

# Practical Information: The Appropriate Use of Antipsychotic Medications for those with Dementia

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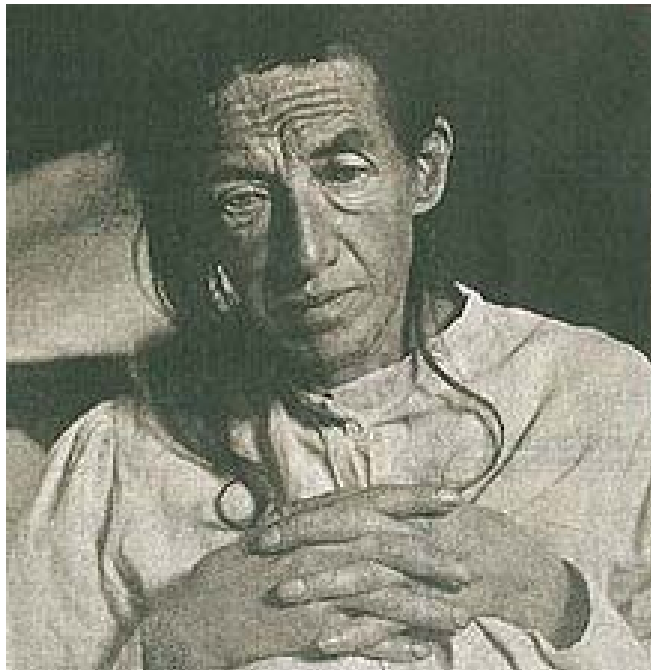
\*\* No financial disclosures, Off label use of medications is discussed

# Objectives

- **Does it EVER make sense to use an antipsychotic medication in someone with dementia???**
- History
  - History of psychosis and neuropsychiatric symptoms in dementia
  - FDA boxed warning
  - History of use of antipsychotics in those with dementia
- Describe why anti-psychotic medications work
- How to appropriately use anti-psychotics in the three symptom clusters of paranoia/delusions, hallucinations and subsequent aggression

# First Case of Alzheimer's Disease

- She died in 1906 at age 56
- Case and autopsy findings presented at 37<sup>th</sup> Conference of Southwest German Psychiatrists Tubingen



Auguste D and Alzheimer's Disease. Maurer, Volk & Gerbaldo, *The Lancet*. 1997. 349:1546-1549

# Dr Alzheimer's patient

- 1901, symptoms began at age 51
- History of progressive cognitive impairments, and...
- **Reason for admission: Hallucinations, delusions and psychosocial incompetence**
- Paranoia that husband was having affair, memory impairment, fearful that someone wanted to kill her, shouting, disoriented, then speech became unintelligible and she became severely apathetic.
- “she becomes excited again and screams terribly (November 1901), she is in a state of fright, anxious and completely disoriented, violent towards everything (February 1902), completely rebellious, screams and stamps her feet when someone goes near her (June 1902)”.
- Alzheimer and his disease: a brief history. *Neurol Sci.* 2011. 32:275-279

# Neuropsychiatric Inventory (NPI)

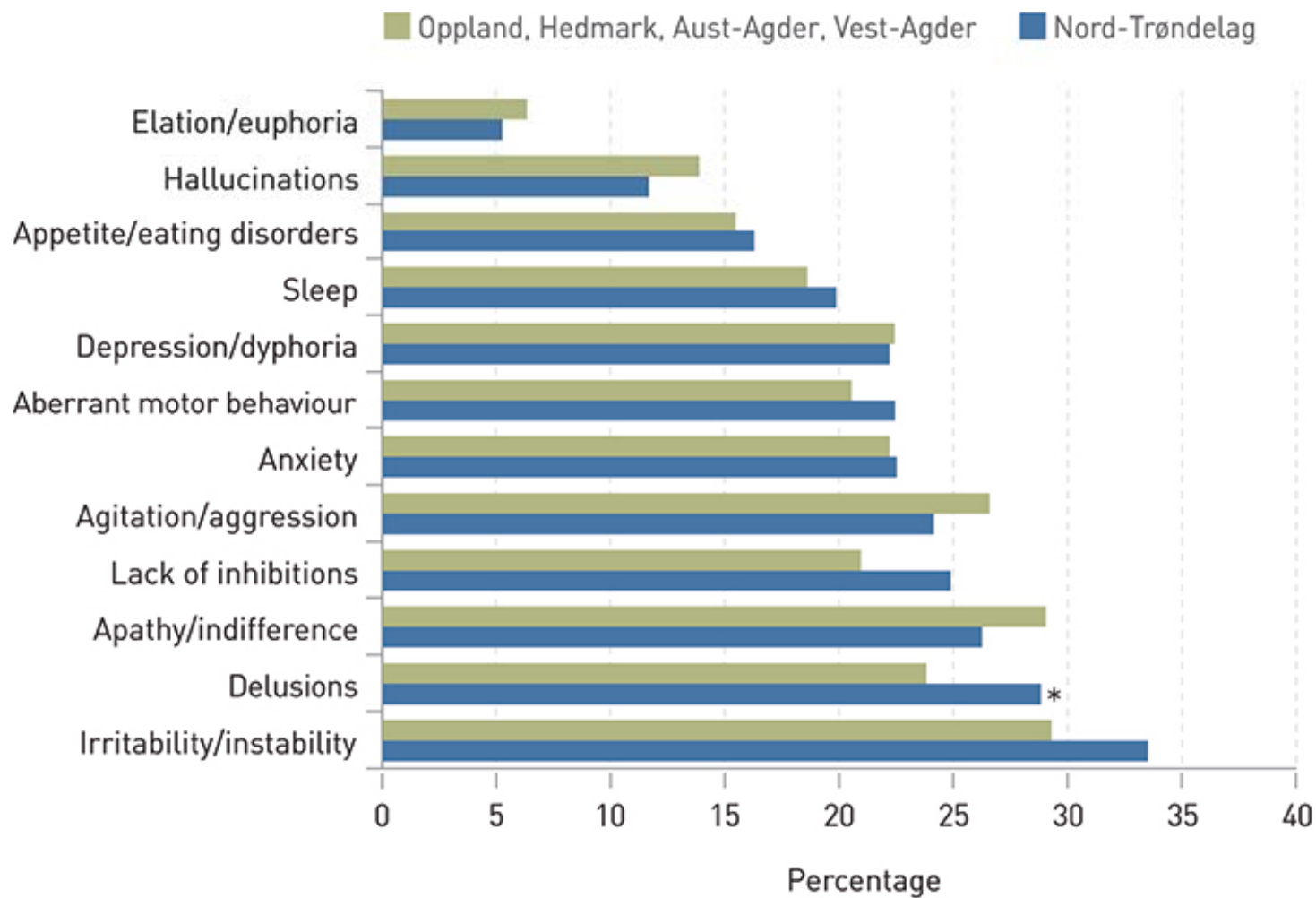
Symptom	Anytime during illness	Shown in last month
Delusions	50%	35%
Hallucinations	28	20
Agitation/Aggression	63	52
Depression	54	45
Anxiety	50	44
Apathy	76	75

A cross-sectional study of neuropsychiatric symptoms in 435 patients with Alzheimer's disease. Craig et.al, 2005. 13(6):460-8.

# Neuropsychiatric Inventory (NPI)

Symptom	Anytime during illness	Shown in last month
Euphoria	17	23
Irritability	63	55
Aberrant Motor Behaviors	65	57
Sleep Disturbance	54	42
Appetite	64	54

A cross-sectional study of neuropsychiatric symptoms in 435 patients with Alzheimer's disease. Craig et.al, 2005. 13(6):460-8.



\* P = 0,033 on the chi-square test

Dementia and neuropsychiatric symptoms in nursing-home patients in Nord-Trøndelag County, Bergh S et al. Journal of the Norwegian Medical Association 2012

## Select look at aggression in US or Canadian nursing homes

- April 2013: 81 yo M kills 87 yo M in Toronto, ON
- April 2013: 85yo F pushed by peer and killed in PA
- May 2012: 86yo M kills 84yo M in MI
- Mar 2011: 66yo M kills 80yo M in IL
- Feb 2011: 78yo M kills 70yo M in PA
  - 2 staff injured
- Dec 2009: 98yo F kills 100yo F in MA
  
- Source: online newspaper articles



# Staff (and family members) are in danger

- Aggression towards staff
- 138 nursing assistants at 6 Nursing Homes
  - 59% assaulted once per week
  - 16% assaulted daily

(Gates & Meyer, 1999)

# Verbal and physical aggression directed at NH staff by residents.

- 2 week period of time, prevalence cohort study, staff response rate: 89 %
- 16 % of residents had aggressive behaviors
  - (3 % physical, 8 % verbal, 0.5 % sexual, and 5 % both verbal and physical).
- Most common type was verbal (12%), screaming at the CNA (9% of residents).
- Physical aggression 8 % of residents, most common hitting (4% of residents).

# Quotes from Family:

- “I don’t want my Mom’s last days filled with fear and terror because of the delusion that someone is trying to hurt her or steal her money.”
- “I don’t want Mom to hurt anyone.”
- “If my Dad knew what he was doing, he would be so embarrassed.”
- “I’m afraid Dad is going to kill my Mom.”

# Regulatory Issues

# **OBRA: Omnibus Reconciliation Act of 1987**

- Formalized “nursing home reform”
- Legislation based on Institute of Medicine report
- Inadequate care was common in US nursing homes
- Inadequate assessment, poor quality of life, violations of basic rights, failure to recognize and treat reversible causes of physical and functional decline
- There was a significant concern that residents were being “drugged” to control behaviors. This was before atypical antipsychotics existed.

# Concerns expressed by many:

- “You are just drugging people”
- “These medicines only should be used in certain severe mental illnesses”
- “Antipsychotics are tranquilizers”

# **CMS in 2012 Partnership to improve dementia care in nursing homes**

- Hand in hand training series with an emphasis on non-pharmacological interventions
  - Person centered care
  - Prevention of abuse
  - High quality care
- **Stated goal of reducing antipsychotic use by 15%**
  - **No clinical goal such as: improve quality of life or quality of care,**

# FDA Boxed Warning on antipsychotics (also known as a black box warning)

- FDA warning in 2004 on risperidone
- FDA in 2005 added a boxed warning on all atypical antipsychotics at the time: Risperidone, Clozapine, Olanzapine, Ziprasidone, Aripiprazole and Quetiapine

The warning is for increased mortality with the off-label use of antipsychotics in the elderly/dementia population

Data upon which warning was based:

- Average age of person's who died: 85yo
- Medications not prescribed for psychosis
- Causes of mortality were quite varied



# Discussion about the boxed warnings with Dr. Tom Laughren and Dr. Mitchell Mathis of the FDA March 29, 2012

- “We don’t understand the signal”
- Warning based on a meta-analysis of data collected prior to 2005
- This data NOT of those with psychosis or aggression, there was a mix of “behavior disturbance” without any definition of what this is
- Hospice patients, those with delirium and other conditions with high mortality were NOT excluded
- Risk highest at start of treatment, “perhaps increased risk is due to excess sedation.” They did not consider that this is when those dying of other conditions most likely to receive an antipsychotic.
- “The boxed warning is not a contraindication to using these medications.”

# Effect of FDA warning

- Within one year of 2005 warning, 19% decreased use of atypical antipsychotics among those with dementia
- By 2008, 50% decrease in use of atypical antipsychotics among those with dementia
- Use of atypical antipsychotics decreased for everyone, not just those with dementia

Dorsey et al. Impact of FDA black box advisory on antipsychotic medication use. Arch Int Med 2010

# FDA Boxed Warnings

- Later, FDA recognized that typical antipsychotic medications were at least as dangerous as atypical antipsychotics
- Based on a study in 2007, FDA added the boxed warning on typical or first generation antipsychotics
- The warning is for increased mortality with the off-label use of antipsychotics in the elderly/dementia population

# Informed Consent for all treatments including pharmacological

- Discussion and documentation of discussion with patient, family or surrogate decision-maker of:
  - Risks
  - Benefits
  - Alternatives (including the risks of no treatment)
  - Common risks of no treatment of paranoia and delusions: **patient or peers injured, staff injured**, loss of placement, **social isolation**-being avoided by peers and staff, increased neuropsychiatric symptoms, **decreased quality of life**, increased institutionalization

# **Antipsychotic Medications**

# How FDA approves medications:

- Approves medications for a specific illness even if the medication treats only some symptoms of the illness
- Once approved, can be prescribed for anything
- It costs millions of dollars to have a new indication added for an existing medicine
- What matters to most people - helping people with symptoms while having

# Dopamine

- Cocaine and other pro-dopamine meds cause psychosis
- Antipsychotic meds lower dopamine and treat psychosis regardless of cause of psychosis
- Discovered while looking for new antihistamines (allergy meds).
- Older antipsychotics meds block histamine and can cause significant sleepiness due to this

The American Psychiatric  
Association Practice Guideline on  
the use of Antipsychotics to Treat  
Agitation or Psychosis in Patients  
with Dementia published in 2016



# APA Practice Guideline: Review of Research Evidence

- Risperidone treats psychosis (paranoia, delusions, hallucinations and thought disorder)
- Risperidone, olanzapine, and aripiprazole for agitation/aggression.
- There was insufficient information from trials of **quetiapine**.
- Lewy Body Dementia and Parkinson's Disease Dementia are exceptions and there is evidence to use quetiapine and clozapine

# APA Practice Guideline (PG): Evidence shows

- Behavioral & Psychological Symptoms of Dementia overall

moderate efficacy

- Aripiprazole
- Risperidone

- Agitation/Aggression moderate efficacy

- Olanzapine
- Risperidone

- Psychosis moderate efficacy

- Risperidone

# APA PG: How to use antipsychotics

- Assess risk/benefit/alternative of med
- Start with lowest dose, monitor carefully for side effects.
- If an antipsychotic successful the decision about possible tapering of antipsychotic medication should be person centered with input from family or others involved with the patient.
- Past experience with antipsychotic medication trials and tapering attempts should be considered.

# APA PG continued

- While antipsychotic medication is being tapered, assessment of symptoms should occur at least monthly during the taper
- and for at least 4 months after medication stopped to identify signs of recurrence
- If symptoms recur, this should trigger a reassessment of the benefits and risks of antipsychotic treatment

# Other studies of Antipsychotic Meds

## Treating Psychosis - delusions and hallucinations

- Be careful of dosage, however.
- In patients with dementia using risperidone for psychosis and agitation/aggression, 1 mg/day was associated with a decreased fall risk (?secondary to reducing agitation), but 2 mg/day increased fall risk
- risperidone and haloperidol were compared in dementia patients with behavioral disturbances, risperidone worked better with less side effects
- Very few studies have used ziprasidone

Katz IR et al, Am J Geriatr Psychiatry 12:499-08, 2004

Suh G, et al, Am J Geriatr Psychiatry 12:509-16, 2004

# Dosage Ranges Used

<b>–Medication</b>	<b>Usual Dosage Range in patients with dementia</b>
–Risperidone	0.5-1 mg po bid
–Ziprasidone	20-80 mg po bid w food
–Olanzapine	2.5-10 mg once daily
–Aripiprazole	2.5-20 mg once daily

–In general, quetiapine is not useful for psychosis in patients with Alzheimer's or Vascular Dem.

–It is anticholinergic at doses above 150mg and usually much higher doses are needed for successfully treating psychosis.

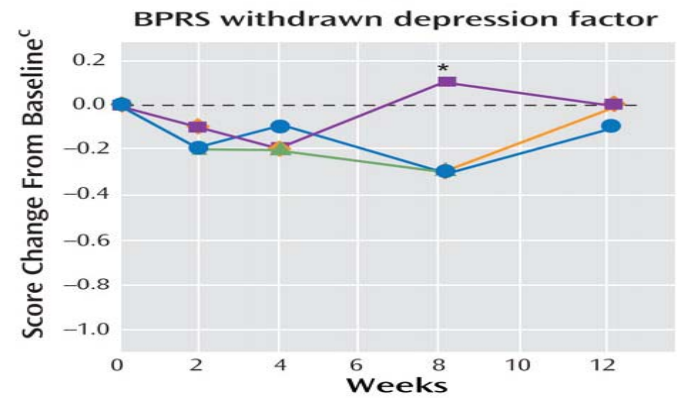
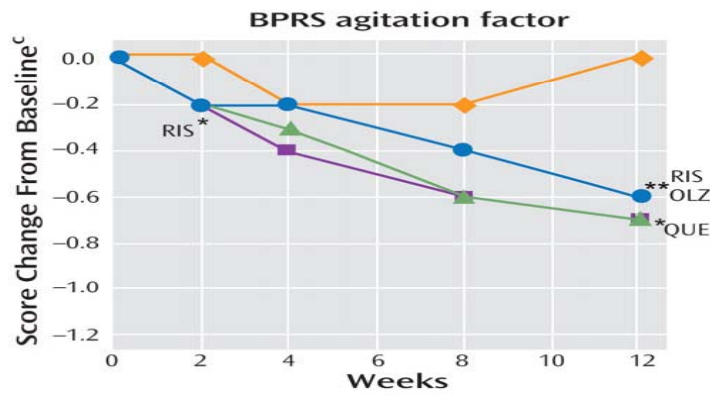
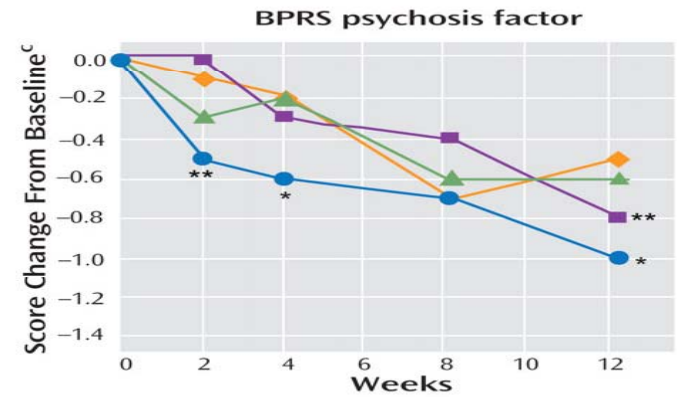
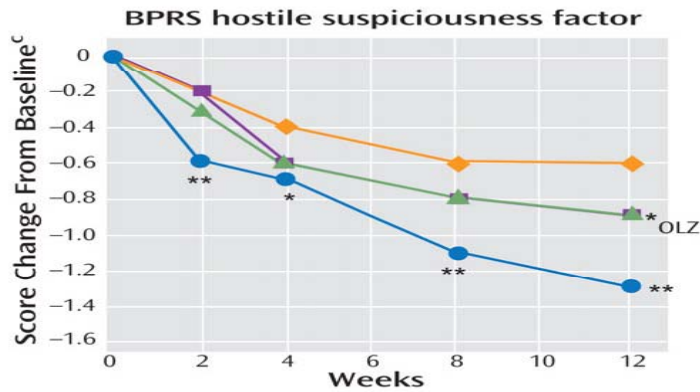
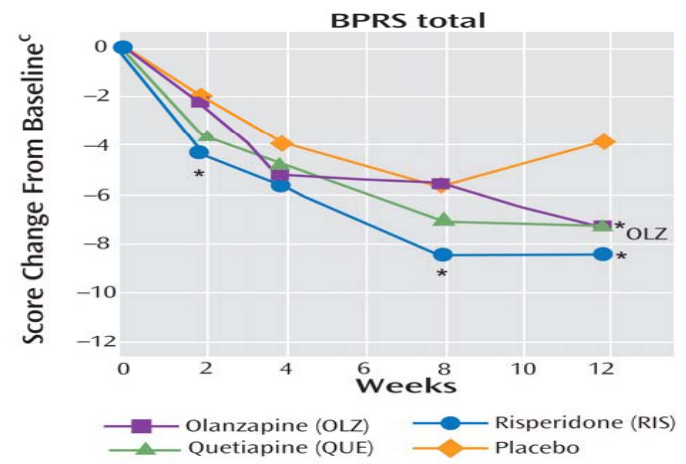
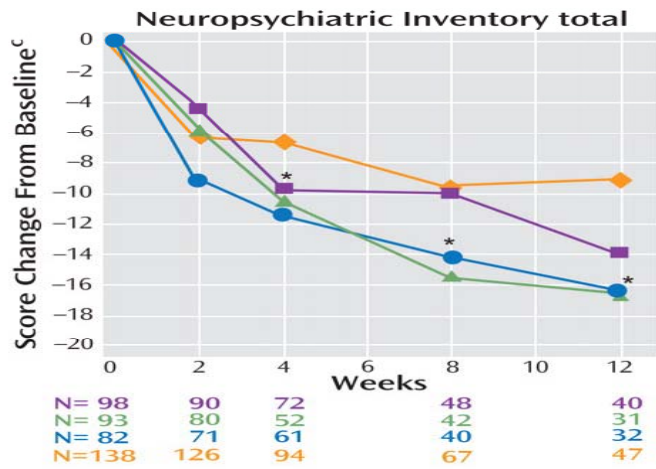
**–Lewy Body Dementias including Parkinson's Disease**

# CATIE-AD – large NIMH funded study

- **Initial analysis did not look at efficacy of treating the symptoms!** Reanalysis in 2008 did.
  - OLZ-olanzapine, RIS-risperidone, QTP-quetiapine, Placebo
  - Patients were more likely to stop placebo due to lack of effectiveness and stop drug because of side effects.
  - If patient tolerated the medicine and stayed on it, there was improvement – modest – **anger, aggression and paranoia**. But care needs, functioning did not improve.

Schneider et al. NEJM 155(15):1525-38, 2006

Sultzer et al. AJP 165:844-54, 2008





Can we **predict**  
what is likely to happen if there is  
indiscriminate discontinuation of  
antipsychotic medications  
in patients with dementia and  
psychosis/agitation-aggression who  
have responded to them?

# What happens if one stops risperidone in someone who has responded to it?

- People with Alzheimer's Dementia + psychosis or agitation-aggression who responded to 16 weeks of open label treatment with risperidone then
- Continue risperidone for 32 weeks
  - Relapse - 33% at 16 wks, 15% at 32 weeks
- Continue risperidone for 16 weeks then placebo
  - Relapse - 48% on placebo
- Switch to placebo
  - Relapse - 60% on placebo

Devenand et al. Oct 2012 NEJM 1497-1507 Relapse risk after discontinuation of risperidone in Alzheimer's disease

# Typicals antipsychotics have more risk

- Mortality ratio for risperidone 1.3
- Mortality ratio haloperidol 2.14
- Cardiovascular or infectious causes were the major reasons for death, and could not be directly associated with the drugs.
- Highest period of risk within 40 days of starting prescription

Schneeweiss S, et al CMAJ 176:627-32, 2007

Gill SS et al Ann Int Med 146:775-86, 2007

# Typical antipsychotics have more risk

- Wang et al did retrospective of nearly 23,000 patients over 65 years old in Pennsylvania who received conventional or atypical antipsychotics from 1994-2003.
- Conventional/Typicals were associated with a significantly higher risk of death than atypicals in all subgroups. Highest risk was early in therapy and at higher doses.

**Which medications are the  
most dangerous for older  
adults?**

# 4 Drugs Cause Most Drug Related Hospitalizations in Older Adults

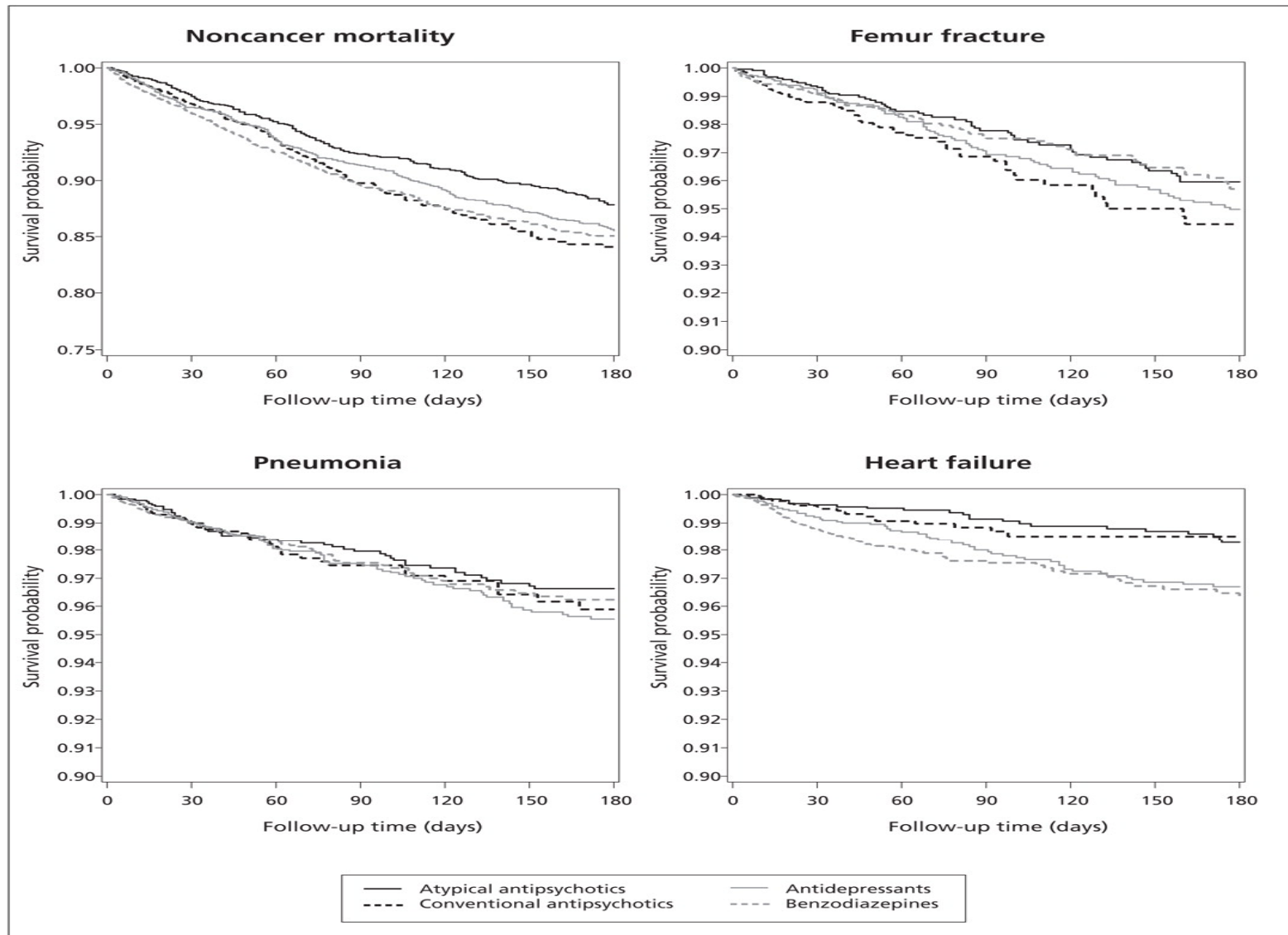
- Warfarin/coumadin
- Insulin
- Aspirin/clopidogrel/plavix and other “blood thinners”
- Oral hypoglycemics – diabetes medicines like metformin, glucophage, glipizide etc

Budnitz, DS, et al. **Emergency Hospitalizations for Adverse Drug Events in Older Americans.** *N Engl J Med.* 2011;365:2002-

# Comparison of Risk of Hospitalization & Mortality

- 10,900 Nursing Home patients in Canada
- Risks of older antipsychotics, antidepressants & benzodiazepines vs risks of atypical antipsychotics
- Risk of death:
  - Older AP and antidepressants 1.47
- Risk of femur fracture:
  - Older AP 1.61 and antidepressants 1.29
- Users of Benzodiazepines (like lorazepam)
  - Risk of death 1.8, Heart Fail 1.54, Pneumonia 1.85

# Kaplan–Meier estimation of the probability of no events over time



Huybrechts K F et al. CMAJ 2011;183:E411-E419

CMAJ·JAMC



# **Dementia specific medications**

# **Dementia Specific Medications**

## **Low risk + moderate efficacy**

- Memantine
- Cholinesterase Inhibitors:
  - Donepezil
  - Rivastigmine oral or topical patch
  - Galantamine

# Behavioral effects of memantine

- 24 weeks, double blind, placebo controlled moderate/severe DAT. Dosage of 20 mg/day. All on donepezil as well.
- Neuropsychiatric Inventory scores decreased (improvement)
- Subscales agitation/aggression, eating/appetite and irritability/lability improved the most
- **Those patients without aggression at the start had less emergence of it after 24 weeks compared to placebo**

# Cholinesterase Inhibitors (CI)

- CI drugs are help with the neurobehavioral symptoms of dementia
  - All three drugs (donepezil, galantamine and rivastigmine) in a meta-analysis - 10 studies using the NPI and 6 using the ADAS-noncog – showed all three drugs have a benefit, modest, but very consistent, on neuropsychiatric/functional/behavioral outcomes.
- Improvements often include reduced agitation and reduced need for anti-depressants, anti-anxiety and anti-psychotics.

Trinh H et al: JAMA 289(2):210-216, 2003

# Cholinesterase Inhibitors

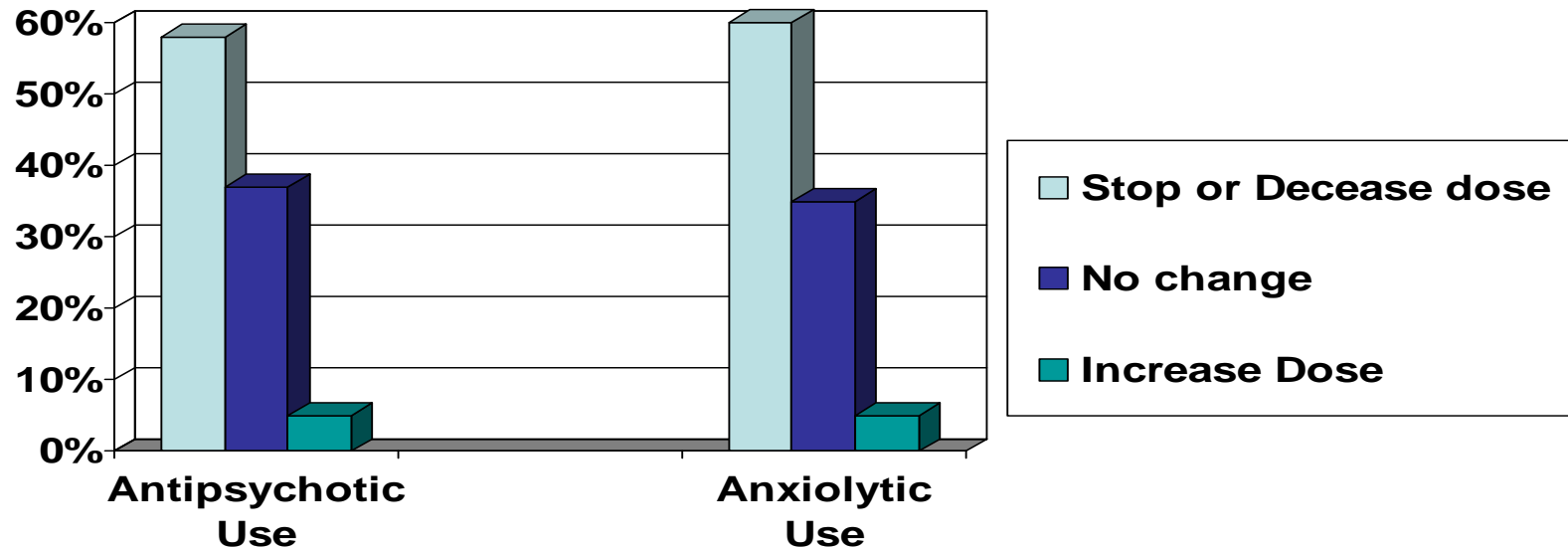
## Rivastigmine

657 patients, open label

mild-Mod ALZ

already on other meds for behaviors

Follow-up 4-6 months later



Verny et al J Drug Asses. 7:123-134, 2004

# NICE (Nat'l Institute for Health and Care Excellence) guidelines

in UK

- 2001 – ChE-I used until “there was no effect then stop”
- 2005 – insufficient to use ChE-I (BMJ 2005; 330:495)
- 2006 – clinically and cost effective for those with moderate Alzheimers (BMJ 2006; 332:195)
- 2011 – ChE-I recommended for mild and moderate Alz disease

# Canadian Review of Evidence led to changes in recommendations in 2013

- 15 revised or new recommendations approved by consensus.
- ChEIs possess a class effect and any of the agents can be used for Alzheimer's Disease across the spectrum of severity and with co-existing cerebrovascular disease.
- ChEIs were recommended as a treatment option for dementia with Parkinson's disease.

Herrmann N, et al. Alzheimers Res Ther. 2013 Jul 8;5(Suppl 1):S5. Pharmacological recommendations for the symptomatic treatment of dementia: the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia 2012.

# 2015 European Academy of Neurology Guidelines: Use Combined Treatment

- Cholinesterase Inhibitor plus Memantine
- Beneficial effects of combination therapy compared to ChEI monotherapy
- **The quality of evidence was**
  - high for behaviour
  - moderate for cognitive function
  - low for ADLs
- The evidence was weak for cognition, GCI and ADL so that the general recommendation for using combination therapy was weak



# Questions