Mortality and Antipsychotic Use in Dementia-related Behavioral Disorders

December 10, 2024

Duke | MARGOLIS INSTITUTE *for* Health Policy

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Welcome and Overview

Nancy Allen LaPointe

Duke-Margolis Institute for Health Policy

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Mute

- **You have been placed on mute**; speakers can mute/unmute throughout

Questions

- Please feel free to type your question into the Q&A box and we will use your questions to inform the open discussion portions of the event

Zoom Issues? Please Zoom message Hannah Vitiello or email hannah.vitiello@duke.edu

Event Agenda

12:00 pm	Welcome and Overview
12:05 pm	FDA Opening Remarks
12:15 pm	Session 1: Introduction to Antipsychotic Use in Dementia-related Behavioral Disorders
12:50 pm	Session 2: Review of Data Analysis and Literature Review Findings
1:45 pm	Break
2:00 pm	Session 3: Stakeholder Perspectives on Considerations Regarding the Use of Boxed Warnings for Antipsychotics
2:55 pm	Session 4: Opportunities for Further Characterizing Value and Need for Boxed Warnings for Antipsychotics
3:55 pm	Closing Remarks and Adjournment

All times listed in ET

FDA Opening Remarks

Tiffany Farchione

U.S. Food and Drug Administration

Mortality and Antipsychotic Use in Dementia-related Behavioral Disorders: Introductory Comments

Tiffany R Farchione, MD
Director, Division of Psychiatry
Office of Neuroscience | Office of New Drugs
Center for Drug Evaluation and Research | FDA

Duke-Margolis Center for Health Policy Meeting: Mortality and Antipsychotic Use in Dementia-Related Behavioral Disorders

Clinical Overview

- Alzheimer's disease (AD) is the most common cause of dementia, with an estimated US prevalence of 6.5 million people aged ≥ 65 years
- Although cognitive decline is the predominant symptom, neuropsychiatric symptoms (NPS) are common
  - Heterogeneous range of non-cognitive symptoms that can include agitation, aggression, delusions, hallucination, depression, anxiety, apathy, disinhibition, sleep disturbances.
- NPS are associated with a higher risk of accelerated disease progression, functional decline, decreased quality of life, greater caregiver burden, increased out-of-home placement, and earlier death
- Clinical presentation and frequency of NPS may vary; most patients experience initial onset of symptoms in later stages of AD and worsening symptoms as AD progresses

Unmet Medical Need

- Clinical management of NPS remains a challenge:
  - Non-pharmacological approaches include: cognitive stimulation, group therapy, exercise, music therapy, and multisensory therapy
  - Off-label pharmacological options include: benzodiazepines, antihistamines, antidepressants, antiepileptics, and antipsychotics
- Studies evaluating off-label pharmacologic treatments are highly heterogeneous in design and patient population
- Results have demonstrated only small improvements in efficacy with serious risk and tolerability concerns

Antipsychotics for the Treatment of NPS

- In 2005, the U.S. Food and Drug Administration (FDA) added a Boxed Warning to all antipsychotics for the increased risk of mortality in elderly patients with dementia-related psychosis receiving antipsychotic treatment
- After the implementation of the Boxed Warning, various regulatory bodies and healthcare institutions have taken action to decrease off-label antipsychotic prescribing
- Drug utilization data indicate a decrease in antipsychotic use and an increase in the use of opioids, antiepileptics, and benzodiazepines among elderly patients with dementia

Clinical Implications

- Antipsychotics currently used as a first-line treatment choice
  - American Psychiatric Association Practice Guideline recommends the use of “non-emergency antipsychotic medications” for the treatment of agitation in patients with dementia
  - One antipsychotic approved for agitation in Alzheimer’s disease; one for hallucinations and delusions in Parkinson’s disease
  - Other antipsychotics commonly prescribed off-label, despite the limited benefit described in the current literature and the increased risk of mortality

Introduction to the Workshop

- The 2005 Boxed Warning on all atypical antipsychotic medications was based on the analysis of randomized controlled studies showing increased mortality in older adults with dementia-related psychosis.

- With additional scientific evidence becoming available and clinical practice guidance changes occurring since that time, as well as with the introduction of new treatments to the market, there is an opportunity to re-evaluate the need and value of the Boxed Warning included in the approved labeling of antipsychotic medications for impacted populations.

Scope of the Workshop

- This Workshop is a first step that the Agency is taking to initiate a dialogue with the scientific and clinical community, patients' representatives and other stakeholders.

- Attendees will hear insights from experts on a re-analysis of the data that supported the regulatory action related to the Boxed Warning as well as findings from a recently conducted literature review.

- Workshop attendees will also hear reflections from participants on the available evidence and further considerations related to the assessment of risks associated with the use of antipsychotics within this patient population.

- This Workshop is not focused on methodology issues related to the development of treatments neuropsychiatric symptoms of dementia.


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Session 1: Introduction to Antipsychotic Use in Dementia-related Behavioral Disorders

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Neuropsychiatric Symptoms of Dementia

Julia Biernot, M.D.
Division of Neurology 1 | Office of Neuroscience | Office of New Drugs
Center for Drug Evaluation and Research | FDA

Duke-Margolis Center for Health Policy Meeting: Mortality and Antipsychotic Use in Dementia-Related Behavioral Disorders

Dementia

- Dementia involves decline in one or more cognitive domains that represents a decline from prior function and is severe enough to interfere with daily function
- Before the early 2000s, the only method to know whether a person had Alzheimer's disease, or another type of dementia was after death through autopsy
- In the biomarker era, some types of dementia can be diagnosed by the presence of measurable indicators, or biomarkers

Neuropsychiatric Symptoms (NPS)

- NPS are a group of noncognitive symptoms of dementia that include disturbances of mood, behavior, thought content and perception
- Also referred to as behavioral and psychological symptoms of dementia (BPSD)
- Nearly all individuals with dementia develop at least one NPS during disease course
- Nearly 50% of those with mild cognitive impairment exhibit ≥ 1 NPS from onset of cognitive decline
- Etiology is multifactorial and includes biological, social and environmental factors

Example of Proposed Neuropsychiatric Symptom Groups

- Different NPS often co-occur
- Symptoms may be grouped to reflect different prevalence, biological correlate, psychosocial determinants, etc.

Affective	Psychosis	Hyperactivity	Euphoria
Depression Dysphoria Anxiety Apathy	Hallucinations Delusions	Agitation Aggression Disinhibition Irritability Aberrant motor behavior	

Symptoms with inconsistent grouping include eating and night-time behavior disturbances

Proposed Diagnostic Criteria

2015
Agitation in Cognitive Disorders

- Excessive motor activity
- Verbal aggression
- Physical aggression

2020
Psychosis in Major and Minor Neurocogntive Disorders

- Visual or auditory hallucinations
- Delusions
- Associated features: agitation or depression

2021
Apathy in Neurocognitive Disorders

Diminished:

- Initiative
- Interest
- Emotional expression or responsiveness

Apathy

- Originally defined by Marin (1991) as a disorder of motivation with cognitive, sensory, motor, and affective subtypes
- A consensus definition was developed for apathy in "neurocognitive disorders" by scientific societies in 2021:
  - ✓ The patient exhibits at least one symptom in at least two of the following three dimensions:
    - Diminished initiative
    - Diminished interest
    - Diminished emotional expression or responsiveness
  - ✓ These symptoms cause clinical impairment and are not explained by other disorders

Psychosis

- Multiple diagnostic criteria have been proposed for psychosis
- Limitations include symptom heterogeneity; unclear definitions of hallucinations and delusions; unclear temporal development
- The International Psychogeriatrics Association arrived at a consensus definition, published in 2020
  - ✓ Definition applies to psychosis occurring in all major and mild neurocognitive disorders
  - ✓ Provides examples of **hallucinations** and **delusions**
  - ✓ Clarifies time course, impact, and exclusionary criteria

Agitation

- Until recently, agitation in dementia was poorly defined
- In 2015 the IPA published a provisional consensus clinical and research definition of agitation in cognitive disorders
  - ✓ Criteria for cognitive impairment or dementia syndrome are met
  - ✓ Patient exhibits excessive motor activity; verbal aggression; physical aggression, persistently or frequently recurring and causing distress
  - ✓ Behaviors produce excess disability or are associate with distress
  - ✓ Behaviors are not solely attributable to another condition
- This definition has been widely used in clinical research
- "Provisional" was recently removed from the definition

Prevalence of NPS

- Across studies, apathy, depression and anxiety are among the most prevalent symptoms in AD and other dementias
- Apathy prevalence in MCI has been reported to be around 50%, with increasing prevalence with more severe cognitive impairment
- Agitation prevalence increases with dementia severity. Cumulative and persistent agitation has been reported to be as high as 60% in nursing home patients.
- The prevalence of psychosis varies depending dementia type (75% in Lewy bodies; 30% in AD; 50% in Parkinson's disease)

Burden of NPS

Neuropsychiatric symptoms are associated with:

- Faster progression to severe dementia
- Increased functional decline (independent of cognitive impairment)
- Increased hospitalization
- Earlier institutionalization
- Increased patient and caregiver morbidity and mortality
- Increased caregiver burden, distress and lower quality of life
- Higher cost of dementia care

Management of NPS

- Non-pharmacologic strategies are recommended by multiple expert groups as the preferred first-line treatment approach
- A key problem for developing recommendations for the pharmacological treatment of NPS is the small number of RCTs
- Guidelines based on meta-analysis support off-label use of antipsychotics in severe agitation and psychosis in dementia despite some Authors reporting biases in the estimation of efficacy
- Other classes of drugs continue to be used off-label including benzodiazepines, antidepressants and mood stabilizers despite modest efficacy and side effects

FDA-approved treatments for NPS

- In 2023, the Agency approved brexpiprazole (REXULTI) for the treatment of agitation associated with dementia of the Alzheimer's type
- In 2016, pimavanserin (NUPLAZID) was approved for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis
- NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis

Conclusions

- NPS are a non-cognitive symptoms common in all types of dementia
- They represent a high burden for patients and caregivers and are associated with higher rates of morbidity and institutionalization
- Treatment of NPS is challenging
- Clinical practice guidelines are limited by lack of data from adequate randomized trials
- Various classes of drugs are used off-label
- There is a high unmet need for safe and effective therapies


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A Regulatory History of the Antipsychotic Boxed Warning for the Increased Risk of Mortality in Elderly Patients

Shamir N. Kalaria, PharmD, PhD
Division of Psychiatry | Office of Neuroscience | Office of New Drugs
Center for Drug Evaluation and Research | FDA

Duke-Margolis Center for Health Policy Meeting: Mortality and Antipsychotic Use in Dementia-Related Behavioral Disorders

Identification of Cerebrovascular Events in Clinical Trials Evaluating Atypical Antipsychotics

- Starting in 2001, FDA received a cluster of cases of serious cerebrovascular events (CVAE) among subjects with dementia-related psychosis receiving antipsychotic treatment. Following the identification of the increased risk of CVAE, FDA issued warning statements to risperidone (2003), olanzapine (2004), and aripiprazole (2005) product labels.

- Reponses to data request on CVAEs for atypical antipsychotic programs also described higher mortality in many studies evaluating dementia-related behavioral disorders

- In 2005, FDA conducted a meta-analysis to systematically assess the available data to estimate the mortality risk

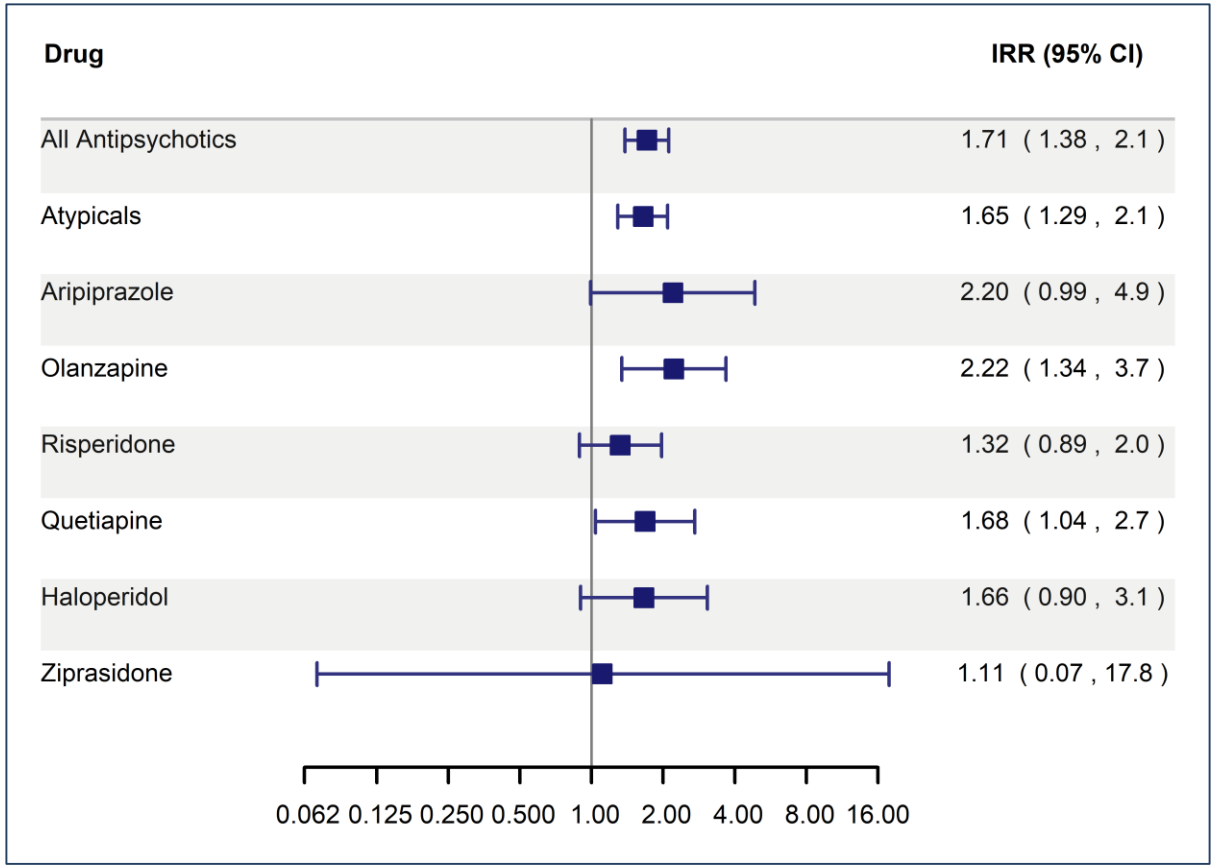
FDA's 2005 Meta-Analysis

- Based on 17 randomized, short-term, placebo-controlled trials evaluating antipsychotics in patients with dementia-related behavior disorders
- Drugs included risperidone, olanzapine, aripiprazole, quetiapine, ziprasidone, and haloperidol
- Timing and cause of deaths based on summary-level data from clinical study reports
- Various sampling timeframes were evaluated to count deaths (e.g., deaths within 4 days of treatment, deaths within the intended period of observation, all deaths)

Number of Trials	17
Sample Size	Total: 5377 Antipsychotic: 3611 Placebo: 1766
Study Duration	4 to 26 weeks
Age Range (Average)	44 to 105 years (81 years)

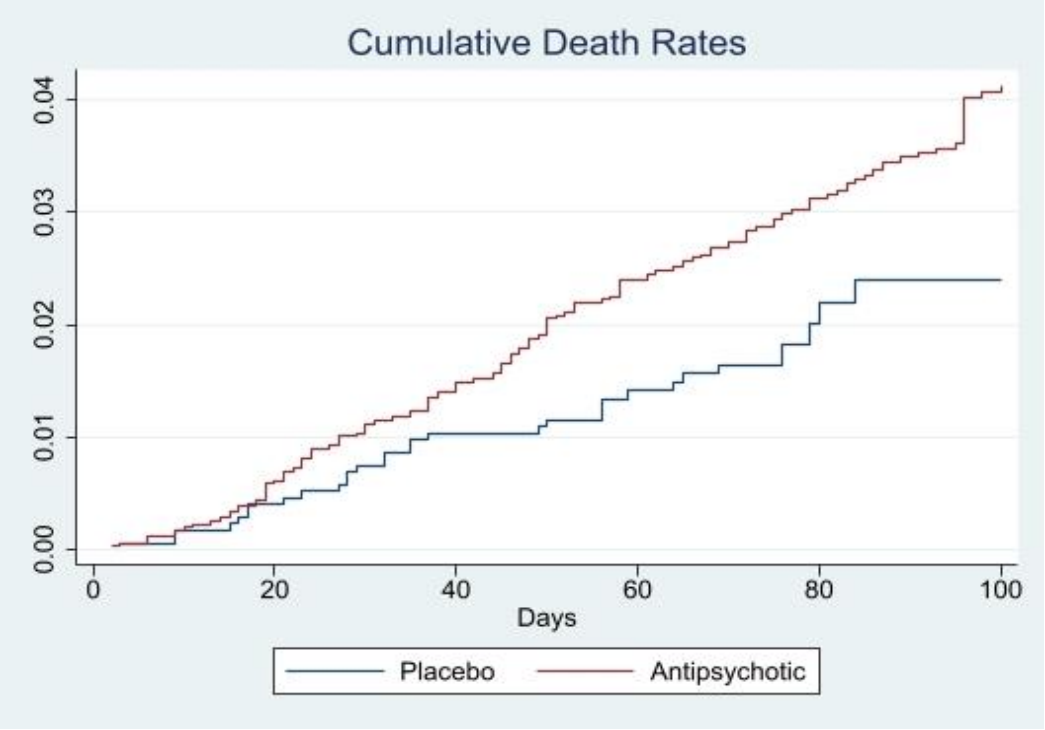
Results of FDA's 2005 Meta-Analysis

- Analysis revealed a 70% increased risk of death among subjects receiving antipsychotic treatment vs. placebo
- Over the course of a typical 10-week trial, the incidence of death was 4.5% in the antipsychotic arm vs. 2.6% in the placebo arm
- Although the causes of death varied, most deaths were cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature



Source: Reviewer's Analysis (Dr. Marc Stone)
Abbreviations: CI = confidence interval; IRR = incident rate ratio
Note: Deaths were counted if they occurred within 30 days of the intended period of observation

Interpretation of Antipsychotic Mortality Data from FDA's 2005 Meta-Analysis



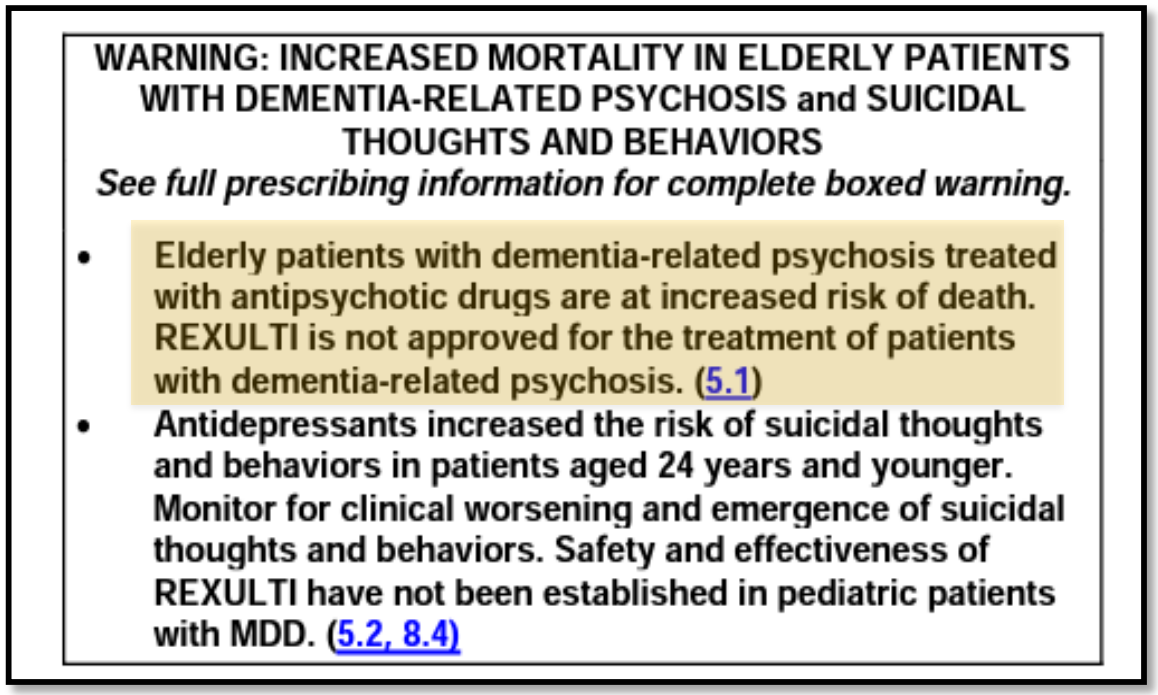
- Lack of a concentration of deaths closer to the time of drug initiation suggests that antipsychotics may not be a major direct cause of death.
- Reports of the timing of death relative to the preceding adverse event and last dose of study medication also support that the drug was not usually the direct cause of death but may be associated with worsening outcomes
- A steady rise in cumulative deaths at a higher rate relative to placebo suggests an indirect effect on death rates due to exogenous causes

Implications of FDA's 2005 Meta-Analysis

- Along with a Drug Safety Communication describing the mortality risk, the Agency issued a Boxed Warning in 2005 for all approved atypical antipsychotics

- In 2006, the Agency presented the meta-analysis at the New Clinical Drug Evaluation Unit (NCDEU) Annual Meeting; a Consensus Statement was also issued.

- Two observational studies in 2007 showed similar findings with typical antipsychotics. In 2008, the Agency recommended labeling all antipsychotics with the Boxed Warning



WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. REXULTI is not approved for the treatment of patients with dementia-related psychosis. (5.1)**
- **Antidepressants increased the risk of suicidal thoughts and behaviors in patients aged 24 years and younger. Monitor for clinical worsening and emergence of suicidal thoughts and behaviors. Safety and effectiveness of REXULTI have not been established in pediatric patients with MDD. (5.2, 8.4)**

Boxed Warning Considerations for Antipsychotics Approved in Elderly Patients: Pimavanserin

- Pimavanserin (NUPLAZID) was FDA-approved in 2016 for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis. Although pimavanserin is not approved for the treatment of patients with dementia-related psychosis, the Agency similarly applied the Boxed Warning to the pimavanserin due to imbalances in events between drug and placebo based on observed data from clinical trials.

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. NUPLAZID is not approved for the treatment of patients with dementia-related psychosis unrelated to the hallucinations and delusions associated with Parkinson's disease psychosis *[see Warnings and Precautions (5.1)]*.

Boxed Warning Considerations for Antipsychotics Approved in Elderly Patients: Brexpiprazole

- In May 2023, the Agency approved brexpiprazole (REXULTI) for the treatment of agitation associated with dementia of the Alzheimer's type.

- During the review, the Agency questioned whether the current Boxed Warning would also apply to dementia with agitation without psychosis or only to dementia with psychosis and agitation. To align with the Boxed Warning for other antipsychotics, the Agency ultimately decided not recommend any additional changes.

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS and SUICIDAL THOUGHTS AND BEHAVIORS

See full prescribing information for complete boxed warning.

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. REXULTI is not approved for the treatment of patients with dementia-related psychosis without agitation associated with dementia due to Alzheimer's disease. (5.1)**
- **Antidepressants increased the risk of suicidal thoughts and behaviors in patients aged 24 years and younger. Monitor for clinical worsening and emergence of suicidal thoughts and behaviors. Safety and effectiveness of REXULTI have not been established in pediatric patients with MDD. (5.2, 8.4)**

Confirmation of Agency's Findings in the Scientific Literature and Next Steps

- Two published meta-analyses examined the risk of mortality using the same studies included in the Agency's meta-analysis. The results were highly comparable and confirmed the Agency's estimate of an increased mortality risk between 60% to 70%.[1,2]
- It is unclear whether there are other demographic or clinical factors, including the type and severity of NPS, that contribute to the observed mortality risk
- Given that the previous meta-analysis was based on summary-level data, the Agency plans to collect subject-level data to further explore the mortality risk.

1. Schneider LS, et al., Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA. 2005 Oct 19;294(15):1934-43
2. Yeh TC, et al., Mortality Risk of Atypical Antipsychotics for Behavioral and Psychological Symptoms of Dementia: A Meta-Analysis, Meta-Regression, and Trial Sequential Analysis of Randomized Controlled Trials. J Clin Psychopharmacol. 2019 Sep/Oct;39(5):472-478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Session 1: Introduction to Antipsychotic Use in Dementia-related Behavioral Disorders

Please submit any clarifying questions using the Zoom Q&A function

Moderator:

- **Nancy Allen LaPointe**, Duke-Margolis Institute for Health Policy

Presenters:

- **Julia Biernot**, U.S. Food and Drug Administration
- **Shamir Kalaria**, U.S. Food and Drug Administration

Session 2: Review of Data Analysis and Literature Review Finding

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Meta-analysis of Antipsychotic Use and Mortality Risk in Elderly Patients with Dementia-related Psychosis and Other Behavioral Symptoms

Fengyu Zhao, PhD
CDER/OTS/OB/DBVII
December 10, 2024

Meta-analysis Objective

- Assess the mortality risk associated with antipsychotic drugs in randomized placebo-controlled clinical trials designed to evaluate the safety and effectiveness of antipsychotics on psychosis and other behavioral symptoms in elderly patients with dementia.

Meta-Analysis Trial Set

- 17 randomized, placebo-controlled trials with antipsychotics on psychosis and other behavioral symptoms associated with dementia.
- Treatment duration between 4 to 26 weeks

Drug	Trial ID	Treatment (N)	Placebo (N)	DB Duration (days)	Dose of Treatment	Patient-level Data Available
Aripiprazole	CN138004	366	121	70	2mg, 5mg, 10mg	N
	CN138005	131	125	70	2-15mg	N
	CN138006	105	102	70	2-5mg	N
Olanzapine/risperidone(AC)	F1D-MC-HGAO	120	118	56	1-8mg	Y
	F1D-MC-HGEU	160	46	42	5mg, 10mg, 15mg	Y
	F1D-MC-HGGU	400	94	70	2.5-10mg, 0.5-2mg AC	N
	F1D-MC-HGIC	78	90	182	2.5-5mg	N
	F1D-MC-HGIV	523	129	70	1mg, 2.5mg, 5mg, 7.5mg	N
Quetiapine/haloperidol(AC)	5077IL/0039	252	125	70	100-600mg, 2-12mg AC	N
	5077US/0046	241	92	70	100mg, 200mg	N
Risperidone/haloperidol(AC)	RIS-BEL-14	20	19	28	1-4mg	N
	RIS-USA-232	235	238	56	1-1.5mg	Y
	RIS-INT-24	230	114	84	0.5-2mg, 0.5-2mg AC	Y
	RIS-AUS-5	167	170	84	0.5-2mg	Y
	RIS-USA-63	462	163	84	0.5mg, 1mg, 2mg	Y
	RIS-INT-83	10	8	84	1-1.5mg	Y
Ziprasidone	128-105	11	12	42	2-6mg	N

AC: Active Control; DB: Double-blind

Statistical Approach

- Primary endpoint: All-cause mortality
- Comparison: Drug vs Placebo
  - Multiple doses of drug and active control drug are pooled within trial
- Analysis Population
  - Elderly patients with dementia-related psychosis or other behavior symptoms who were enrolled in the 17 randomized, placebo-controlled trials
- Handling of treatment discontinuation: On-treatment Analysis
  - Includes deaths occurring within four days of treatment discontinuation
  - Data after treatment discontinuation uncertain

Mortality Ascertainment

- Based on clinical review of case narratives of all deaths
- Relevant dates captured for analysis
  - First dose
  - Last dose
  - Death
- Consistent approach across all 17 trials

Exposure Time Calculation

- Patient-level data available
  - Drug exposure starts at dose start date
  - Follow-up censored at the earliest of dose end date + 4 days, date of death, or end of double-blind study period
- No patient-level data
  - Drug exposure days for each treatment arm extracted from study report

Analysis Methods

- Incidence rate (IR) is calculated as the number of deaths per 100 patient-years of drug exposure
- Incidence rate difference (IRD) and 95% confidence intervals (CIs) are estimated by a random-effect meta-analysis
- Incidence rate ratio (IRR) and 95% CIs are estimated by a negative binomial model to account for zero event trials, considering trial as random effect
- Study heterogeneity is assessed by I^2 (smaller value means less heterogeneity)

Aggregate Summary of Demographics

Characteristics	Treatment (N=3,611)	Placebo (N=1,766)
Age		
Mean	80.8	81.3
Gender, n(%)		
Male	1,094 (30.3)	500 (28.3)
Female	2,517 (69.7)	1,266 (71.7)
Race, n(%)		
White	3,033 (84.0)	1,481 (83.9)
Other*	326 (9.0)	160 (9.1)
Missing	252 (7.0)	125 (7.1)
Baseline MMSE		
Mean	11.0	11.1
Missing, n (%)	554 (15.3)	160 (9.1)

*Race is tabulated only by the category of "White" in study reports, details for other racial groups are not provided and included here as "Other".
Standard Deviation for Age and Baseline MMSE are not available.

Average Exposure Time per trial

Drug	Trial ID	DB Duration (days)	Treatment Average Exposure Time (days)	Placebo Average Exposure Time (days)
Aripiprazole	CN138004	70	55.9	53.7
	CN138005	70	58.6	53.5
	CN138006	70	64.4	63.4
Olanzapine/risperidone(AC)	F1D-MC-HGAO	56	44.1	46.4
	F1D-MC-HGEU	42	37.0	38.1
	F1D-MC-HGGU	70	55.3	61.4
	F1D-MC-HGIC	182	128.6	150.1
	F1D-MC-HGIV	70	62.4	69.9
Quetiapine/haloperidol(AC)	5077IL/0039	70	51.0	54.6
	5077US/0046	70	55.0	56.0
Risperidone/haloperidol(AC)	RIS-BEL-14	28	23.7	25.0
	RIS-USA-232	56	48.5	49.6
	RIS-INT-24	84	66.5	67.9
	RIS-AUS-5	84	73.3	70.0
	RIS-USA-63	84	68.3	70.6
	RIS-INT-83	84	29.2	32.0
Ziprasidone	128-105	42	36.5	30.4

AC: Active Control; DB: Double-Blinded

Average exposure time is calculated as total exposure time/number of patients

Meta-Analysis Results

	Treatment (N = 3,611)			Placebo (N = 1,766)			IRD*, per 100 PY (95% CI)	IRR** (95% CI)
	Events	PY	IR*, per 100 PY	Events	PY	IR*, per 100 PY		
On-Treatment	59	606.4	7.0	17	304.5	2.3	4.7 (1.6, 7.9)	1.76 (1.02, 3.04)

PY: person-year; IR: incidence rate; IRD: incidence rate difference; IRR: incidence rate ratio; CI: Confidence intervals.

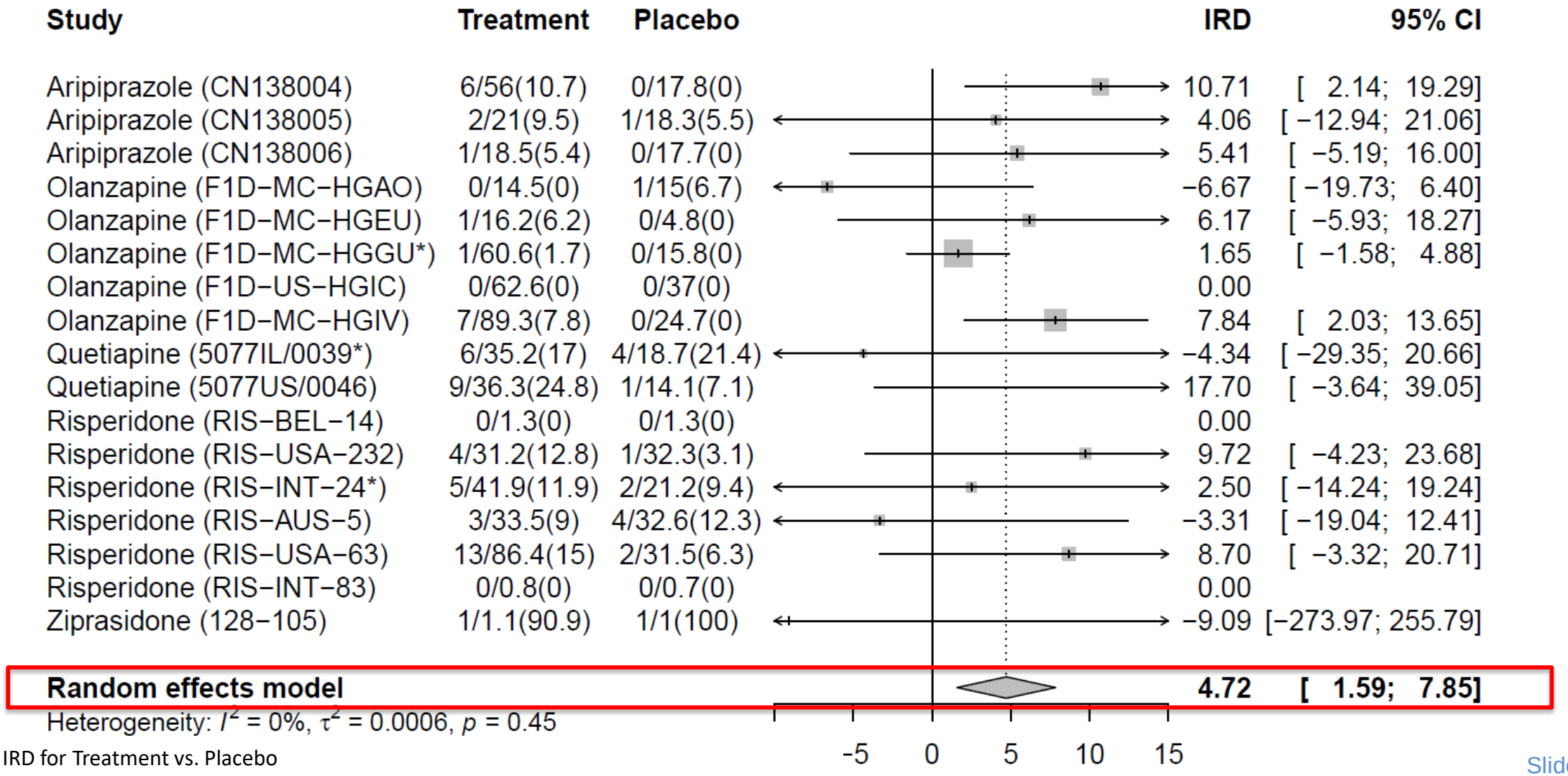
Haloperidol is active control in trial 5077iL/0039 and RIS-AUS-5,and it is included in the treatment group.

Risperidone is active control in trial F1D-MC-HGGU, and it is included in the treatment group.

*IRs and IRDs are estimated from a random-effect meta-analysis using inverse variance weights.

**IRRs are estimated from negative-binomial random-effect model.

Meta-Analysis: Incidence Rate Difference (per 100 PY)

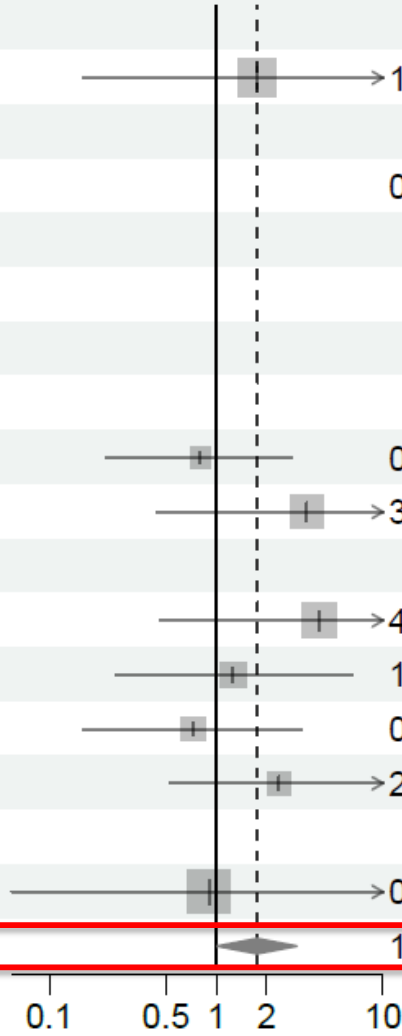


IRD for Treatment vs. Placebo

* Active control "Haloperidol“ and “Risperidone” are included in the treatment group.

Meta-Analysis: Incidence Rate Ratio

Study	Treatment	Placebo	IRR	95% CI
Aripiprazole (CN138004)	6/56(10.7)	0/17.8(0)		
Aripiprazole (CN138005)	2/21(9.5)	1/18.3(5.5)	1.74	[0.16; 19.22]
Aripiprazole (CN138006)	1/18.5(5.4)	0/17.7(0)		
Olanzapine (F1D−MC−HGAO)	0/14.5(0)	1/15(6.7)	0	[0; NA]
Olanzapine (F1D−MC−HGEU)	1/16.2(6.4)	0/4.8(0)		
Olanzapine (F1D−MC−HGGU*)	1/60.6(1.7)	0/15.8(0)		
Olanzapine (F1D−US−HGIC)	0/62.6(0)	0/37(0)		
Olanzapine (F1D−MC−HGIV)	7/89.3(7.8)	0/24.7(0)		
Quetiapine (5077IL/0039*)	6/35.2(17)	4/18.7(21.4)	0.8	[0.22; 2.82]
Quetiapine (5077US/0046)	9/36.3(24.8)	1/14.1(7.1)	3.5	[0.44; 27.59]
Risperidone (RIS−BEL−14)	0/1.3(0)	0/1.3(0)		
Risperidone (RIS−USA−232)	4/31.2(13.8)	1/32.3(3.1)	4.14	[0.46; 37.05]
Risperidone (RIS−INT−24*)	5/41.9(11.9)	2/21.2(9.4)	1.26	[0.25; 6.52]
Risperidone (RIS−AUS−5)	3/33.5(9.0)	4/32.6(12.3)	0.73	[0.16; 3.26]
Risperidone (RIS−USA−63)	13/86.4(15)	2/31.5(6.3)	2.37	[0.53; 10.5]
Risperidone (RIS−INT−83)	0/0.8(0)	0/0.7(0)		
Ziprasidone (128−105)	1/1.1(90.9)	1/1(100)	0.91	[0.06; 14.53]
Random effects model			1.76	[1.02; 3.04]



IRR for Treatment vs. Placebo

* Active control "Haloperidol“ and “Risperidone” are included in the treatment group.

Meta-Analysis Summary

- Across 17 trials, 76 deaths occurred within 4 days of treatment exposure
  - 59 out of 3,611 randomized antipsychotics participants
  - 17 out of 1,766 randomized placebo participants
- Meta-analysis suggestive of an increased risk of death when treating with an antipsychotic compared with placebo
  - Estimated IRD (per 100 PY) = 4.7 with 95% CI (1.6, 7.9)
  - Estimated IRR = 1.76 with 95% CI (1.02, 3.04)

Analysis Considerations

- Meta-analysis based on an on-treatment approach
  - Selected due to lack of information available after treatment discontinuation
  - With available data, no reliable approach to be consistently applied across all trials for on-study analysis
  - Important to acknowledge that on-treatment analysis comparisons break integrity of randomization and may be subject to bias due to differences between arms in treatment discontinuation rates and types of participants who stop treatment
  - Limited available data precludes further assessment
- Data unavailable on subgroups to identify any potential populations at increased risk

Future Steps

- FDA sent an information request to individual Sponsors requesting patient-level data related to cases of death for each of the 17 trials
- Intent of patient-level meta-analysis
  - Assess mortality effect through end of double-blind treatment period (i.e. on-study analysis)
  - Assess if any subgroup of patients are more at risk

Mortality Risk in Patients With Dementia Following Antipsychotic Use: Findings From Observational Studies

Youngsin (Jessica) Jung, MD, PhD
Division of Neurology I | Office of Neuroscience | Office of New Drugs
Center for Drug Evaluation and Research | FDA

Duke-Margolis Center for Health Policy Meeting: Mortality and Antipsychotic Use in Dementia-Related Behavioral Disorders

Objectives

Based on observational studies in patients with dementia,

- To summarize findings related to:
  - Mortality risk, including long-term risk, following antipsychotic exposure
  - Potential factors contributing to mortality risk following antipsychotic exposure

Limitations of Dataset From Prior RCTs

- Studies with a randomized parallel-arm design and a placebo control most appropriate to understand and address questions pertaining to mortality risk in patients with dementia exposed to antipsychotics.
- However, available dataset from prior RCTs has a few limitations.
  - Generally small studies
  - Highly selected samples
  - Settings are not always generalizable (several studies in nursing home patients)
  - Varying degree of dementia severity
  - Short duration of observation (< 12 weeks)
  - Low event rates, requiring combined data/meta-analysis to estimate the mortality risk

Review of Observational Studies

- Literature search through PubMed/MEDLINE
- Search term: “death,” mortality,” “antipsychotics,” “dementia”
- Published between 2008 and 2024
- 15 articles interested in the relationship between exposure to conventional and/or atypical antipsychotics as a class and overall all-cause mortality risk in patients with dementia selected as the main articles for review

1. Is antipsychotic use by patients with dementia associated with increased mortality?

Characteristics of Observational Studies Examining Overall Mortality Risk Following Antipsychotic Use in Dementia

	Higher mortality risk (9 studies published 2011-2022)	**No statistical difference in mortality risk** (5 studies published 2014-2022)	**Lower mortality risk** (1 study published in 2018)
Type of study	Mostly cohort studies		
Data source	National registry, claims data, prescription data, health records, research database		
Sample	Many with population-based cohorts with sample of ~4,000 to 60,000 elderly patients with dementia	Regional >population-based cohorts with sample of ~500 to 9,000 elderly patients with dementia	
Type of antipsychotics	Conventional (at least haloperidol) and/or atypical antipsychotics		
Follow-up duration	180 days - 10 years		

Study	Data source	Population	Sample size	Overall mortality risk
Jennum 2015	Danish National Patient Registry	All cause dementia and matched controls	26,821 patients (1,091 exposed) 44,286 controls	First-generation antipsychotics: HR **1.18** (SD 0.074) Second-generation antipsychotics: HR **1.38** (SD 0.042)
Koponen 2017	Finnish national register-based MEDALZ study	Alzheimer's disease	57,755 patients (17,731 newly exposed)	Overall: aHR **1.61**; 95% CI 1.53–1.70
Langballe 2014	Norwegian Prescription Database	Dementia outpatients	26,940 patients (8,214 exposed)	aHR $_{[30days]}$ = **2.1**; 95% CI 1.6–2.9 aHR $_{[730–2,400days]}$ = **1.7;** 95% CI: 1.6–1.9
Maxwell 2018	Ontario health administrative databases	Dementia or elderly with significant cognitive impairment	9910 patients (4955 exposed)	aHR ($_{1mo}$) = **2.08**; 95% CI 1.79–2.43 aHR ($_{3mo}$) = **1.52**; 95% CI 1.31–1.75 aHR ($_{6mo}$) = **1.24**; 95% CI 1.02–1.51
Mueller 2021	SLaM Clinical Record Interactive Search	Dementia	10,106 patients (1,115 exposed)	aHR **1.14**; 95% CI 1.05–1.24
Musicco 2011	Italian National Health System	Dementia	4,369 patients (1,093 exposed)	First-generation antipsychotics: aHR **3.7**; 95% CI 2.6–5.1 Second-generation antipsychotics: aHR **2.5**; 95% CI 2.0–3.0
Nielsen 2016	Danish National Registries	Alzheimer's disease	45,894 patients (18,094 exposed)	aHR **2.28**; 95% CI 2.20–2.35
Nørgaard 2022	Danish National Registries	Dementia	32,974 patients (8,244 exposed)	aHR **1.35**; 95% CI 1.27–1.43
Schwertner 2019	Swedish Dementia Registry	Dementia	58,412 patients (2,526 exposed)	aHR **1.4**; 95% CI 1.3–1.5
Gardette 2012	French memory centers prospective cohort	Alzheimer's disease	534 patients (102 newly exposed)	aHR **1.12**; 95% CI 0.59-2.12
Chu 2018	Taiwan National Health Insurance Research Database	Alzheimer's disease	2,169 patients (735 exposed, 735 matched unexposed)	aHR **0.66**; 95% CI 0.58–0.75
Dennis 2017	Welsh Secure Anonymised Information Linkage databank	Dementia	9,674 patients (3,735 exposed)	aHR **1.06**; 95% CI 0.99–1.13
Lopez 2013	Alzheimer's Disease Research Center of Pittsburgh	Alzheimer's disease	957 patients (241 exposed)	First-generation antipsychotics: aHR **0.83**; 95% CI 0.63–1.09 Second-generation antipsychotics: aHR **1.02**; 95% CI 0.69–1.50
Hamedani 2022	U.S. National Health Aging Trends Study, Health Retirement Study	Dementia	1,703 patients (284 exposed)	aHR **0.94**; 95% CI 0.68–1.28
Sultana 2014	SLaM Clinical Record Interactive Search	Vascular dementia	1,531 patients (337 exposed)	aHR **1.05**; 95% CI 0.87–1.26

HR: Hazard ratio; aHR: Adjusted HR (various covariates, mostly socio-demographics); CI confidence interval; SD standard deviation; SLaM South London and Maudsley NHS Foundation Trust, UK

Mortality Risk Following Antipsychotic Exposure in Dementia: Summary

- Most studies found higher risk in overall mortality in patients with dementia exposed to antipsychotics.
  - In studies using Cox regression models, the hazard ratio (HR) ranged from 1.18 (Jennum et al., 2015) to 3.7 (Musicco et al., 2011).
- Of the studies that demonstrated no statistical difference in mortality risk,
  - Three studies estimated HR to be 0.94 – 1.06 (95% CIs include 1).
  - In Gardette et al., 2012 and Lopez et al, 2013, HR became no longer significant (i.e., 95% CI including 1) after adjusting for dementia severity along with other patient characteristics and neuropsychiatric symptoms, respectively.
- One study conducted in Taiwan (Chu et al., 2018) found lower mortality risk in patients with AD exposed to antipsychotics.

Limitation of Cross-Study Comparisons in Observational Studies

- Most observational studies are conducted in a single country, and the findings may reflect unique aspects of clinical care.
- Clinical and demographic characteristics of the samples are different across studies.
- The exposed vs non-exposed groups differ in size.
- The denominator (person years) varies across studies with different duration of exposure.
- The covariates used to adjust Cox's proportional hazards models vary across studies.

2. Does the mortality risk change over time in patients with dementia exposed to antipsychotics?

Long-Term Mortality Risk Following Antipsychotic Use in Dementia

- Most studies examined short vs. long-term risk for 180 days, but some up to 6 years
- Mortality risk following antipsychotic use appears to be higher short-term, especially in the first 30 days
- No increased mortality risk after 30 days (Rossom et al., 2010) or decreased mortality after 30 days compared to the first 30 days (Maxwell et al., 2018), although some suggest persistent risk long-term (Langballe et al., 2014)
- Greater risk of mortality short term may suggest unmeasured medical confounders associated with the need for antipsychotic use
- Lower risk with longer durations of treatment may reflect survivor bias

3. Is antipsychotic use an independent factor contributing to increased mortality in patients with dementia? Are there other risk factors?

Potential Risk Factors for Mortality Following Antipsychotic Use in Dementia

- **Dementia severity**
  - Limited studies examining the effects of dementia severity on mortality risk following antipsychotic use to draw meaningful conclusions
  - Not all studies adjusted for dementia severity when examining the mortality risk associated with antipsychotic use
  - Studies adjusted for "dementia severity" used indirect measures (e.g., age at dementia diagnosis, duration of dementia)
  - In a study by Gardette et al. (2012), no increased mortality associated with antipsychotic use when adjusted for dementia severity measured by MMSE and ADL scores as well as other patient characteristics in community-dwelling patients with mild to moderate AD
    - Dementia severity may play a role, but the change in risk estimate cannot be solely attributed to dementia severity

Potential Risk Factors for Mortality Following Antipsychotic Use in Dementia (Cont'd)

- **Type of dementia**
  - In a study by Mueller, et al. (2021),
    - Increased all-cause mortality in patients with Alzheimer's and vascular dementia on antipsychotics
    - Increased all-cause mortality risk following antipsychotic use strengthened in vascular dementia but not in Alzheimer's dementia when testing for interactions
  - Overall, insufficient data on whether type of dementia differentially affect risks associated with antipsychotic use
    - Most studies do not specify dementia type
    - When specified, difficult to determine diagnostic accuracy given the data sources typically used for observational studies (e.g., claims data, electronic health records, etc.)

Potential Risk Factors for Mortality Following Antipsychotic Use in Dementia (Cont'd)

- **Neuropsychiatric symptoms**
  - Limited studies investigated the contributing effects of neuropsychiatric symptoms on mortality following antipsychotic use to draw meaningful conclusions
  - In one study, no increased mortality when adjusted for neuropsychiatric symptoms for which treatment was prescribed in patients with probable AD (Lopez et al., 2013)
  - In general, severity and/or type of neuropsychiatric symptoms may influence mortality risks in patients with dementia
    - Increased risk of mortality associated with moderate or severe behavioral and psychological symptoms of dementia
    - Psychosis, agitation, aggression, and affective symptoms associated with earlier death in patients with AD
  - However, no clear interactions between neuropsychiatric symptoms and antipsychotics in relation to mortality risk in patients with dementia (Hamedani et al, 2022, Mueller et al, 2021)

Mortality Risk: Interaction Between Antipsychotics and Neuropsychiatric Symptoms

	Overall Mortality HR (95% CI)	Stroke-specific mortality HR (95% CI)
All (n=10,106)	1.14 (1.05–1.24)	1.28 (1.01–1.63)
Ag+ P+ (n=481)	1.00 (0.78–1.27)	0.73 (0.33–1.61)
Ag- P+ (n=579)	1.26 (1.00–1.60)	1.61 (0.82–3.13)
Ag+ P- (n=1,325)	1.16 (0.99–1.36)	1.53 (0.97–2.43)
Ag- P- (n=7,721)	1.13 (1.00–1.28)	1.20 (0.84–1.71)

Adjusted for age, gender, marital status, ethnicity, index of deprivation, MMSE score, dementia subtype, HoNOS scores, and hospitalization in the year prior to dementia diagnosis

Ag: agitation; P: psychosis; +: presence; -: absence

- A sample of patients with Alzheimer's, vascular, mixed, & other/unspecified dementia from UK NHS with a highly homogeneous care setting (Mueller et al., 2021)
- Increased all-cause and stroke-specific mortality risk related to antipsychotic use (especially second-generation antipsychotics) in the whole sample
- No increased mortality risk based on neuropsychiatric symptoms
- No significant interaction between neuropsychiatric symptom strata and antipsychotic-related mortality

Limitations of Literature Review Using Observational Studies

- **Lack of randomization → potential for biases**
- Publication bias
- Unmeasured confounders
- Cross-comparisons of studies and their findings challenging due to variations in study design and analysis

Summary

- Literature generally reported higher risk of mortality in patients with dementia who are exposed to antipsychotics.
- Mortality risk appears to be greater short-term, although survivor bias may be present.
- Other factors, such as dementia severity/type and neuropsychiatric symptoms, may refine the relationship between antipsychotic exposure and mortality risk.
- Overall, it is challenging to draw meaningful conclusions in the presence of conflicting findings and limitations of observational studies included in this review.
- Internal validity of the observational studies needs further assessment.

Session 2: Review of Data Analysis and Literature Review Finding

Please submit any clarifying questions using the Zoom Q&A function

Moderator:

- **Christina Silcox,** Duke-Margolis Institute for Health Policy

Presentation:

- **Jessica Jung**, U.S. Food and Drug Administration
- **Fengyu Zhao**, U.S. Food and Drug Administration

Break

1:45 – 2:00 pm ET

Session 3: Stakeholder Perspectives on Considerations Regarding the Use of Boxed Warnings for Antipsychotics

Antipsychotic Use in Neurodegenerative Diseases: AD, PD and DLB

Daniel Weintraub, M.D.

Professor of Psychiatry and Neurology, University of Pennsylvania School of Medicine; Parkinson's Disease Research, Education and Clinical Center, Philadelphia Veterans Affairs Medical Center

December 2024

Alzheimer’s Disease (AD)

Antipsychotics Efficacious for AD Psychosis / Agitation: Risperidone Withdrawal Study

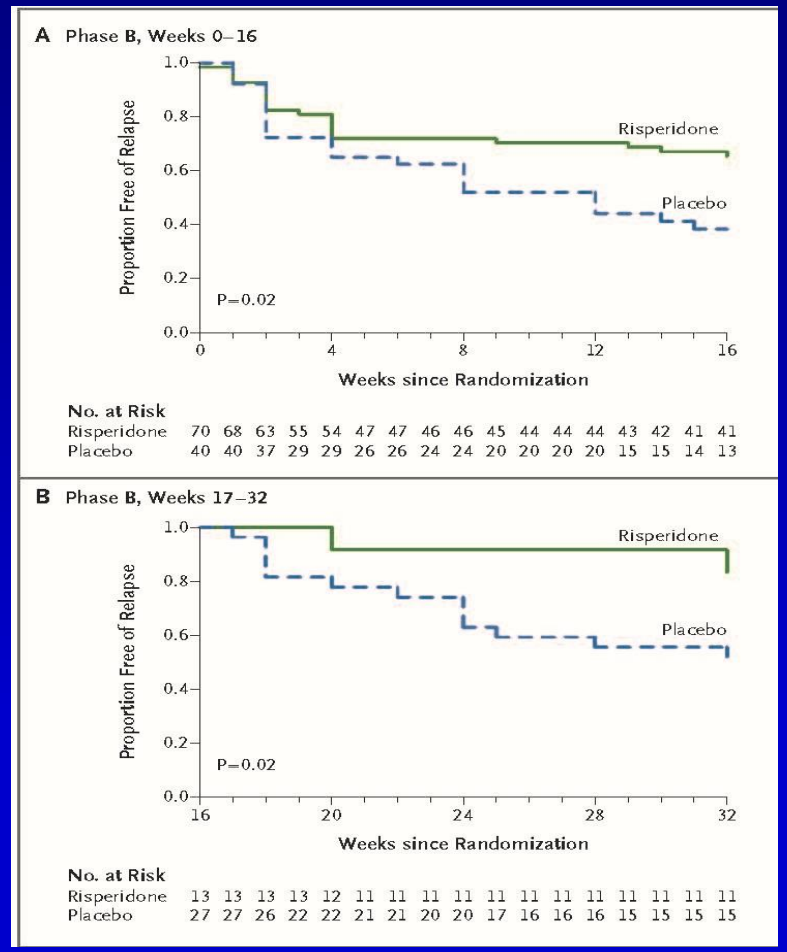
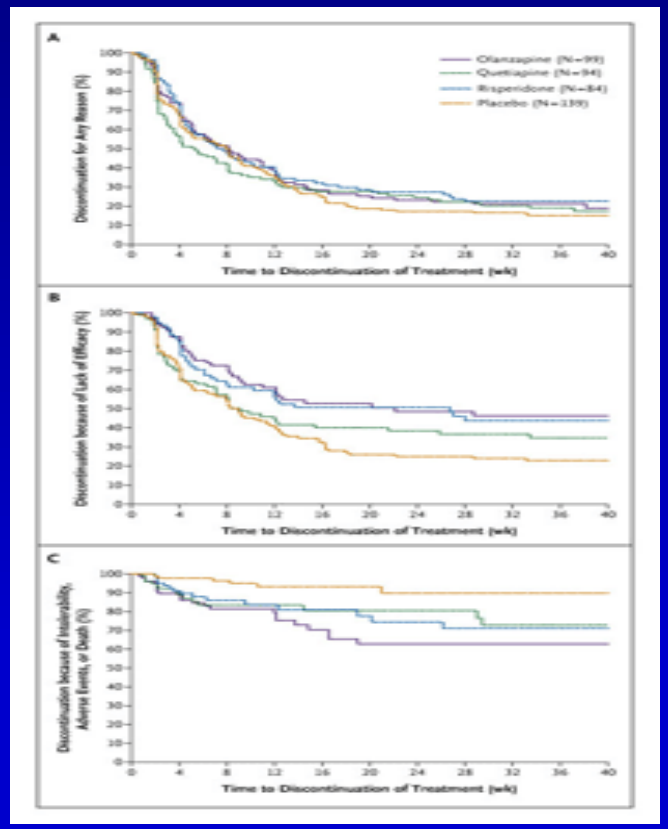


Figure 2. Time from Randomization to Relapse among Patients Receiving Risperidone and Those Receiving Placebo.

Panel A shows Kaplan–Meier curves for the risk of relapse during the first 16-week period of phase B (weeks 16 to 32 of the study) among the 70 patients who were randomly assigned to continue to receive risperidone (groups 1 and 2) and the 40 patients who were assigned to be withdrawn from risperidone at the end of phase A and switched to placebo (group 3). Panel B shows Kaplan–Meier curves for the risk of relapse during the second 16-week period of phase B (weeks 33 to 48 of the study) among the 13 patients who continued to receive risperidone (group 1) and the 27 patients who were switched to placebo at the end of the first 16-week period (group 2).

Devanand et al. *NEJM* 2012;367:1497-1507.

CATIE-AD Study:
Antipsychotics (APs) *Efficacious* but Not *Effective*



The NEW ENGLAND JOURNAL of MEDICINE

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Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease

Lon S. Schneider, M.D., Pierre N. Tariot, M.D., Karen S. Dagerman, M.S., Sonia M. Davis, Dr.P.H., John K. Hsiao, M.D., M. Saleem Ismail, M.D., Barry D. Lebowitz, Ph.D., Constantine G. Lyketsos, M.D., M.H.S., J. Michael Ryan, M.D., T. Scott Stroup, M.D., David L. Sultzer, M.D., Daniel Weintraub, M.D., and Jeffrey A. Lieberman, M.D., for the CATIE-AD Study Group*

ABSTRACT

BACKGROUND

Second-generation (atypical) antipsychotic drugs are widely used to treat psychosis, aggression, and agitation in patients with Alzheimer's disease, but their benefits are uncertain and concerns about safety have emerged. We assessed the effectiveness of atypical antipsychotic drugs in outpatients with Alzheimer's disease.

METHODS

In this 42-site, double-blind, placebo-controlled trial, 421 outpatients with Alzheimer's disease and psychosis, aggression, or agitation were randomly assigned to receive olanzapine (mean dose, 5.5 mg per day), quetiapine (mean dose, 56.5 mg per day), risperidone (mean dose, 1.0 mg per day), or placebo. Doses were adjusted as needed, and patients were followed for up to 36 weeks. The main outcomes were the time from initial treatment to the discontinuation of treatment for any reason and the number of patients with at least minimal improvement on the Clinical Global Impression of Change (CGIC) scale at 12 weeks.

RESULTS

There were no significant differences among treatments with regard to the time to the discontinuation of treatment for any reason: olanzapine (median, 8.1 weeks), quetiapine (median, 5.3 weeks), risperidone (median, 7.4 weeks), and placebo (median, 8.0 weeks) (P=0.52). The median time to the discontinuation of treatment due to a lack of efficacy favored olanzapine (22.1 weeks) and risperidone (26.7 weeks) as compared with quetiapine (9.1 weeks) and placebo (9.0 weeks) (P=0.002). The time to the discontinuation of treatment due to adverse events or intolerability favored placebo. Overall, 24% of patients who received olanzapine, 16% of patients who received quetiapine, 18% of patients who received risperidone, and 5% of patients who received placebo discontinued their assigned treatment owing to intolerability (P=0.009). No significant differences were noted among the groups with regard to improvement on the CGIC scale. Improvement was observed in 32% of patients assigned to olanzapine, 26% of patients assigned to quetiapine, 29% of patients assigned to risperidone, and 21% of patients assigned to placebo (P=0.22).

CONCLUSIONS

Adverse effects offset advantages in the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer's disease. (ClinicalTrials.gov number, NCT00015548.)

From the Keck School of Medicine, University of Southern California, Los Angeles (L.S.S., K.S.D.); the Banner Alzheimer's Institute, Phoenix, AZ (P.N.T.); Quintiles, Research Triangle Park, NC (S.M.D.); the National Institute of Mental Health, National Institutes of Health, Bethesda, MD (J.K.H.); the University of Rochester Medical Center, Rochester, NY (M.S.I., J.M.R.); the School of Medicine, University of California, San Diego, La Jolla (B.D.L.); the Department of Psychiatry, Johns Hopkins Bayview, Johns Hopkins University, Baltimore (C.G.L.); the School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill (T.S.S.); Veterans Affairs Greater Los Angeles Healthcare System, University of California, Los Angeles, Los Angeles (D.L.S.); the School of Medicine, University of Pennsylvania, Philadelphia (D.W.); and the College of Physicians and Surgeons, New York (J.A.L.). Address reprint requests to Dr. Schneider at the Keck School of Medicine, University of Southern California, 1510 San Pablo St., HCC 600, Los Angeles, CA 90033, or at lschneid@usc.edu.

*Members of the Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease (CATIE-AD) Study Group are listed in the Appendix.

N Engl J Med 2006;355:1525-38.

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"Adverse events offset advantages in the efficacy of atypical AP drugs for the treatment of psychosis, aggression, or agitation in patients with AD."

Treatment Discontinuation by *Efficacy*

- Time to treatment discontinuation for *lack of efficacy* longer in risperidone (26.7 weeks) and olanzapine (22.1 weeks) than in placebo groups (9.0 weeks)
  - Quetiapine treatment (9.1 weeks) did not differ from placebo
- Hazard ratio (HR) for treatment discontinuation for lack of efficacy was 0.51 ($p<0.001$) for olanzapine and 0.61 ($p=0.01$) for risperidone compared with placebo

Treatment Discontinuation by Intolerability or Adverse Events (AEs)

- Time to treatment discontinuation for study drug intolerance, AEs, or death favored placebo
  - 24% (olanzapine), 18% (risperidone), 16% (quetiapine) and 5% (placebo)
- Higher rates of parkinsonism or EPS in olanzapine and risperidone (12% each) than quetiapine (2%) or placebo (1%) groups
- Sedation more common with all 3 drugs (15-24%) than placebo (5%)
- Confusion or mental status changes more common with olanzapine (18%) and risperidone (11%) than placebo (5%)
- Also need to worry about Type 2 diabetes, orthostatic hypotension, dry mouth, dizziness, constipation

Do APs Have Adverse Impact on Cognition?

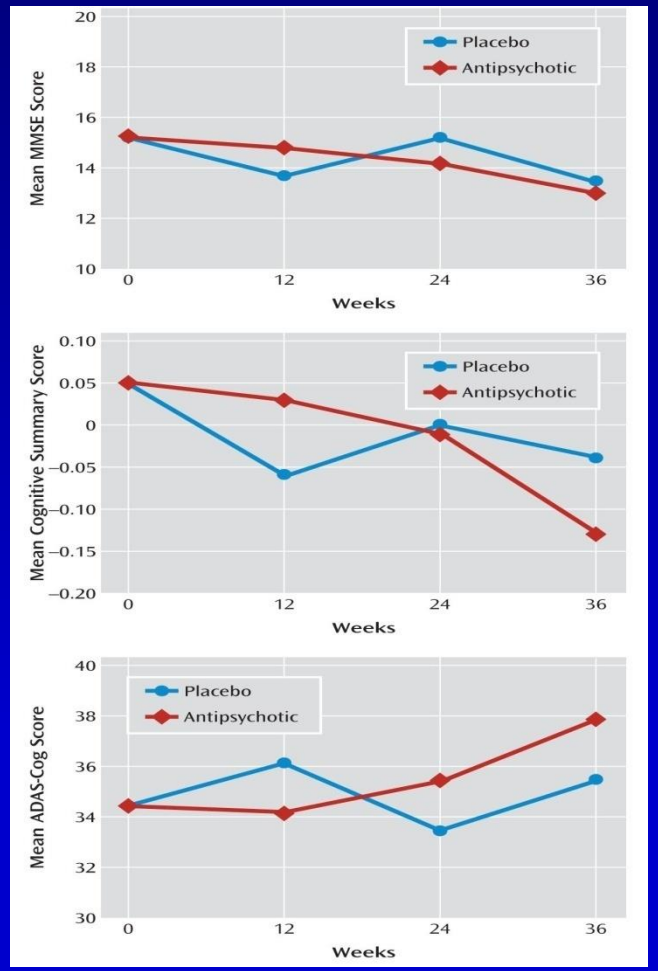


TABLE 2. Weekly Rates of Change in Cognitive Function in Patients With Alzheimer's Disease and Psychosis or Agitated/Aggressive Behavior in a Randomized Placebo-Controlled Study of Atypical Antipsychotics and by Treatment Group

								Mean Difference From Placebo[d]					
		Weekly Rate of Change in Total Sample			Weekly Rate of Change in Placebo Group			Olanzapine Compared With Placebo		Quetiapine Compared With Placebo		Risperidone Compared With Placebo	
Measure	Favorable Direction[a]	Change[b]	p[c]	df	Change[b]	p[c]	df	Change[e]	p[f]	Change[e]	p[f]	Change[e]	p[f]
Mini-Mental State Examination score	↑	−0.067	<0.001	343	−0.007	0.81	104	−0.080	0.05	−0.045	0.26	−0.055	0.19
Brief Psychiatric Rating Scale, cognitive factor	↓	0.010	0.003	356	−0.010	0.47	118	0.014	0.46	0.036	0.05	0.008	0.68
Alzheimer's Disease Assessment Scale													
Cognitive subscale score	↓	0.123	<0.001	308	0.050	0.46	82	0.073	0.41	0.073	0.40	0.141	0.13
Concentration/distractibility subscale	↓	0.006	0.01	317	0.001	0.92	89	0.014	0.32	0.006	0.67	0.008	0.60
Number cancellation subscale	↑	−0.054	<0.001	281	−0.002	0.97	70	−0.061	0.30	−0.033	0.57	−0.114	0.07
Executive function (maze) subscale	↓	0.174	0.21	268	0.62	0.39	69	−0.785	0.40	−0.192	0.84	−0.100	0.92
Tests of category instances	↑	−0.041	<0.001	290	−0.024	0.34	73	−0.003	0.92	−0.019	0.55	−0.052	0.14
Finger tapping, preferred hand	↑	−0.057	0.001	262	0.083	0.41	71	−0.174	0.18	−0.100	0.44	−0.166	0.17
Finger tapping, nonpreferred hand	↑	−0.047	0.04	260	0.074	0.46	70	−0.136	0.30	−0.112	0.38	−0.270	0.06
Trail Making Test, Part A (time in seconds)	↓	0.866	<0.001	234	−0.513	0.50	52	1.60	0.12	1.66	0.10	1.51	0.15
Working memory deficit	↓	−0.003	0.51	58	−0.020	0.42	8	0.007	0.82	0.039	0.23	0.027	0.47
Cognitive summary[g]	↑	−0.011	<0.001	277	−0.001	0.89	71	−0.013	0.04	−0.011	0.08	−0.018	0.001

[a] Direction in which a change in score indicates improved function.
[b] Mixed-effects regression model β in time in weeks (i.e., the weekly change in cognitive variables), adjusted for age, gender, education, and pooled study site.
[c] Adjusted for age, gender, education, and pooled study site.
[d] Mean difference from placebo in change per week among patients who had been on the same medication or placebo for at least 2 weeks at time of assessment. The numbers of patients on the same treatment for at least 2 weeks at the 12-week, 24-week, and 36-week assessments, respectively, were as follows: placebo: 48, 27, 25; olanzapine: 58, 41, 42; quetiapine: 64, 55, 44; risperidone: 60, 51, 35.
[e] Mixed-effects regression model β in time in weeks, compared with placebo (i.e., by atypical antipsychotic, the weekly change in cognitive variables in excess of that observed in placebo patients), adjusted for age, gender, education, and pooled study site.
[f] Adjusted for age, gender, education, and pooled study site.
[g] The cognitive summary was the normalized average of the sign-adjusted, normalized, baseline z scores for each of the 11 components of the Alzheimer's Disease Assessment Scale cognitive subscale, as well as the concentration/distractibility, number cancellation, and executive function (mazes) subscales; tests of category instances; the mean of the scores for the preferred and the nonpreferred hand on the finger tapping test; the Trail Making Test, Part A; and the working memory deficit.

Vigen et al. *Am J Psychiatry* 2011;168:831-839.

Increased Mortality Risk in AD: Dementia AP Withdrawal Trial (DART-AD)

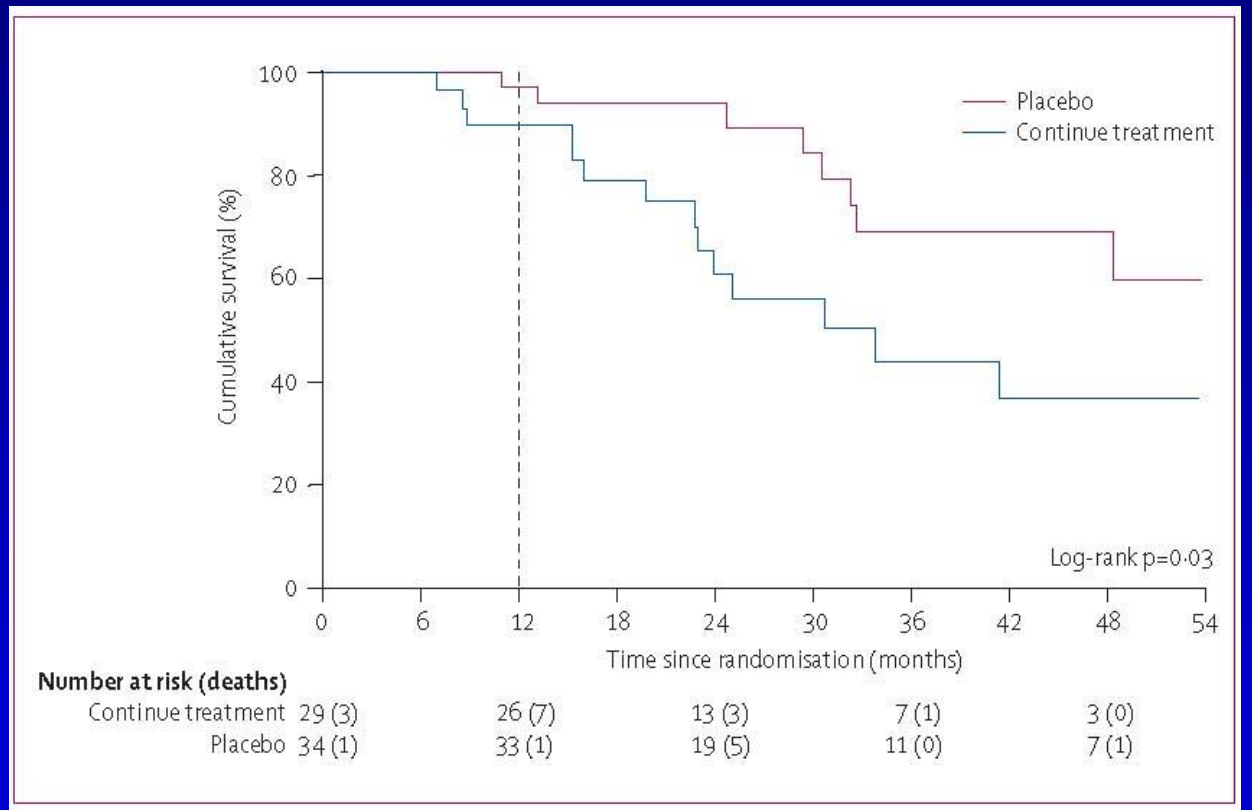


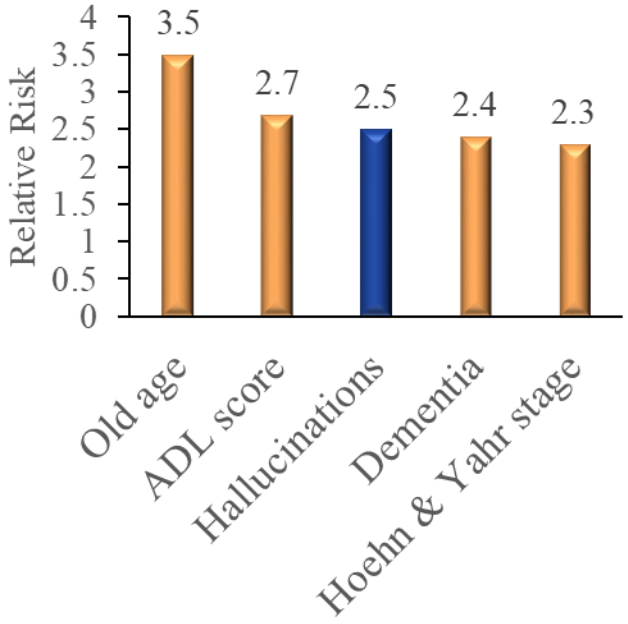
Figure 3: Kaplan–Meier survival estimates of participants who received at least one dose of treatment and continued allocated treatment for 12 months
The broken vertical line indicates the end of the 12-month randomised trial.

Ballard et al. *Lancet Neurology* 2009;8:151-157.

Parkinson’s Disease (PD) & Dementia with Lewy Bodies (DLB)

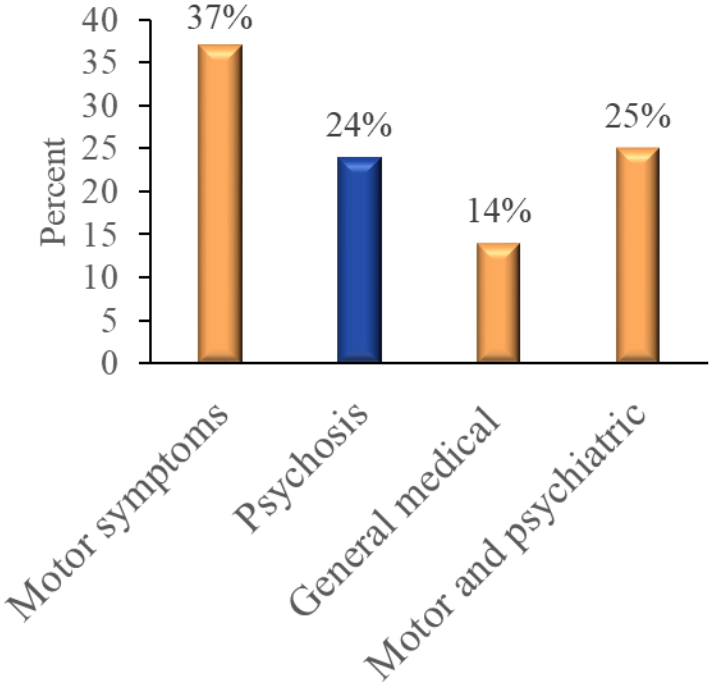
PD Psychosis Often a Problem: Long-Term Care and Hospitalizations

Long-Term Care



Baseline psychosis (UPDRS thought score >1) also with relative risk of 2.0 on Cox proportional hazards linear regression analysis

Hospitalizations



Psychosis was the most significant cause of repeated and prolonged admissions

Aarsland et al. *J Am Geriatr Soc*. 2000;48:938-942.
Klein et al. *J Neural Transm*. 2009;116:1509-1512.

PD Psychosis Predicts an Even Worse Outcome: Mortality

	HR (95% CI)	*P*
Male sex	1.63 (1.21-2.20)	0.001
Age at onset, 10-years increase	1.40 (1.03-1.88)	0.029
Age, 10-years increase	1.51 (1.01-2.24)	0.043
UPDRS motor score, 10-points increase	1.18 (1.08-1.29)	<0.001
Levodopa equivalent dose (LED), 100-mg increase	1.00 (0.95-1.06)	0.907
Psychosis	**1.45 (1.02-2.07)**	**0.039**
Dementia	1.89 (1.29-2.78)	0.001
REM sleep behavior disorder (RBD)	1.33 (0.92-1.93)	0.130
Antipsychotic drugs[a]	1.05 (0.70-1.58)	0.807

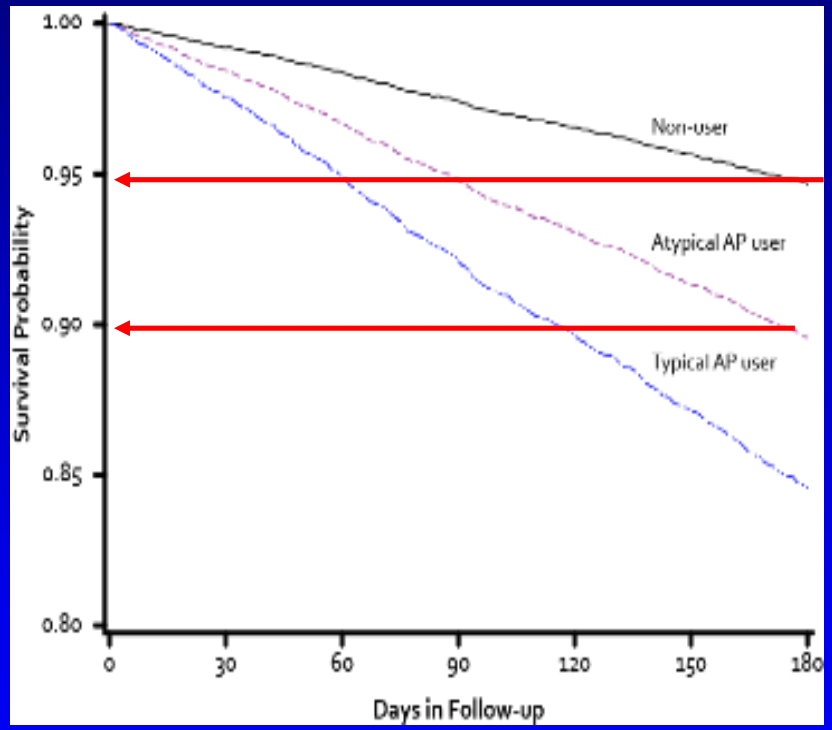
230 patients with PD applying multivariate Cox proportional hazards model with time-dependent covariates

[a]Antipsychotics used by 47 out of 230 patients (20%), accounting for 91 out of 595 observations (clozapine: n=28, olanzapine: n=29, quetiapine: n=14, risperidone: n=5; melperone, perphenazine, levopromazine, prochlorperazine: each n=3; haloperidol: n=2; chlorprothixene: n=1).

Forsaa et al. *Neurology*. 2010;75:1270-1276.

Evidence for Elevated Mortality Rates With Atypical AP Use in PD Too

Group	Intention-To-Treat Analysis		Exposure Only Analysis	
	Hazard Ratio (95% CI)	*P*-value	Hazard Ratio (95% CI)	*P*-value
No AP Use	1.0	-	1.0	-
AP User	2.35 (2.08-2.66)	<0.001	2.15 (1.82-2.55)	<0.001
No AP Use	1.0	-	1.0	-
Atypical AP	2.26 (1.98-2.57)	<0.001	2.09 (1.75-2.49)	<0.001
Typical AP	3.65 (2.47-5.39)	<0.001	3.11 (1.72-5.60)	<0.001

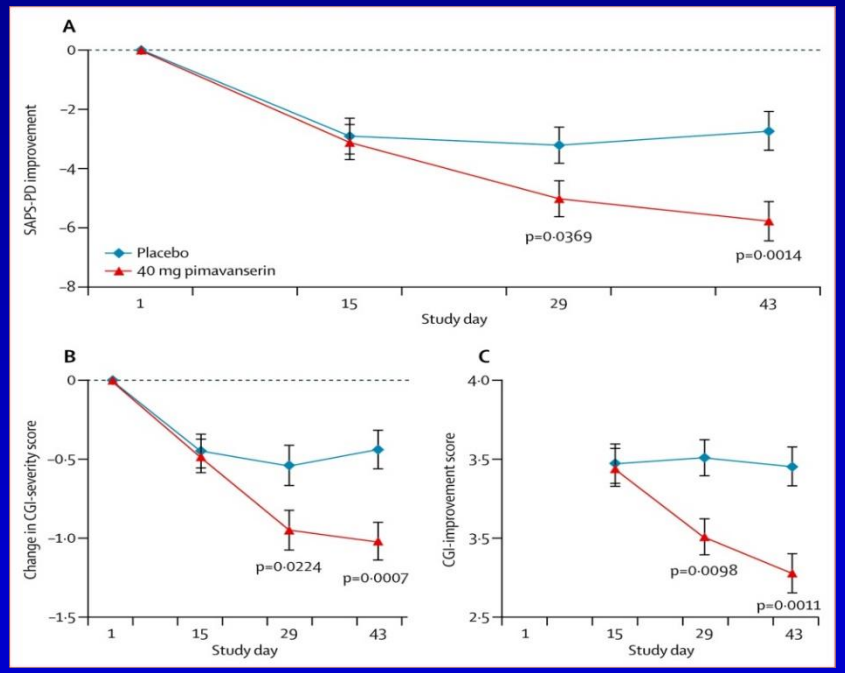


CI=Confidence Interval; AP=Antipsychotic

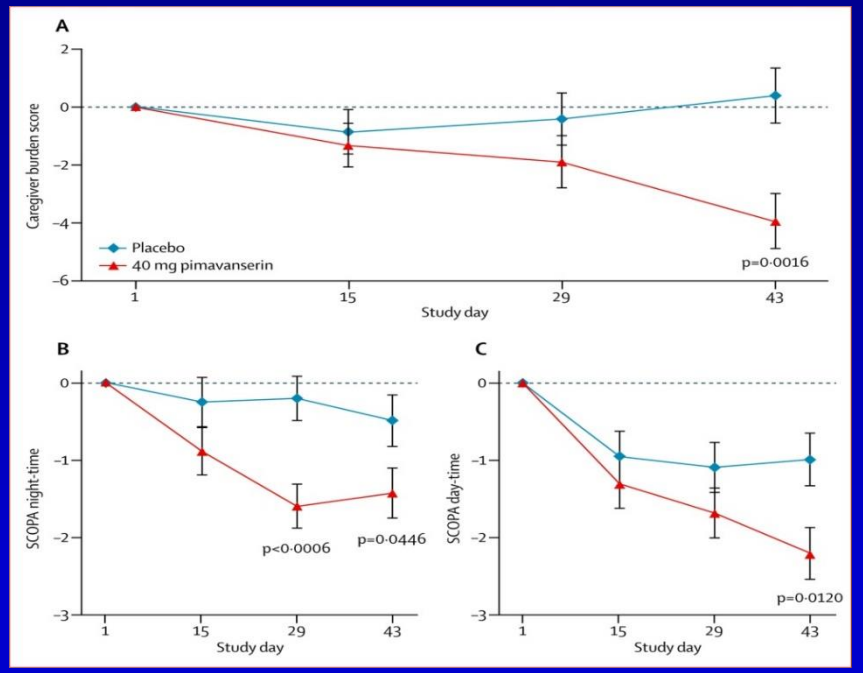
Weintraub et al. *JAMA Neurol* 2016;73(5):535-541.

Pimavanserin Efficacious for PD Psychosis

Selective 5HT-2A Inverse Agonist/Antagonist



Psychosis



Caregiver burden and sleep

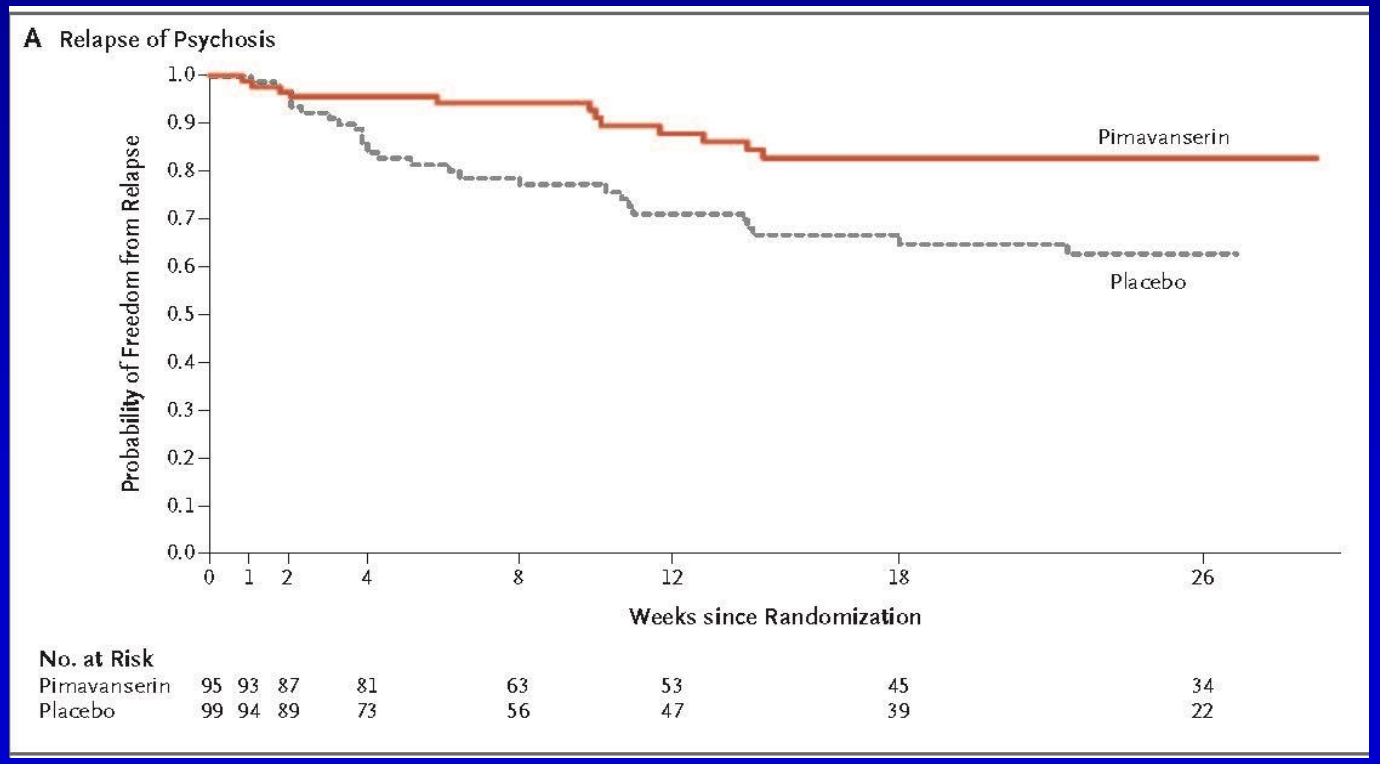
Cummings et al. *The Lancet* 2013;383:533-540.

ORIGINAL ARTICLE

Trial of Pimavanserin in Dementia-Related Psychosis

Pierre N. Tariot, M.D., Jeffrey L. Cummings, M.D., Sc.D.,
Maria E. Soto-Martin, M.D., Ph.D., Clive Ballard, M.D., Deniz Erten-Lyons, M.D.,
David L. Sultzer, M.D., Davangere P. Devanand, M.D., Daniel Weintraub, M.D.,
Bradley McEvoy, Dr.P.H., James M. Youakim, M.D.,
Srdjan Stankovic, M.D., M.S.P.H., and Erin P. Foff, M.D., Ph.D.

HARMONY Study



Tariot et al. *NEJM* 2021;385:309-319.

HARMONY Study PD Dementia Subgroup: Pimavanserin Safety Good

Table 3. Overall Summary of Treatment-Emergent Adverse Events

TEAEs, n (%)	Open-Label Period	Double-Blind Period	
	Pimavanserin 34 mg (N=49)	Placebo (N=20)	Pimavanserin 34 mg (N=16)
Any TEAE	23 (46.9)	9 (45.0)	5 (31.3)
Serious TEAE	5 (10.2)	-	-
Related TEAE	5 (10.2)	3 (15.0)	-
Related serious TEAE	-	-	-
TEAE leading to discontinuation or study termination	7 (14.3)	2 (10.0)	1 (6.3)
TEAE resulting in death[a]	1 (2.0)	-	-

Numbers presented represent patients. Events with a missing relationship were counted as related.
[a]One patient died during the open-label period from myocardial infarction, which was considered unrelated to trial drug by the investigator.
TEAE, treatment-emergent adverse event.

- The most common TEAEs during the open-label period were decreased weight (8.2%), decreased appetite (8.2%), somnolence (8.2%), and insomnia (8.2%) (**Table 4**).

Table 4. Treatment-Emergent Adverse Events Occurring in ≥3% of Patients in the Open-Label Period

Preferred Term, n (%)	Open-Label Period
	Pimavanserin 34 mg (N=49)
Decreased weight	4 (8.2)
Decreased appetite	4 (8.2)
Somnolence	4 (8.2)
Insomnia	4 (8.2)
Fall	3 (6.1)
Urinary tract infection	3 (6.1)
Constipation	2 (4.1)
Diarrhea	2 (4.1)
Nausea	2 (4.1)
Fatigue	2 (4.1)
Nasopharyngitis	2 (4.1)
Confusional state	2 (4.1)
Psychotic disorder	2 (4.1)
Orthostatic hypotension	2 (4.1)

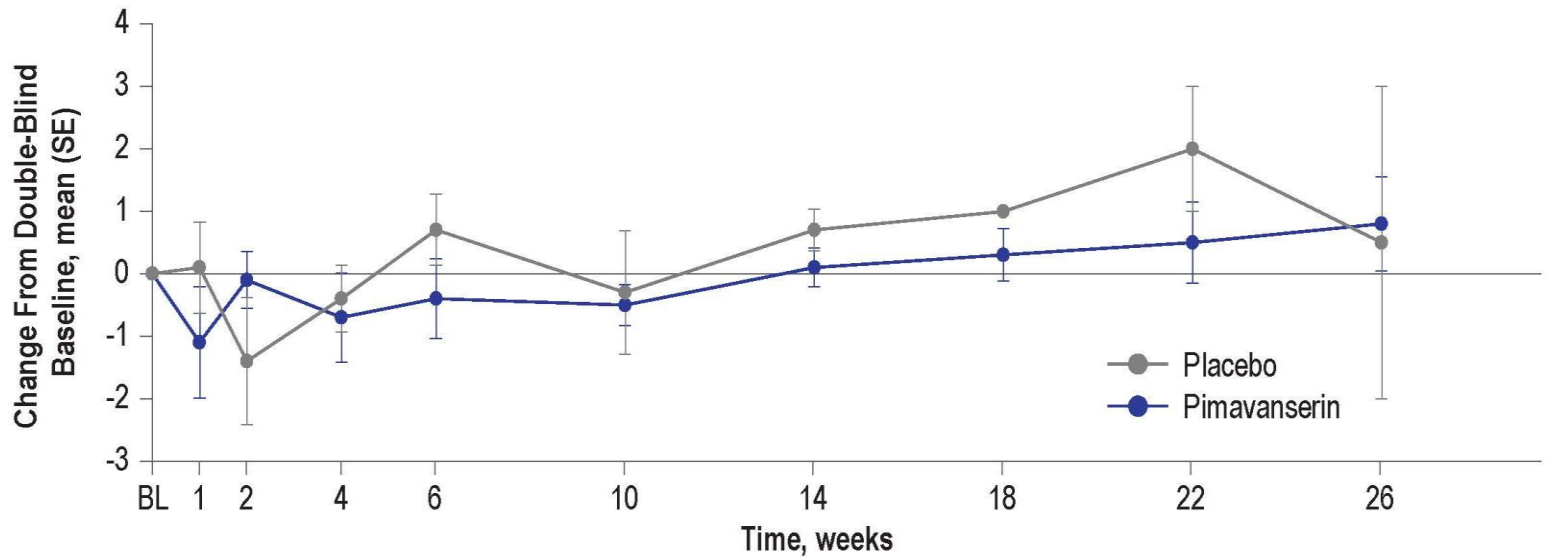
Numbers presented represent patients. Events with a missing relationship were counted as related.

- In open-label phase no adverse events occurred in >10% of patients
- In double-blind phase adverse event rates similar for pimavanserin and placebo

Weintraub et al. *Parkinsonism Relat Disord* 2024;119:105951.

HARMONY Study PDD Subgroup: No Motor or Cognitive Adverse Effects

Figure 4. MMSE Score Change From Double-Blind Baseline



BL, baseline; MMSE, Mini-Mental State Examination; SE, standard error.

Weintraub et al. *Parkinsonism Relat Disord* 2024;119:105951.

Antipsychotic Sensitivity in DLB

- *"The use of antipsychotics for the acute management of substantial behavioral disturbance, delusions, or visual hallucinations comes with attendant mortality risks in patients with dementia, and particularly in the case of DLB they should be avoided whenever possible, given the increased risk of a serious sensitivity reaction."*
- Examples include severe increased parkinsonism, fever, unresponsiveness, confusion, myoclonus, agitation, sedation
  - 30+ years ago now, all older antipsychotics, on inpatient unit so more severe cases

McKeith et al. *Neurology* 2017;89:88-100.
McKeith et al. *BMJ* 1992;305:673–678.

Key Takeaways for AP Use in Neurodegenerative Diseases

- Psychosis, agitation and related disorders common in dementia (AD, PD(D), DLB)
- Associated with worse outcomes (e.g., institutionalization, morbidity, mortality, caregiver burden, insomnia)
- Often requires treatment
- Non-pharmacological approaches (education, support, behavioral management techniques) can be helpful but may be insufficient
- Evidence for non-antipsychotic medications limited (e.g., antidepressants, cholinesterase inhibitors)
- APs are efficacious, but many may not be effective
  - Atypical APs an improvement (e.g., less tardive dyskinesia)
  - However, still concerns about tolerability, morbidity, mortality (although increased mortality risk may be small)

Session 3: Stakeholder Perspectives on Considerations Regarding the Use of Boxed Warnings for Antipsychotics

Moderator:

- **Christina Silcox,** Duke-Margolis Institute for Health Policy

Panelists:

- **Jacobo Mintzer**, Medical University of South Carolina
- **Russ Paulsen**, USAgainstAlzheimer's
- **Sue Peschin**, Alliance for Aging Research
- **James Taylor**, Care Giver; Voices of Alzheimer's
- **Daniel Weintraub**, University of Pennsylvania School of Medicine

Session 3: Stakeholder Perspectives on Considerations Regarding the Use of Boxed Warnings for Antipsychotics

Discussion Questions

1. How do providers communicate risks and benefits of antipsychotic medications with patients and care partners when discussing potential use for management of dementia-related behavioral disorders?

    a) How does the risk information contained in the boxed warning and communicated by providers impact the decision-making process for patients and care partners when considering use of these products?

2. What considerations might providers weigh when assessing utility and appropriateness of antipsychotics for treatment of dementia-related behavioral disorders?

    a) How does the boxed warning inform prescribing practices of healthcare providers?

3. What research questions may need to be addressed to best inform patients, families, and clinicians of key considerations and appropriate use of antipsychotics for this patient population?

Session 4: Opportunities for Further Characterizing Value and Need for Boxed Warnings for Antipsychotics

Opportunities for Further Characterizing Value and Need for the Boxed Warning

Shamir N. Kalaria, PharmD, PhD
Division of Psychiatry | Office of Neuroscience | Office of New Drugs
Center for Drug Evaluation and Research | FDA

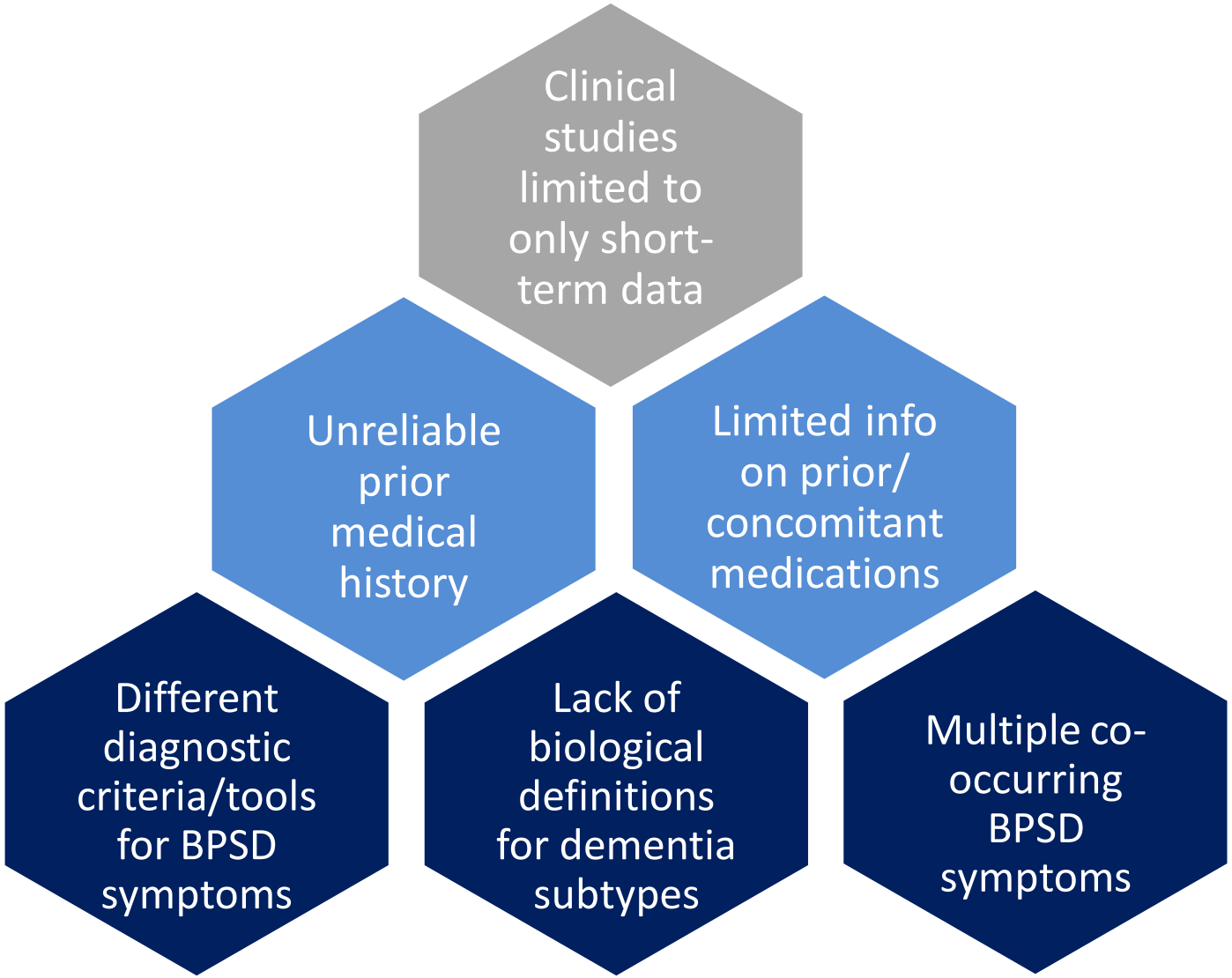
Duke-Margolis Center for Health Policy Meeting:
Mortality and Antipsychotic Use in Dementia-Related Behavioral Disorders

Limitations of Available Subject-Level Data

No Long-Term Data

Missing Patient Info

Heterogenous Eligibility Criteria



Future Steps

- Comphrensive analysis of questions and discussion items from this workshop to inform need for additional data and analyses
- Pending responses from sponsors, conduct a subject-level analysis from available randomized controlled trials (including data from the brexpiprazole and pimavanserin programs).
- Potentially conduct a meta-analysis of observational studies available from the current literature

Outstanding Questions

- How might the Agency consider risk modifiers such as type of neuropsychiatric symptoms (e.g., psychosis or agitation) or type of dementia (e.g., Alzheimer's type or vascular)?

- Can risk modifiers related to medical comorbidities be realistically accounted for in the analysis? What would be an adequate research method?

- If a new product with an indication for the treatment of neuropsychiatric symptoms of dementia is submitted to the Agency, how might the Agency evaluate whether there is an associated increased risk in mortality and, if relevant, contextualize that risk?


FDA
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ADMINISTRATION

Session 4: Opportunities for Further Characterizing Value and Need for Boxed Warnings for Antipsychotics

Moderator:

- **Nancy Allen LaPointe**, Duke-Margolis Institute for Health Policy

Panelists:

- **Rebecca Edelmayer**, Alzheimer's Association
- **Valentina Mantua**, U.S. Food and Drug Administration
- **Kristina McLinden**, National Institute on Aging
- **Mat Soukup**, U.S. Food and Drug Administration
- **Paul Rosenberg**, Johns Hopkins University School of Medicine
- **Chad Worz**, American Society of Consultant Pharmacists

Session 4: Opportunities for Further Characterizing Value and Need for Boxed Warnings for Antipsychotics

Discussion Questions

1. How might the Agency consider risk modifiers such as type of neuropsychiatric symptom (e.g., psychosis or agitation) or type of dementia (e.g., Alzheimer's type or vascular)?

2. Can risk modifiers related to medical comorbidities be realistically accounted for in the analysis? What would be an adequate research method here?

3. If a new product with an indication for neuropsychiatric symptoms of dementia is submitted to the FDA, how might the Agency evaluate whether there is an associated increased risk in mortality and, if relevant, appropriately contextualize that risk?

Adjournment

Mortality and Antipsychotic Use in Dementia-related Behavioral Disorders

December 10, 2024

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DC office: 202-621-2800
Durham office: 919-419-2504

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