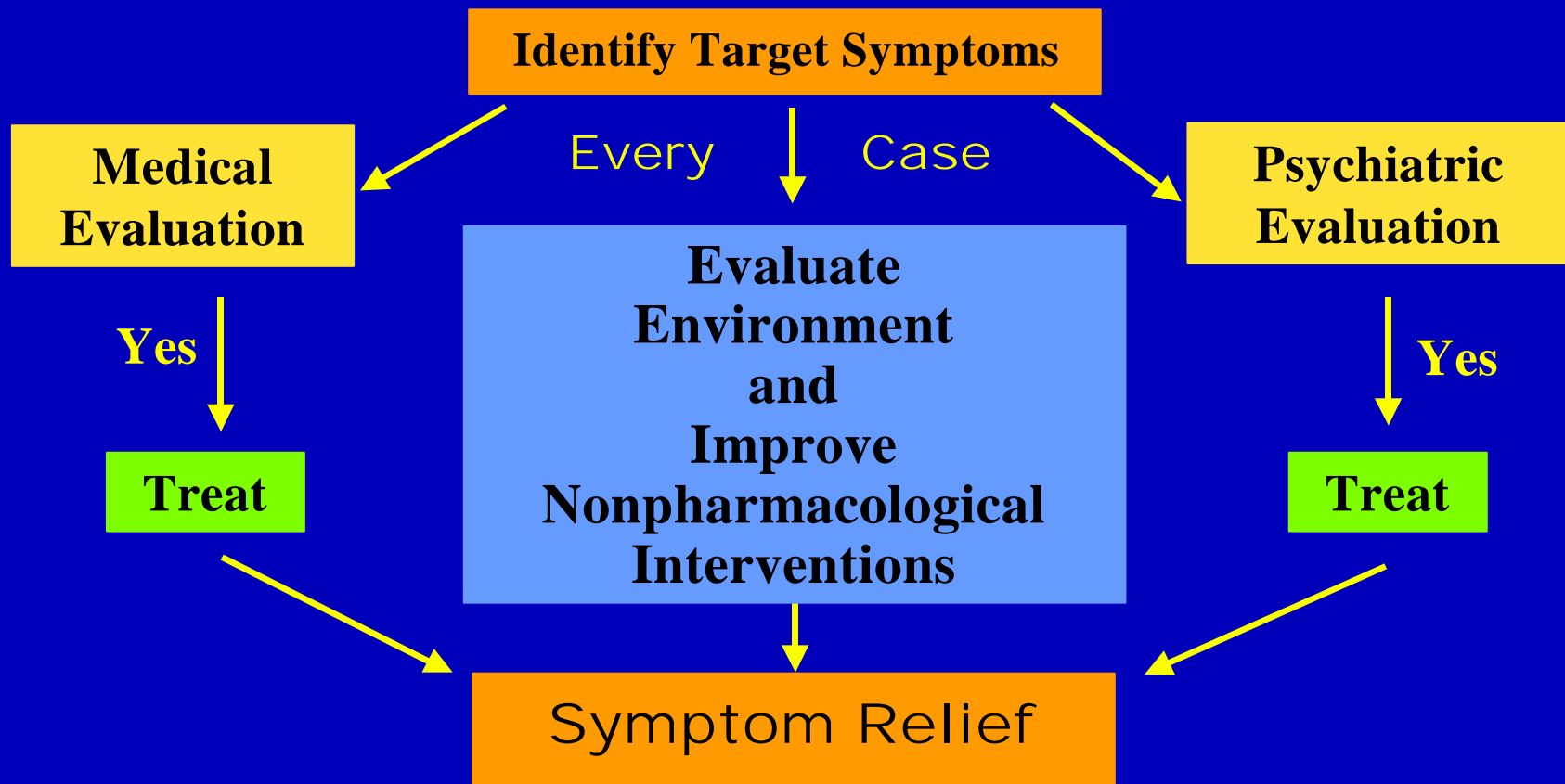
Define objectives—There are multiple goals!

- Make the behavior go away.
- Treat the underlying cause.
- Improve patient outcomes.
- Comply with OBRA guidelines.
- Restore calm and safety to the situation and the unit.

What are the possible causes of the behavior?

- **Inherent changes of disease process**
- **Medical comorbidities**
- **Environmental disruptions**
- **Lack of staff knowledge**
- **Lack of family education about disease process**

Comprehensive Approach to Assessing Distressed Behavior



Detective Work

- **Identifying environmental stressors**
- **Identifying any trends**
- **Working on a “crisis plan” with family, patient, or significant others**
- **Enlist the help of specific staff members**
- **Use of adjunct therapies and specialized interventions**

Environmental Stressors

- **Room location**
- **Excess noise (t.v., overhead pager)**
- **Glare from windows, mirrors, floors**
- **Slamming doors**
- **Proximity to bathrooms**
- **Proximity to peers of opposite sex**

Case Study -- Trends

- “Sophie” is a 78 yo married female
- Dx of schizophrenia and mild dementia
- Precipitants to admission: refusing to take meds, hitting, biting, kicking, FTT, depression
- Upon admission, most of meds had been administered IM. Pt was withdrawn, refusing to eat, refusing fingersticks and blood draws, refusing meds. Refusing phone calls from husband.
- Primary problems?

Trends, “Sophie”, cont.

- Whose problem is it?
- Objectives:
 - Ensure physical status is stable
 - Psychopharm assessment
 - Strategize on ways to get Sophie to “buy in” to treatment
 - Return her to LTC facility with strategies for success

What did we do?

- **What has worked before?**
- **Simplify!**
- **Work with the patient's schedule, don't ask her to work with ours.**
- **Be creative. Remember that affect means more than words. Don't push! Talk to each other—a lot about patient's responses to treatment. Took our cues from the patient.**

Crisis plan

Systematic assessment at admission of patient coping strategies.

Quiet time in own room

Time in the sensory room with staff

Pacing the hallways

Talking with someone individually

Rummaging through clothes

Covering up with a blanket

Taking a shower

Calling a family member

Use of weighted blanket

Case Study--Crisis Plan

- John is 78 yo
- Dx of schizophrenia, vascular dementia
- Precipitant to admission: sexual disinhibition.



“John”

- **Upon admission, crisis plan completed**
 - Activity/ Exercise
 - Pacing the hallways
 - Talking with someone individually
 - Covering up with a blanket
 - Having a snack
 - Quiet time in own room

Course of hospitalization

- **Jumpsuits**
- **Use of rewards, coping strategies from crisis plan**
- **Medication**

Sensory Stimulation Rooms

- interventions designed to stimulate one or more of the five senses
- promotes self-soothing on the part of agitated or distressed individuals
- Based on Dutch concept of Snoelezen® rooms (to sniff, to doze)

Sensory Room -- GNU, McLean



Sensory equipment

- Sand tray
- Weighted blankets
- Aroma therapy
- Tactile objects
- Soft lighting
- Music
- Sensory tower



Case study—Use of Sensory Room



- “Mary” 78 yo widowed female
- Lived at home with family until 2 months prior to hospitalization
- Admitted to McLean from LTCF because of
 - *aggression with ADLS
 - *constant calling out
 - *general irritability
 - *refusal to take meds

**WHAT WAS THE PROBLEM FOR
OUR STAFF?**

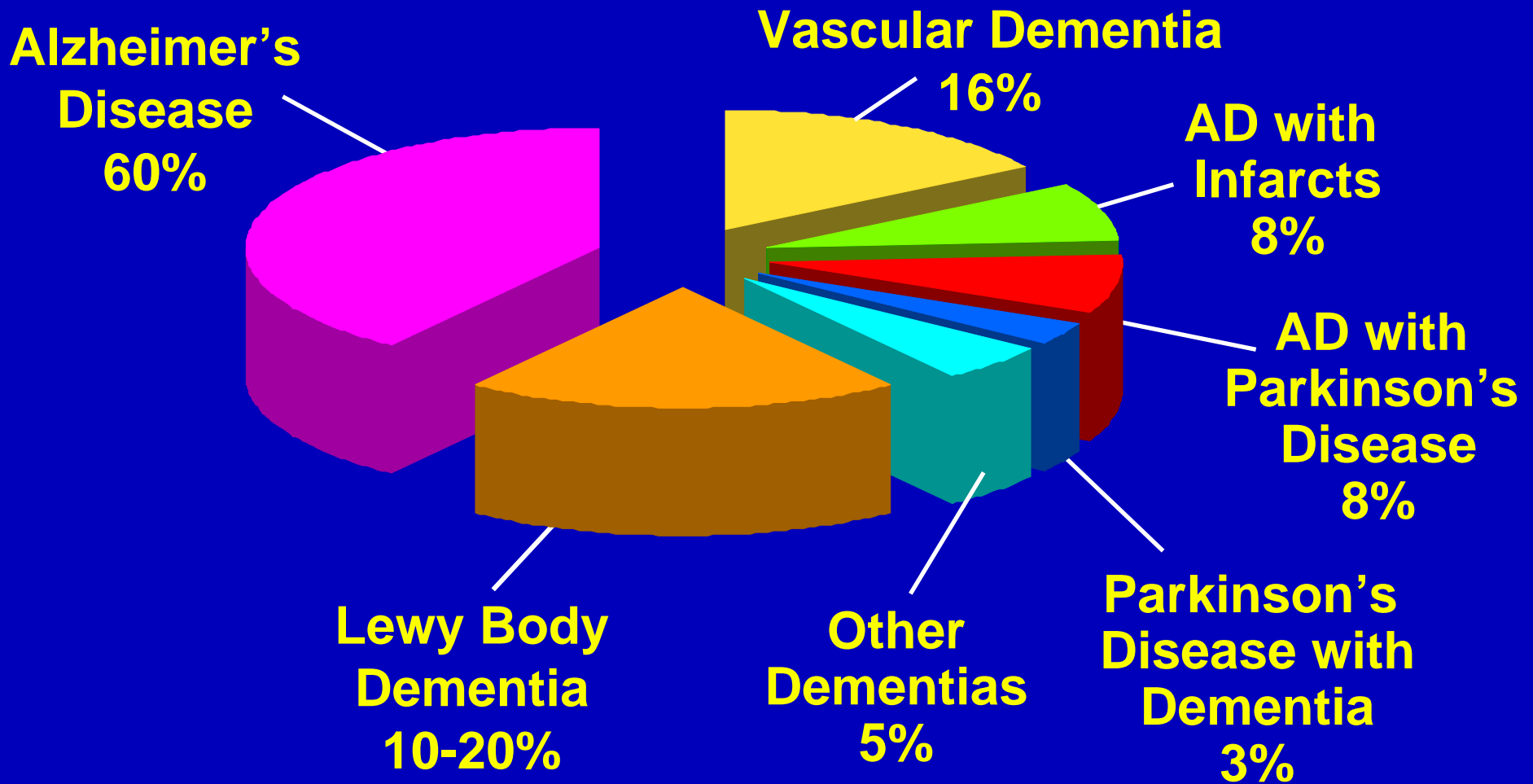
Use of Sensory Room

- Responded to 1:1 activity
- Yarn rolling
- Sand tray
- Compression vest

Paradigm for Comprehensive Assessment

- **Environment/stressors**
- **Dementia**
 - Alzheimer's Disease
 - Lewy Body Disease
 - Frontal Lobe Impairment
- **Delirium**
- **Medical problems**
- **Psychotic disorder**
- **Affective disorder**
- **Anxiety disorder**
- **Personality disorder**

Many Etiologies for Dementia



Delirium

- A **syndrome**
- Altered or fluctuating level of consciousness/attention deficits/alertness
- Not a final diagnosis
- Acute or subacute onset
- Caused by a variety of illnesses or medications
- If psychotic, time-limit use of antipsychotics
- Difficult to assess with dementia
- Must identify to treat appropriately

Possible Causes of Delirium

- **Acute illness**
 - UTI, respiratory infection
- **Chronic illness**
 - CHF, COPD causing hypoxia, renal insufficiency, anemia
- **Sensory impairment**
 - Cataract, hearing loss
- **Iatrogenesis**
 - Many drugs have anticholinergic effects
 - Recent medication change
 - Rule out withdrawal syndrome

Lipowski ZJ. *JAMA*. 1987;258:1789-1792.

Lipowski ZJ. *Psychiatr Clin North Am*. 1992;15:335-46.

Medical Issues to Consider in Behavioral Distress

- **Illnesses: GERD, angina, OA, etc.**
- **Medication side effects**
- **Pain**
- **Constipation**
- **Hearing or vision impairment**
- **Sleep deprivation**
- **Dental problems**

Psychosis

- Impaired connection to reality **or** auditory or visual hallucinations **or** delusions
- Psychosis is a **symptom**, **not** a final diagnosis
- Psychosis is a result of well-defined illnesses
- Differential diagnosis includes dementia (all types), delirium, chronic psychotic disorders (schizophrenia, bipolar disorder, others), psychotic depression
- Impaired memory from dementia can be easily mistaken for psychosis (i.e., not all delusions are “psychotic”)
 - Theft
 - House is not home
 - Mother is waiting
 - They need to go to work
 - Caregiver is an impostor
 - Mate is unfaithful
- The working diagnosis indicates **duration** of treatment

Pharmacological Approaches to BPSD: Basic Principles

- Pursue etiology of behavioral disturbance
- Identify target symptoms
- Employ behavioral approaches ALWAYS along with pharmacological interventions
- Choose pharmacotherapy by identifying key psychiatric syndromes in patient's presentation:
 - Psychosis
 - Depression
 - Mania
 - Aggression
 - Spontaneous Disinhibition

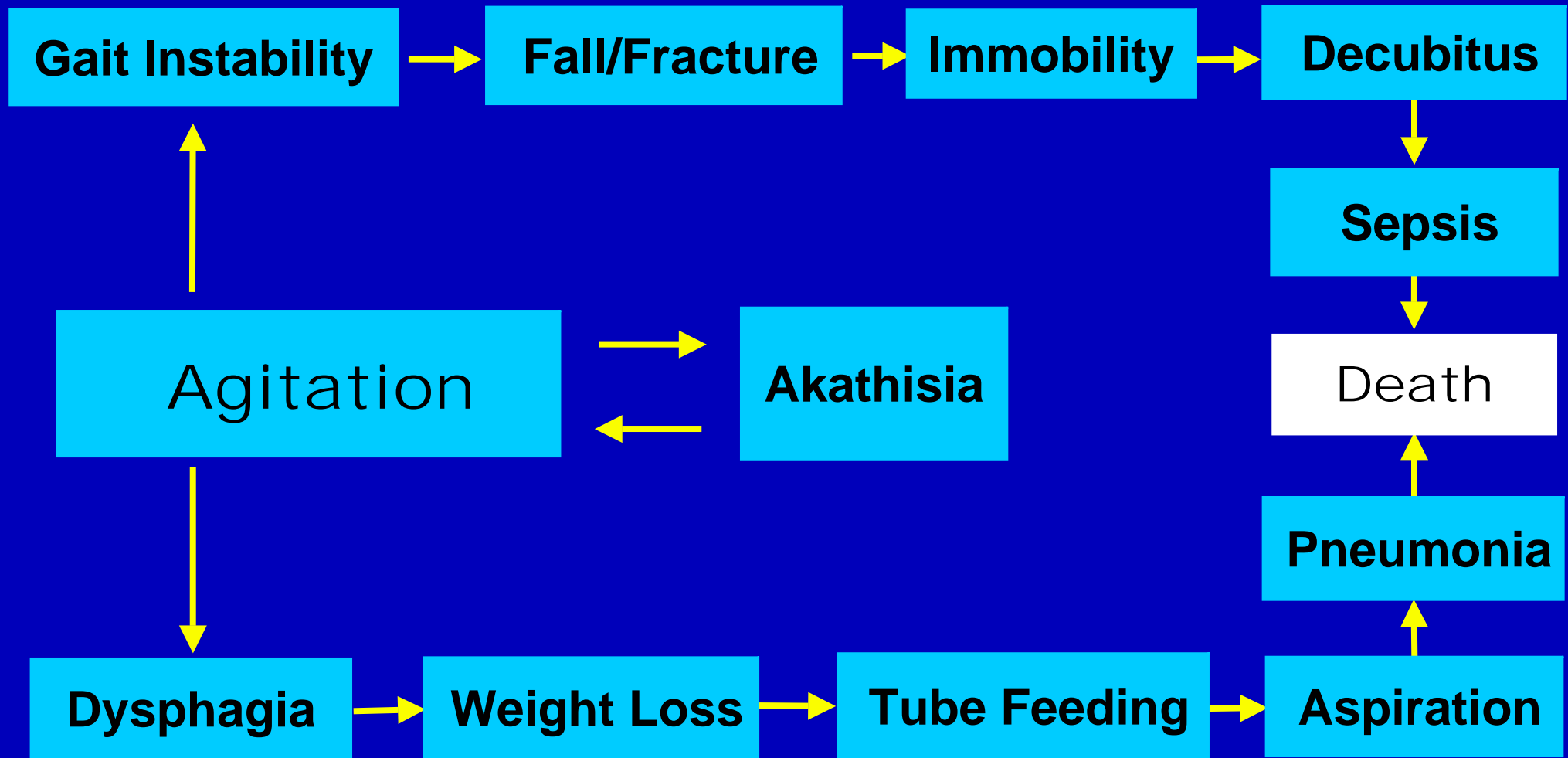
OBRA Guidelines: Antipsychotics

- Use **only** if patients exhibit symptoms that impair functioning or cause danger to themselves or others and/or interfere with provision of care
- **Agitated behavior** is an insufficient reason to use an antipsychotic medication (i.e., must be psychotic or aggressive)
- Considered **unnecessary** if initiated as treatment in the absence of documentation of the approved indications
- Use requires **approved** diagnosis and symptoms

Conventional Antipsychotics in Dementia

- Limited efficacy, substantial toxicity
- Associated with a risk of falls
- Cardiac toxicity (i.e., thioridazine)
- Associated with EPS
 - Parkinsonism (bradykinesia, rigidity, tremor)
 - Akathisia
 - Tardive dyskinesia: 28% after 1 year, 50% after 2 years, 63% after 3 years

Possible Consequences of Drug-Induced Parkinsonism in the Elderly



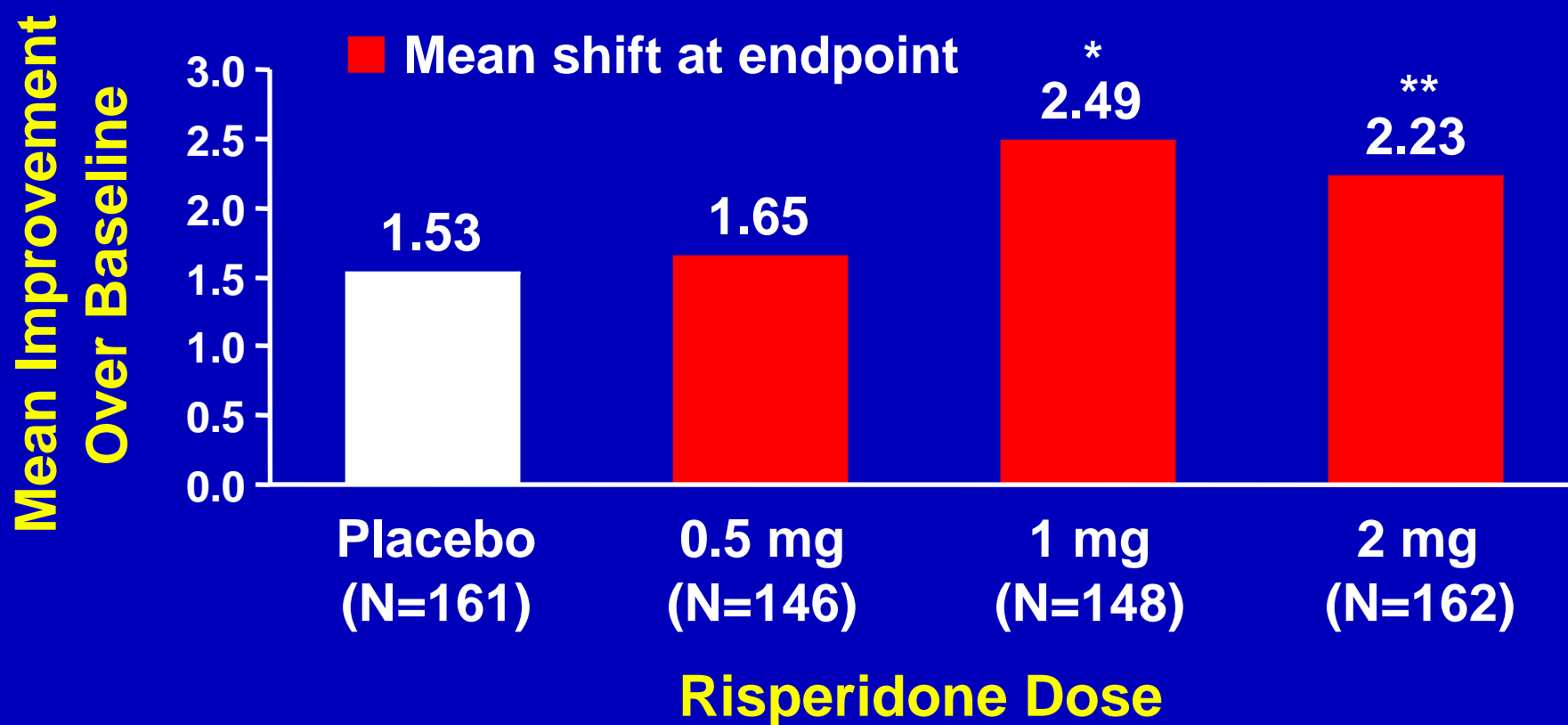
Atypical Antipsychotic Doses

Drug	Initial (mg/Day)	Typical Range (mg/Day)	OBRA Max (mg/Day)
Clozapine	12.5	25-50	Unknown
Risperidone	0.5	1-2	2
Olanzapine	2.5	5-10	10
Quetiapine	25.0	50-250	200
Ziprasidone	Unknown	Unknown	Unknown
Aripiprazole	2.5-5.0	5-10	Unknown

- **Must attempt a gradual reduction every 6 months unless:**
 - The patient has 1 of the 10 approved conditions
 - For a diagnosis of organic mental syndrome
 - 2 previous attempts have been made in the last year to establish that the dose is reduced to the lowest level to control symptoms
 - Document justification including: diagnosis, symptoms, differential diagnosis, consideration of medical causes, risk/benefit analysis

Risperidone in Dementia

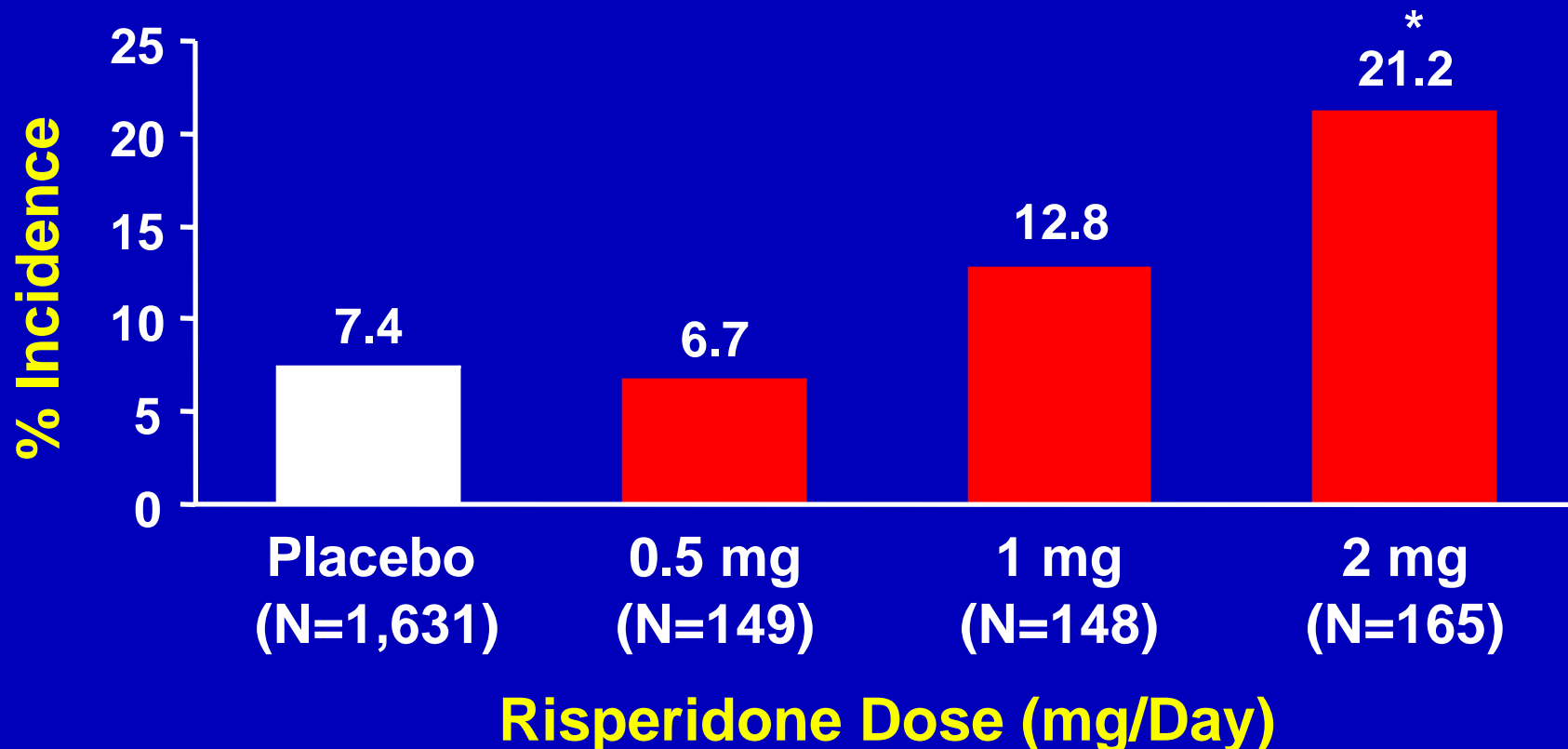
Psychosis Subscale: BEHAVE-AD



N=625 NH patients, 12-week study, Alzheimer's, vascular or mixed dementia, all with behavioral symptoms or psychosis; *p=0.005 vs. placebo; **p<0.01 vs. placebo; Katz IR, Jeste DV, Mintzer JE, et al. J Clin Psychiatry. 1999(Feb);60(2):107-115

Risperidone in Dementia-Associated Behavioral Disturbances and Psychosis

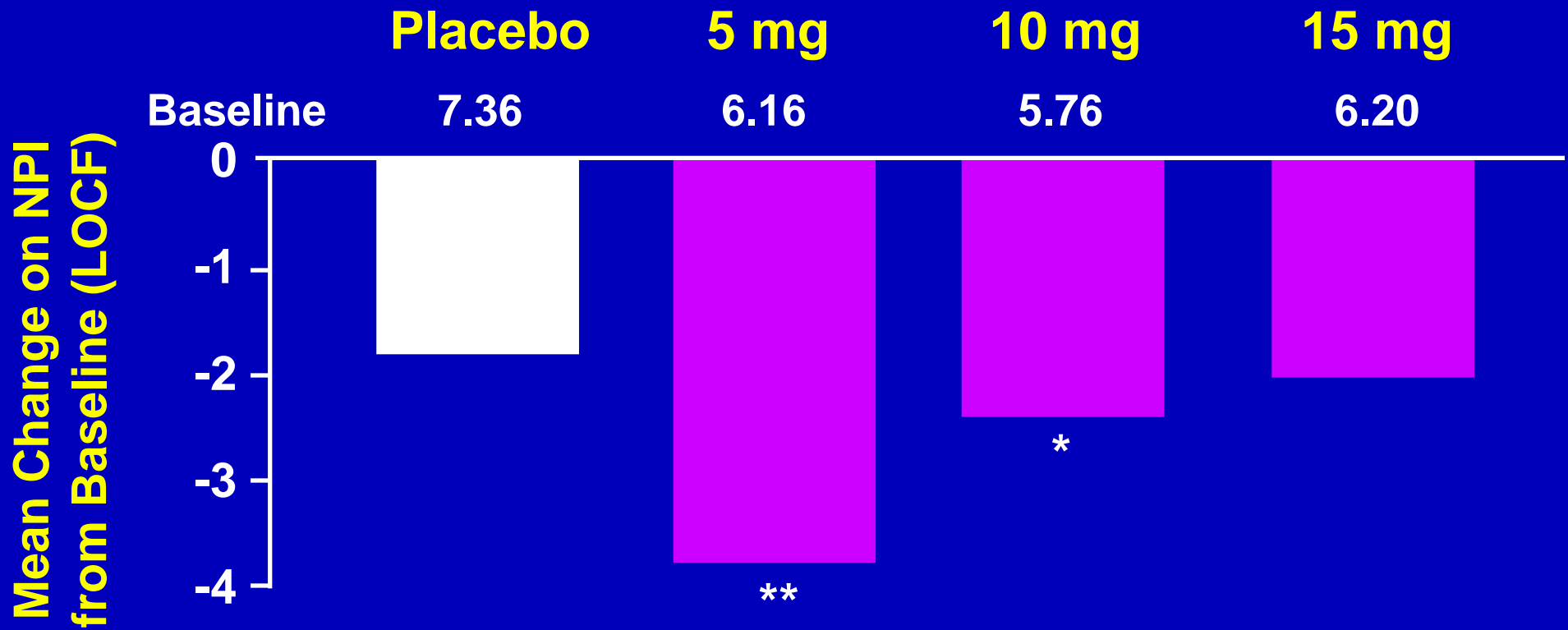
Incidence of EPS



*p<0.05 vs. placebo; Katz IR, Jeste DV, Mintzer JE, et al. J Clin Psychiatry. 1999(Feb);60(2):107-115

Olanzapine in Dementia

Delusions and Hallucinations



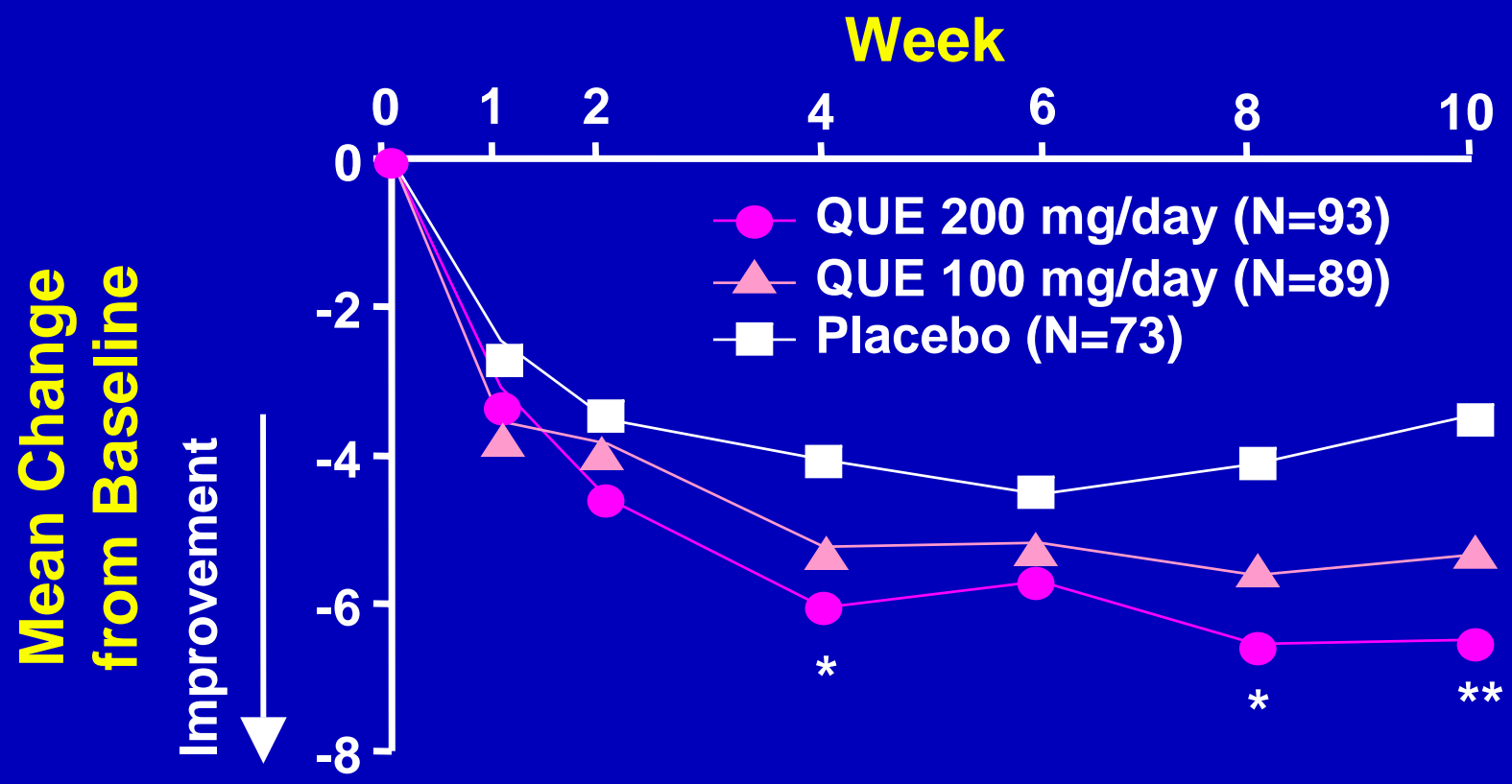
*p<0.05 vs. placebo; **p≤0.001 vs. placebo; LOCF = last observation carried forward; NPI/NH = Neuropsychiatric Inventory-Nursing Home; Street et al. Eur Neuropsychopharmacol. 1999;9(suppl 5)

Efficacy and Safety of Quetiapine (QUE) for Agitation Associated with Dementia: STAR Trial

- 10-week, 55 sites, DB, PC, fixed-dose study in LTC
 - Primary efficacy measure: change from baseline in PANSS-EC
 - Secondary efficacy measures: CGI-C, NPI-NH, CMAI
- Ambulatory NH/ALF residents with possible/probable AD or vascular dementia
- Quetiapine 100 mg/day vs. quetiapine 200 mg/day vs. placebo
 - 50 mg bid by day 4 and 100 mg bid by day 8
- Mean age = 83 years, mean MMSE = 5-6
- Agitation due to pain, delirium, medication, etc., were excluded
- Lorazepam 4 mg/day and some hypnotics allowed until day 14

Zhong K. Presented at 9th International Conference on Alzheimer's Disease and Related Disorders, Philadelphia; July, 2004

Star Trial: PANSS-EC: Mean Change from Baseline QUETIAPINE



ITT-LOCF; *p<0.05; **p<0.01 vs. placebo; Zhong K. Presented at the 9th International Conference on Alzheimer's Disease and Related Disorders. Philadelphia; July 2004

Aripiprazole for Psychosis in AD: 10-Week, Placebo Controlled Trials

- **Psychosis in AD: Outpatient, N=208, flexible dose 2-15 mg/d, BPRS core and psychosis scores reduced at endpoint**
- **Psychosis in AD: Nursing Home, N=190, flexible dose 2-15 mg/d**
- **Psychosis in AD: Nursing Home, N=480, fixed dose 2,5,10 mg/d**
 - **CMAI, NPI-psychosis, BPRS total, sig improved both studies. Effective dose = 10 mg a day.**
- **Streim, Presented at AAGP Meeting, March 2003, Honolulu, Hawaii**
- **Jeste, Presented at AAGP meeting, February 2004, Baltimore, MD**

Atypical Antipsychotic Medications: Safety Issues

- **Most common issues: Somnolence, orthostasis, falls**
- **American Diabetes Association warning for risk of diabetes with all atypical antipsychotics**
- **EKG abnormalities**
- **Extrapyramidal symptoms**
- **Lowering of seizure threshold (olanzapine 0.9%)**
- **FDA CVAE Warning - March 2003 for RISP**
 - **UK Committee of Safety Of Medicines (CSM) cautioned against the use of RISP and OLZ for BPSD**
- **FDA Mortality Warning - April 11, 2005**

Cerebrovascular Adverse Events

- **Class warning for elevated risk of cerebrovascular adverse events**
 - **Risperidone (3.8%) vs. Placebo (1.5%); N=1230**
 - **Olanzapine (1.3%) vs. Placebo (.4%); N=1882**
 - **Aripiprazole (1.3%) vs. Placebo (.6%); N=938**
 - **Quetiapine (0.3%) vs. Placebo (1.9%); N=568**

Recommended Monitoring Protocol for Patients on Atypical Antipsychotics*†

	Baseline	4 Weeks	8 Weeks	12 Weeks	Annually	Every 5 Years
Personal/ family history	X					
Weight (BMI)	X	X	X	X		
Waist circumference	X					X
Blood pressure	X			X	X	
Fasting blood sugar	X			X	X	
Fasting lipid profile	X			X		X

*More frequent assessments may be warranted based on clinical status; †Focused on schizophrenia and bipolar illness; American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity. Diabetes Care. 2004(Feb);27(2):596-601

FDA Warning on Mortality

- Announced April 11, 2005
- **Boxed Warning: atypical antipsychotics used to treat dementia-related psychosis carry an “increased risk of death compared with placebo”**
- 17 PCTs reviewed enrolling 5377 elderly pts with dementia related behavioral disorders (3611 drug, 1766 placebo)
- Rate of death in drug treated patients was 4.5% vs. 2.6% in placebo group
- Risk of death 1.6 to 1.7 times that seen in placebo group
- Cause of death - heart related or infectious
- Six drugs involved in trials: aripiprazole (3), olanzapine (5), risperidone (7), quetiapine (2), ziprasidone (1), haloperidol (2)
- 7 medications will have warning including clozapine, ziprasidone and Symbyax (olanzapine/fluoxetine)

Class Warning

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10 week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. RISPERDAL® (risperidone) is not approved for the treatment of patients with Dementia-Related Psychosis.

Risk of Death with Atypicals in Dementia

- Meta-analysis of 15 RCTs, 10-12 weeks in duration¹
- Aripiprazole (3), olanzapine (5), quetiapine (3), risperidone (5)
- 3353 patients randomized to drug, 1757 pts to placebo
- Death occurred more often among pts randomized to drug: 118 (3.5%) vs. 40 (2.3%); Odds ratio = 1.54
- No evidence for differential risks for individual drugs, severity of dementia, sample selection or diagnosis
- Excess mortality not recognized by examining any individual trial
- For every 9-25 patients who benefit from treatment, there may be 1 death.

•1. Schneider et al. *JAMA* 2005;294:1934-1943.

Conventional Antipsychotics and Mortality

- 22,890 elderly persons (ages 65 and over) beginning therapy with antipsychotic medications¹
- Four cohorts examined (≤ 180 days, 0-40 days, 40-80 days, 80-180 days)
- Conventional antipsychotics had a 37% higher, dose-dependent risk of death in the short term than those for whom atypical agents were prescribed (Odds Ratios: 1.27-1.56)
- Greatest risk after initiation of treatment and when using higher doses

• Wang PS, et al. *N Engl J Med* 2005; 353:2335-2341

Efficacy of Atypicals in Dementia: Meta-Analysis¹

- Efficacy on rating scales observed for risperidone and aripiprazole, not for olanzapine; lack of evidence for or against quetiapine (different selection criteria and rating scales used)
- Response rates often not reported
- Smaller effects seen for outpatients, less severe dementia, and patients selected for psychosis
- Drop-out rates 1/3 both groups
- Adverse events: somnolence, urinary incontinence/UTI; EPS and abnormal gait for OLZ and RISP; not falls
- Cognitive scores worsened on medications

1. Schneider et al. *Am J Geriatric Psychiatry* 2006; 14:191-210

What's A Clinician to Do?

- **Caution colleagues about over-reacting – alternative pharmacological choices (conventional antipsychotics, Benzodiazepines) not great evidence-base for efficacy and serious concern regarding tolerability**
- **Thorough assessment of etiology of BPSD is vital**
- **Always employ non-pharmacological strategies which must be studied in well designed clinical trials with and without pharmacotherapy**
- **When using antipsychotics: a careful informed consent with HCP/guardian required**

Frontal Lobe Impairment Symptoms

“Secondary Mania”

- Poor impulse control, disinhibition
- Mood lability or inappropriate affect
- Verbally rude, caustic, bigoted, etc.
- Episodically physically aggressive
- Perseverative
- Restless/grabbing/reacts strongly to stimuli
- Difficult to redirect
- Sexually inappropriate/aggressive
- Apathy

First-Line “Mood Stabilizers”

- **Anticonvulsants**
 - **Valproate**
 - Broad response, better tolerated than carbamazepine
 - **Carbamazepine**
 - Broad response, worrisome side-effect profile
- **Atypical antipsychotics approved for mania**
 - **Olanzapine**
 - **Quetiapine**
 - **Risperidone**
 - **Ziprasidone**

Second-Line “Mood Stabilizers”

Generally Poorly-Tolerated or Very Limited Data

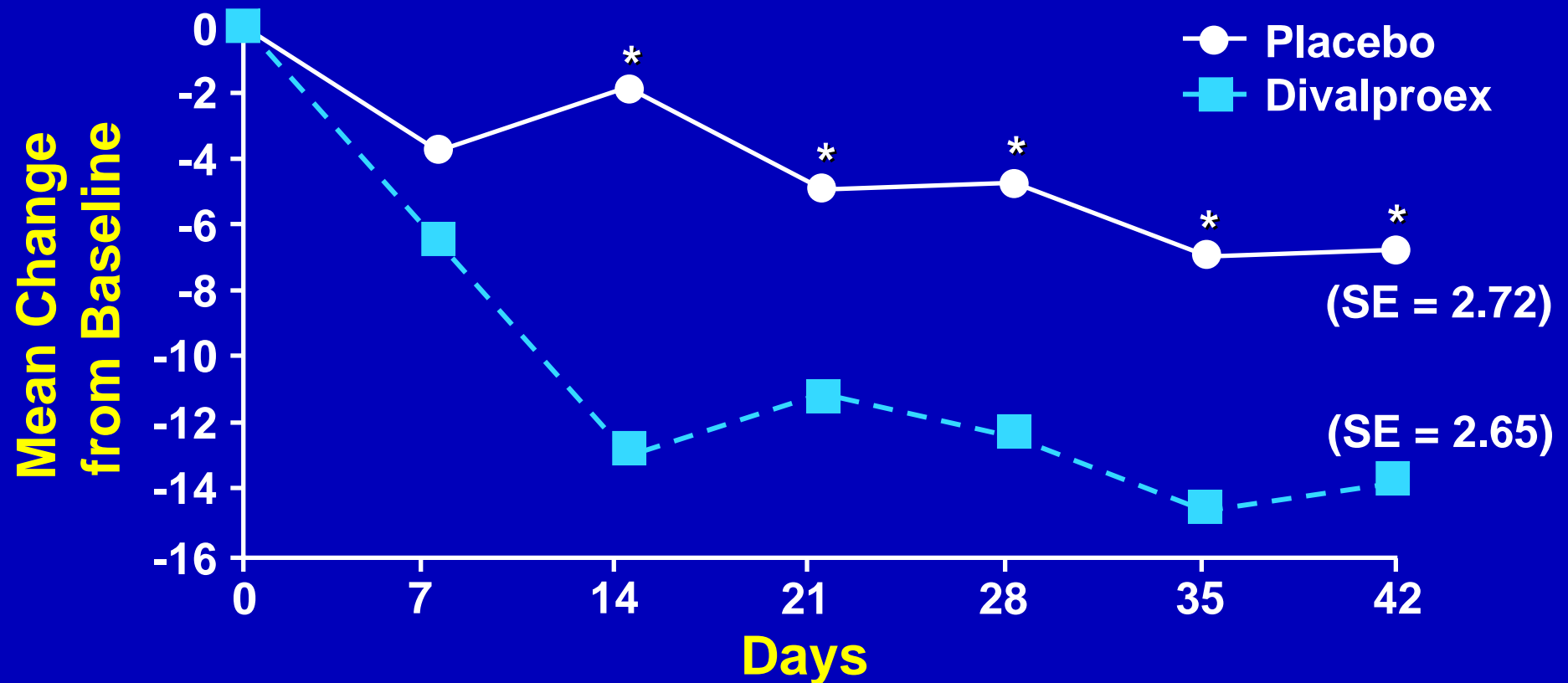
- Lithium
 - Narrow therapeutic index, poorly-tolerated in elders
- Gabapentin
- Lamotrigine
- Topiramate
- Conventional antipsychotics
- Ziprasidone, aripiprazole
- Benzodiazepines
- Serotonergic agents
- Drugs that reduce noradrenergic effects
 - β -blockers (e.g., propranolol)
 - α -agonists (e.g., clonidine)

Divalproex in Elderly Mania/Dementia

- **Double-blind, placebo-controlled, randomized trial of NH residents (N=172)**
- **Met criteria for secondary mania**
- **Target dose 20 mg/kg/day in 10 days**
- **Statistical improvement found on Cohen-Mansfield Agitation Inventory Score (CMAI) (p=0.035)**
- **Study suspended due to side effects (sedation)**

Divalproex in Elderly Mania/Dementia

Cohen-Mansfield Agitation Inventory (Total Scores)



* $p < 0.05$ for group differences; Portsteinsson AP, Tariot PN, Erb R, et al.
Am J Geriatr Psychiatry. 2001(Winter);9(1):58-66

Valproate (Divalproex): Use in Dementia

- **Side effects: somnolence, thrombocytopenia, weight gain, hair changes, tremor, hepatotoxicity, pancreatitis (rare)**
- **Current dose and titration recommendations**
 - **Initial dose 125-250 mg twice daily; increase by 125-250 every 5 days**
 - **Usual range 500-1,250 mg/day**
 - **Usual level 40-90 µg/ml**
 - **Clinical response more important than serum level**
- **Start low and go slow!**

Portsteinsson AP, Tariot PN, Erb R, et al. Am J Geriatr Psychiatry. 2001(Winter);9(1):58-66; Genton P, Gelisse P. In: Levy RH, Mattson RH, Meldrum BS, Perucca E, eds. Antiepileptic Drugs, 5th ed. Philadelphia: Lippincott, Williams & Wilkins; 2002, Chapt. 89, pp. 837-851

Benzodiazepines

- Minimal efficacy data
- Sedating
- Further inhibit learning and memory
- Cause falls
- Paradoxical disinhibition

Neuropsychiatric Effects of Cholinergic Agents

- Tacrine, Donepezil, Rivastigmine, Galantamine
- Effects important in some individuals, modest at group level
- Perhaps most notable benefit in Lewy Body Dementia
- Key effects
 - Decrease psychosis (visual hallucinations)
 - Decrease apathy
 - Decrease agitation but occasional increase
 - Decrease ? anxiety, depression
- Study demonstrating effectiveness of donepezil in treatment of neuropsychiatric symptoms in a randomized withdrawal study¹

•¹Holmes C. et al. *Neurology* 2004;63:214-219.

Summary

- **Distressed behaviors are clues to the diagnosis**
- **Unless urgent, the complete assessment (not just the symptoms) determines the working diagnosis**
- **Use non-pharmacologic interventions in every case**
- **The working diagnosis determines management approach and medication class used**
- **Consider side effects and tolerability in all medication choice**
- **Treatment goals to enhance quality of life of patient and caregiver**