
**FDA Black Box Warnings:
What Do They Mean For The Consumer
--- Atypical Antipsychotics ---**

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Atypical Antipsychotics

Brand	Generic
Risperdal [®]	Risperidone
Zyprexa [®]	Olanzapine
Seroquel [®]	Quetiapine
Geodon [®]	Ziprasidone
Abilify [®]	Aripiprazole
Invega [™]	Paliperidone

Safety Concerns of Atypical Antipsychotics

- Mortality
- Cerebrovascular Adverse Events
- Hyperglycemia and Diabetes Mellitus

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.

Applies to all atypical antipsychotics

Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances

- 15 out of 17 placebo-controlled trials showed numerical increases in mortality in the drug-treated group compared to the placebo-treated patients
 - N = 5106 involving Risperidone (7 trials), Olanzapine (5 trials), Aripiprazole (3 trials) and Quetiapine (2 trials)
 - ~1.6-1.7 fold increase in mortality in active treatment over placebo
 - Rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group
- Specific causes of these deaths:
 - Heart related events (e.g., heart failure, sudden death) or infections (mostly pneumonia)

FDA Public Health Advisory: Deaths with antipsychotics in elderly patients with behavioral disturbances. Accessed January 16, 2006, at www.fda.gov/cder/drug/advisory/antipsychotics.htm

Risk of Death with Atypical Antipsychotics in the Elderly

- Meta-analysis of Randomized, Placebo-Controlled Trials
 - Risk did not differ by drug, psychotic symptoms as criteria for inclusion, living arrangements or cognitive impairment.
- Conventional Antipsychotics
 - Associated with significantly higher adjusted risk of death relative to atypical antipsychotics.

Schneider LS et al, JAMA 2005;294:1934-43.

Wang PS et al. N Engl J Med 2005;352:2335-2341.

WARNING

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia-Related Psychosis – In placebo-controlled trials with risperidone, aripiprazole and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects.

Cerebrovascular Adverse Events (CVAEs) with Risperidone in Patients with Dementia

Study	Risperidone			Placebo		
	N	Serious* CVAEs	All CVAEs	N	Serious* CVAEs	All CVAEs
Australia ¹	167	6 (3.6%)	15 (9.0%)	170	0 (0%)	3 (1.8%)
Multinational ²	115	4 (3.5%)	9 (7.8%)	114	1 (0.9%)	2 (1.8%)
United States ³	462	2 (0.4%)	5 (1.5%)	163	2 (1.2%)	2 (1.2%)
United States ⁴	235	3 (1.3%)	4 (1.7%)	238	1 (0.4%)	1 (0.4%)
Belgium ⁴	20	0 (0%)	0 (0%)	19	0 (0%)	0 (0%)
International ⁴	10	0 (0%)	0 (0%)	8	0 (0%)	0 (0%)
Total	1009	15 (1.5%)	33 (3.3%)[†]	712	4 (0.6%)	8 (1.1%)

*“Serious” events include death, hospitalization, permanent disability, and events judged by the physician to be medically serious. CVAE = cerebrovascular adverse event.

[†]Significantly different vs placebo.

1. Brodaty, H. et al. J Clin Psychiatry. 2003; 64:134-143. 2. De Deyn PP et al. Neurology. 1999;53:946-955.
3. Katz et al. J Clin Psychiatry. 1999;60:107-115. 4. Data on file, Janssen Pharmaceutica.

Cerebrovascular Adverse Events (CVAEs) with Olanzapine in Patients with Dementia

STUDY	Olanzapine			Placebo		
	N	Serious* CVAEs	All CVAEs	N	Serious* CVAEs	All CVAEs
HGAO	118	0 (0%)	0 (0.0%)	118	1 (0.8%)	1 (0.8%)
HGEU ¹	159	0 (0%)	1 (0.6%)	47	0 (0%)	0 (0%)
HGGU	204	4 (2.0%)	5 (2.5%)	94	0 (0%)	0 (0%)
HGIC	177	4 (2.3%)	5 (2.8%)	90	1 (1.1%)	1 (1.1%)
HGIV ²	520	2 (0.4%)	4 (0.8%)	129	0 (0%)	0 (0%)
Total	1178	10 (0.8%)	15 (1.3%)[†]	478	2 (0.4%)	2 (0.4%)

*“Serious” events include death, hospitalization, permanent disability, and events judged by the physician to be medically serious.

[†](vs placebo) p =.18 Fishers; p=.04 Poisson when controlling for age, type of dementia, and gender.

¹Street et al. Arch Gen Psychiatry 2000;57:968. ²De Dyn et al. Int J Geriatr Psychiatry 2004;19:115.

Wooltorton E. CMAJ 2004;170:1395. Cavazzoni P et al. Presentation at NCDEU, June 2004, Phoenix, AZ

Cerebrovascular Adverse Events (CVAEs) with Aripiprazole in Patients with Dementia

STUDY	Aripiprazole		Placebo	
	N	All CVAEs	N	All CVAEs
Trial 1 (Outpt)	105	1 (1.0%)	102	1 (1.0%)
Trial 2 (NH)	130	0 (0%)	121	1 (0.8%)
Trial 3 (NH) [†]	360	7 (1.9%)	120	0 (0%)
Total	595	8 (1.3%)	343	2 (0.6%)

†Dose relationship: ↑dose → ↑risk of CVAEs

Source: Abilify® Package Insert – Revised November 2006

Behavioral Symptoms

- ~30-40% of persons with dementia have significant behavioral and psychiatric symptoms
- Associated with
 - High rates of functional impairment and disability
 - Worse health outcomes
 - Physical injury
 - Increased rates of hospitalization
 - Greater emergency service use
 - Lower rates of retention of nursing home staff

American Geriatrics Society and American Association for Geriatric Psychiatry. Consensus Statement on Improving the Quality of Mental Health Care in U.S. Nursing Homes: Management of Depression and Behavioral Symptoms Associated with Dementia AGS. *J Am Geriatr Soc.* 2003;51:1287-1298.

Treatment of Behavioral and Psychological Symptoms of Dementia: Meta-Analysis of Randomized Controlled Trials

- Atypical antipsychotics (6 RCTs)
 - Modest but statistically significant effects
 - Few adverse events at lower doses
- Typical antipsychotics (2 RCTs)
 - Minimal efficacy, frequent adverse events (may be severe)
- Mood stabilizers/antidepressants (5 RCTs)
 - No efficacy on neuropsychiatric symptoms except depression
- Antiepilepsy drugs (5 RCTs)
 - No efficacy with valproate; conflicting results with carbamazepine
- Cholinesterase Inhibitors (6 RCTs)
 - Minimal effect/conflicting results; statistically significant in 2 RCTs
- Memantine (2 RCTs)
 - Conflicting results

What Consumers Need to Know

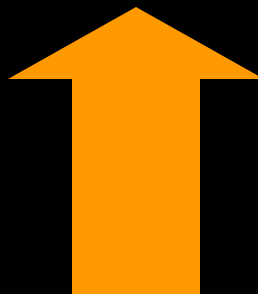
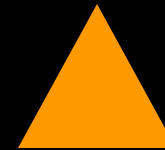
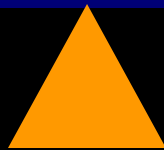
Atypical Antipsychotics for Dementia-Related Psychosis

Take

- ↑ risk of death
 - (~4.5% vs ~2.6%)
- ↑ risk of CVAEs
 - (~1.3 to 3.3% vs 0.4 to 1.1%)

Do Not Take

- Poor Outcome
- Functional Impairment
- ↑ likelihood of placement
- Limited alternative treatments



Risk Factors for Stroke

Beyond Control

- Advancing age, risk doubles after age 55 years
- Male gender
- African-American
- Family history of diabetes
- Family history of stroke or TIA

May be altered

- Medical
 - Hypertension
 - Atrial fibrillation
 - Elevated cholesterol
 - Coronary Heart Disease
 - Sleep Apnea
- Lifestyle
 - Smoking
 - Obesity
 - Excessive Alcohol

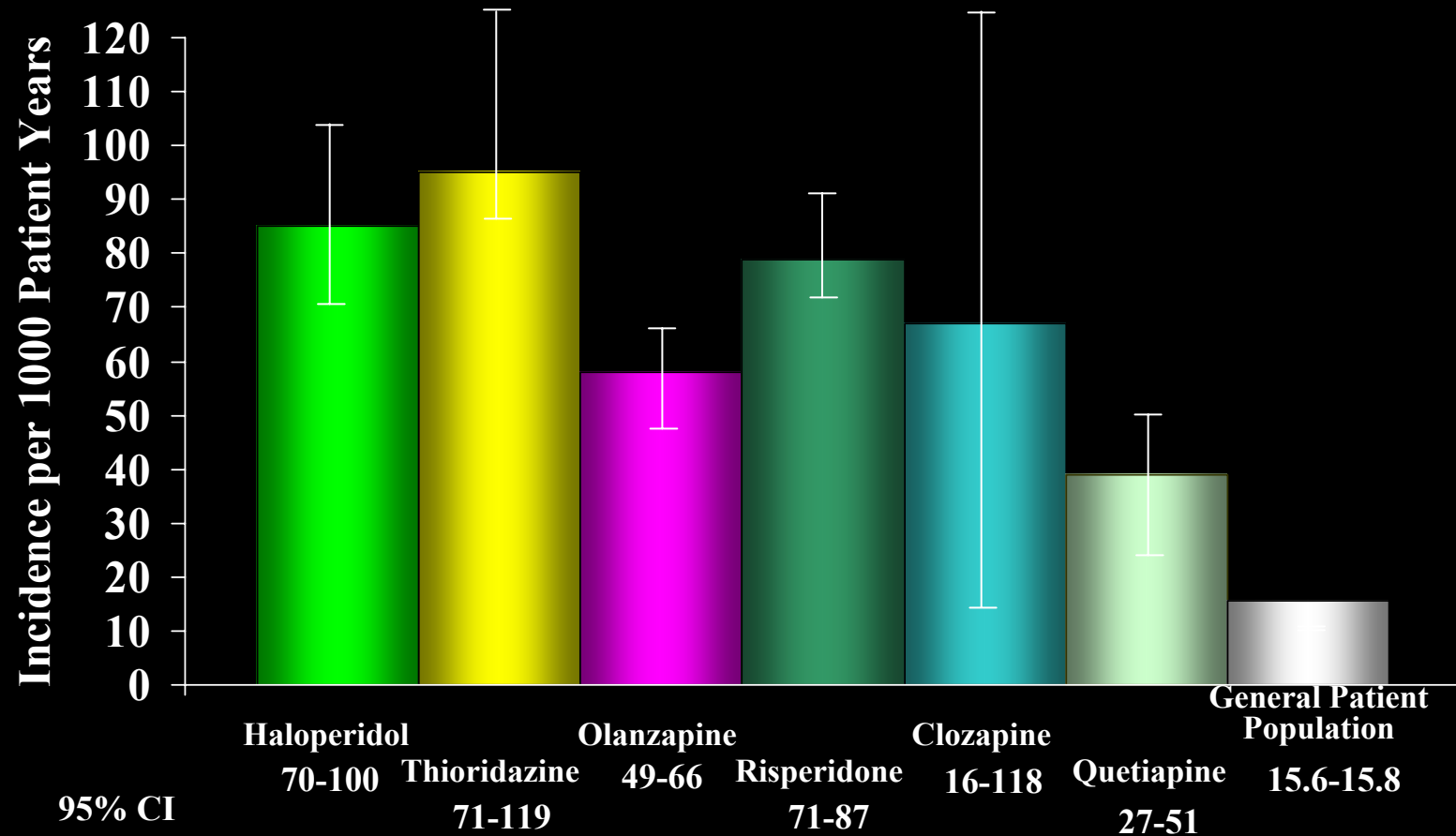
Source: National Stroke Association

WARNING

Hyperglycemia and Diabetes Mellitus –

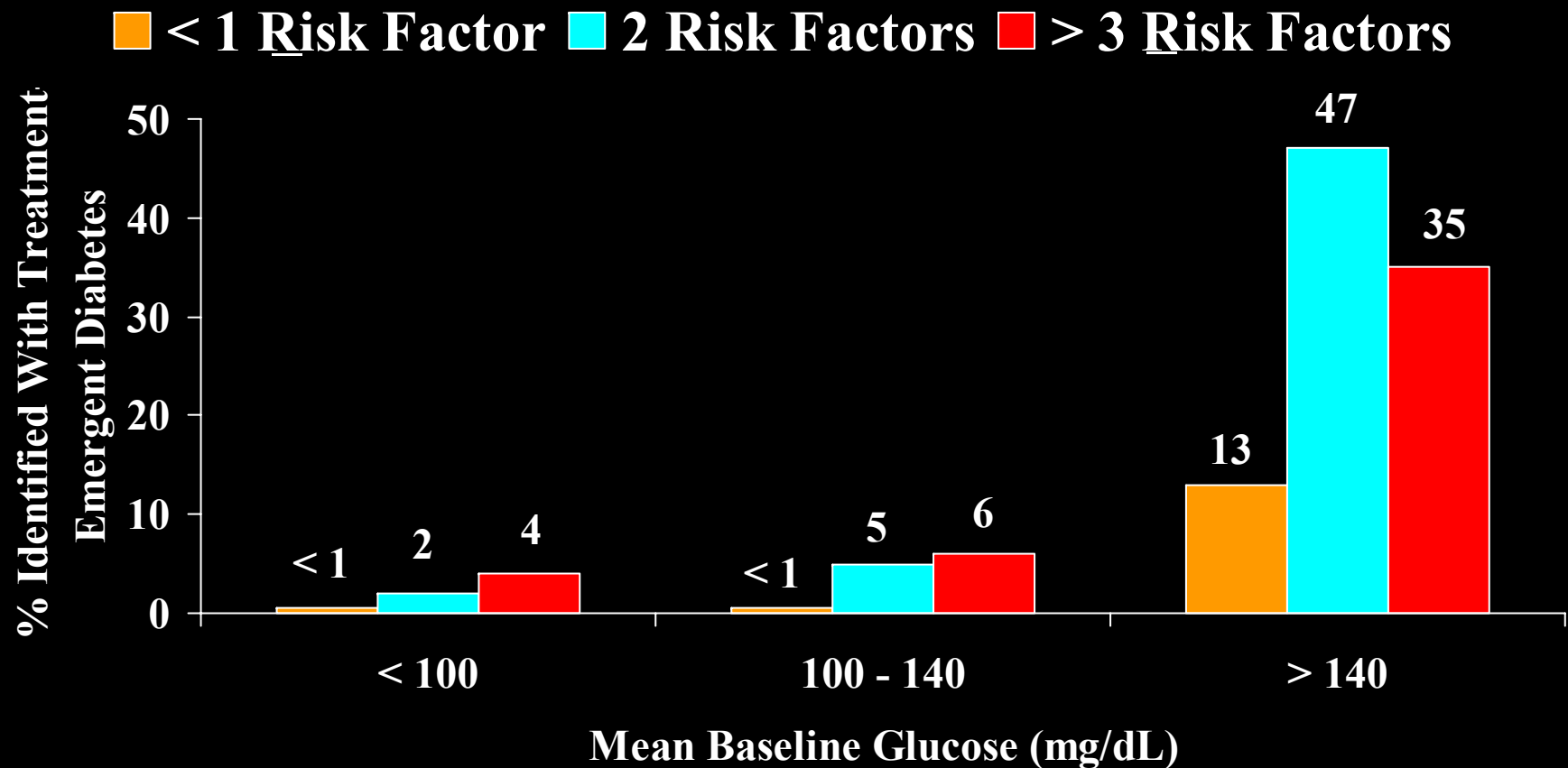
Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics.

Annualized Incidence of New Diagnosis of Diabetes Mellitus in Specific Antipsychotic PCS Treatment Cohorts



Buse JB et al. J Clin Epidemiology 2003;56:164-170.

Interaction Between Baseline Random Glucose and Number of Pre-existing Risk Factors and Risk of Treatment-Emergent Diabetes



Cavazzoni P et al. Br J Psychiatry 2004;47:S94-101.

Medical Comorbidity in People with Serious Mental Illnesses

- High rates of medical comorbidity
 - underdiagnosis of physical illness
 - increased mortality
- Higher rates (vs general population)
 - Obesity
 - Smoking
 - Dyslipidemia
 - Hypertension
 - Diabetes

What Consumers Need to Know

~ Atypical Antipsychotics ~

- Weight Gain and Obesity
 - Monitor weight and waist circumference
- Hyperglycemia and Diabetes Mellitus
 - Monitor glucose/sugar
 - Monitor for symptoms of ↑ glucose or Diabetes Mellitus
 - ↑ thirst
 - ↑ urination, especially at night
 - ↑ hunger
 - fatigue
 - frequent infections
 - blurred vision
 - Weight loss
 - sores that do not heal
- Minimize/reduce diabetes risk factors
 - ↑ risk factors → ↑ treatment emergent diabetes
- Receive routine medical follow-up care

Risk Factors for Type 2 Diabetes Mellitus

- Age - Older than 45 years
- Obesity - Weight >120% of desirable body weight (true for approximately 90% of patients with type 2 diabetes)
- Family history of type 2 diabetes in a first-degree relative
- Hispanic, Native American, African American, Asian American, or Pacific Islander descent
- History of previous impaired glucose tolerance (IGT) or impaired fasting glucose (IFG)
- Hypertension (>140/90 mm Hg) or dyslipidemia (high-density lipoprotein [HDL] cholesterol level <40 mg/dL or triglyceride level >150 mg/dL)
- History of GDM or of delivering a baby with a birth weight of > 9 lbs
- Polycystic ovarian syndrome (which results in insulin resistance)

General Recommendations

- **Do not discontinue or change the dose of treatment without talking to your healthcare provider first.**
 - Benefits may outweigh risks
- **Reduce/eliminate risk for strokes and diabetes mellitus**
- **What Matters Most to Consumers**
 - Symptom relief
 - Reduced caregiver burden
 - Improved Quality of Life
 - Avoidance of unacceptable risks
 - Improved functional status
 - Risk reduction
 - Cost of care