Duke | MARGOLIS INSTITUTE for Health Policy

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Mortality and Antipsychotic Use in Dementia-Related Behavioral Disorders

Meeting Summary

EXECUTIVE SUMMARY

On December 10, 2024, the Duke-Margolis Institute for Health Policy, under a cooperative agreement with the U.S. Food and Drug Administration (FDA) convened a workshop on "Mortality and Antipsychotic Use in Dementia-Related Behavioral Disorders." The focus of this workshop was to review data on the risk of mortality associated with the use of antipsychotic medications in older adults with dementia-related behavioral and psychiatric symptoms that led to a boxed warning. Behavioral and psychiatric symptoms of dementia, also referred to as neuropsychiatric symptoms (NPS), are common and are associated with high risk and burden to patients and their caregivers.

In the workshop, FDA presented the regulatory history of the boxed warning for increased risk of mortality in elderly patients with antipsychotic use, insights on a re-analysis of the data that supported the boxed warning, and findings from a recently conducted literature review of observational studies assessing the association between antipsychotic use in dementia and mortality. The revised meta-analysis continued to suggest an association between antipsychotic use and an increased risk of mortality, but also identified important considerations for the interpretation of the available data; future analyses through the acquisition of patient-level data were also discussed. Most of the identified studies from the literature review found a higher risk of mortality in individuals with dementia who received antipsychotics for NPS. However, study limitations were noted and opportunities for further assessments, such as delineating short-term versus long-term mortality risks and a differentiation of effects by dementia severity or type(s) of NPS, were suggested.

In panel discussions, meeting participants reflected on the unmet needs of patients who experience NPS and their caregivers, the available evidence for the use of antipsychotics, and further considerations for assessing and balancing risks and benefits within this patient population. FDA emphasized that this workshop is a first step to initiate dialogue with stakeholders. FDA plans to use the stakeholder questions and discussion items to inform the need for additional data and analyses that can inform future steps to characterize the value and necessity of the boxed warning.

INTRODUCTION

On December 10, 2024, a public workshop was convened by the Duke-Margolis Institute of Health Policy under a cooperative agreement with the FDA. This initial dialogue with stakeholders was a critical first step in re-evaluating the mortality risk associated with the use of antipsychotic medications in older adults with dementia-related behavioral and psychiatric symptoms. The stakeholder input from this workshop will help inform future steps and characterize the value and need for the boxed warning.

This public workshop fulfills a portion of the FY 2024 House Appropriations Committee (H. Report 118-124) requirement for FDA to review the data regarding risks associated with the use of antipsychotics for mental health conditions in older adults with dementia and the appropriateness of the broad application of the boxed warning for all medicines within the antipsychotic class.

Background

Clinical Overview of Behavioral and Psychiatric Symptoms of Dementia

Alzheimer's disease (AD) is the most common cause of dementia, affecting approximately 6.5 million people aged 65 years and older in the United States and accounting for 60 to 80 percent of dementia cases worldwide.[1] AD, along with other causes of dementia, may result in psychological disturbances that are described as neuropsychiatric symptoms (NPS) and also known as behavioral and psychiatric symptoms of dementia (BPSD). NPS is comprised of a heterogeneous range of non-cognitive symptoms that can include, agitation, aggression, delusions, hallucinations, depression, apathy, and sleep disturbances.[2] These symptoms can significantly impact the quality of life for both patients and their caregivers, often leading to increased morbidity and institutionalization of persons with dementia.[3]

Clinical management of NPS is challenging, with non-pharmacologic strategies recommended as the first-line approach. If those strategies do not achieve the desired outcomes, pharmacologic therapies may be sought. However, a key problem for developing evidence-based recommendations for the pharmacologic treatment of NPS is the small number of high quality, randomized, controlled clinical trials. Many classes of drugs continue to be used off-label despite the lack of established efficacy and known side effects. The U.S. Food and Drug Administration (FDA) approved two drugs for the treatment of NPS in neurodegenerative diseases. Brexpiprazole (Rexulti®) was approved for the treatment of agitation associated with Alzheimer's type dementia. Pimavanserin (Nuplazid®) was approved for the treatment of hallucinations and delusions associated with Parkinson's disease psychosis, which may include patients with cognitive impairment or dementia. However, even with these recent approvals, there remains a high unmet need for safe and effective medicines for the treatment of NPS due to dementia.

Regulatory History of the Boxed Warning for Antipsychotics

In 2005 and 2008, FDA added a boxed warning to the prescribing information for antipsychotics based on clinical trial data that showed higher risk of death among older patients treated with antipsychotics for dementia-related psychosis compared with those that received placebo. A modified version of the boxed warning was also included in the labeling for the approvals of Nuplazid for Parkinson's disease psychosis and Rexulti for agitation due to Alzheimer's disease.

Evolution of the Products in Antipsychotic Class and Opportunity for FDA Re-evaluation

Since the addition of the boxed warning to prescribing information for antipsychotics, there has been an evolution in care practices, treatment options, and new evidence that creates an opportunity to re-evaluate the need and value of the boxed warning. Re-analyzing available data on antipsychotic use in patients with dementia-related behavioral disorders can provide additional clarity on the appropriate use of these therapies and severity of risks for this patient population and identify questions that may warrant further research.

There are outstanding questions about mortality risk that remain unanswered. These include the role of potential risk modifiers such as type of behavioral symptoms (e.g. agitation, apathy, psychosis, etc.); type of dementia (e.g., Alzheimer's type or vascular), and severity of dementia. Additionally, individuals affected by dementia often suffer from other illnesses or chronic conditions and take other medications that also confer risks. Questions remain as to how to adequately account for these illnesses and medications as contributors or confounders to the risk of mortality for marketed drugs and drugs under development for NPS. These questions are relevant for patients, providers, regulatory authorities, and industry, to guide therapeutic development and inform decision-making in clinical care.

Data Analysis and Literature Review Findings

The FDA presented a new meta-analysis of the 17 randomized placebo-controlled trials involving six antipsychotics that originally supported the placement of the boxed warning in the prescribing information for antipsychotics. The analysis which was based on including deaths that occurred within 4 days of treatment exposure, resulted in an estimated incidence rate of 7.0 deaths per 100 person-years in participants randomized to an antipsychotic and 2.3 deaths per 100 person-years in participants randomized to placebo.

Overall, the analysis estimated a 76 percent increased risk of death among subjects receiving antipsychotic treatment compared to those receiving placebo. The FDA discussed the limitations of the available datasets and the implications on interpretation of the analysis findings. The Agency also noted that it had sent a

request for data to individual sponsors to provide patient-level data to facilitate the conduct of additional analyses to address limitations of the current analysis and to identify risk modifiers. The FDA also summarized findings of relevant articles on observational studies in individuals with dementia from the scientific literature. Most observational studies seemed to confirm, despite large variability in the data, a higher risk of mortality in individuals affected by dementia who were prescribed antipsychotics to treat NPS.

Perspectives on Mortality Risk and Boxed Warning for Antipsychotics

Stakeholders emphasized that there is a great need for treatment options that help reduce burden for patients and caregivers and enable patients to remain in their home longer with an improved quality of life. Additionally, they emphasized a critical need to find better ways to measure what is important to patients and caregivers for managing NPS.

Some participants were concerned that the non-specific nature of the boxed warning (relative to type of dementia, severity of dementia, type of NPS, presence of comorbidities, or specific antipsychotic drug used) creates confusion for patients, caregivers, and care providers in treatment decision-making. Patients, caregivers, and providers may not be aware of or understand the limitations of the data supporting the boxed warning when making their treatment decisions. Additionally, the recent inclusion of the modified boxed warning for brexpiprazole and pimavanserin for risk of mortality was thought to further increase confusion. Several stakeholders were further concerned that the boxed warning may negatively impact access to antipsychotics for this patient population by increasing the likelihood of physician reluctance to prescribe because of a lack of clarity of risks, stigma, or payer refusal to provide reimbursement for situations in which a boxed warning exists.

Recognizing that antipsychotic drugs are a diverse group of medications with different mechanisms of action, stakeholders expressed the value of having drug-specific information of risk and more specific boxed warnings for individual drugs rather than a less specific warning on a class basis. Stakeholders felt that this drug-specific data coupled with greater information on risk modifiers such as type of NPS or type of dementia is necessary for communicating with patients and caregivers and facilitating patient-centric treatment decisions.

Opportunities for Clarifying Risk and Need for Boxed Warning

Participants acknowledged the complexity of assessing mortality risk associated with antipsychotic drugs with diverse mechanisms of action in this heterogenous population with dementia and NPS. However, as stated above, stakeholders emphasized the importance of differentiating risk by factors such as dementia type, severity or stage of dementia, type of NPS, severity of NPS, patient comorbidities, antipsychotic drug, and dose and duration of antipsychotic use. Additionally, participants requested that FDA consider the need to balance potential risks of antipsychotics with the distress experienced by patients and their families due to NPS and incorporate the lived experiences of the patient and caregiver in regulatory decisions regarding the antipsychotic boxed warning.

Stakeholders acknowledged that because a large sample size is needed to assess risk of mortality in this population, no single study would be capable of providing adequate data to assess the risk, so there is a need to combine data from different studies. Stakeholders encouraged FDA to include cause of death from death certificates in their ongoing efforts to acquire patient-level data from prior studies to help refine their analyses and inform future studies. These data can help to guide the re-evaluation of the boxed warning and help inform treatment decision-making by patients, caregivers, and providers.

Even if patient-level data was obtained for all the studies that were included in the meta-analyses, stakeholders acknowledged that there are newer diagnostic criteria, biomarkers, and other tests now available that were not available when these studies were conducted. Some of these advancements are key to the differentiation of type of dementia, for example, and are now standard in clinical care and research. Without these data elements, re-analyses with available additional patient-level data still may not answer some of the key questions around risk and the boxed warning. This evolution in science and clinical practice also poses challenges for analyses that may combine data from older and newer studies as well as efforts to compare outcomes from earlier trials to newer trials.

Stakeholders encouraged more discussions on innovative methodologies to leverage and enhance the existing data to answer key stakeholder questions. Many stakeholders identified key limitations and/or gaps in knowledge in the currently available data, as

described above, that could serve as opportunities for informing future research. For example, the randomized controlled trials included in the meta-analyses were short-term studies. Therefore, the long-term effects of these drugs are not well understood, but of great importance, especially when trying to differentiate mortality risk of the underlying disease from mortality risk of antipsychotic drugs. Acquisition of patient level data during longer follow-up, if available, may provide valuable insights.

Stakeholders encouraged efforts to contextualize risk and highlighted several key factors to clarify mortality risk associated with antipsychotic drugs in adult patients with dementia and NPS. They emphasized that clear information and less confusing warning language will improve clinicians' ability to better weigh the magnitude of risk from a specific antipsychotic drug for a specific patient against the risk of distress and suffering from NPS and to convey risks to patients.

CONCLUSION

The FDA emphasized the intent of this public workshop was to initiate a dialogue with stakeholders as part of the first step in a process to inform future work to characterize the value and need for the boxed warning for risk of mortality in adult patients with dementia who receive antipsychotic drugs for NPS. FDA identified some potential next steps that included requests for patient level data from the clinical trials that were included in the meta-analyses to potentially re-analyze the data with additional patient level variables and the potential for a meta-analysis of relevant observational studies. FDA plans to use the stakeholder questions and discussion items from this workshop to inform the need for additional data and analyses and better define the next steps.

REFERENCES

1. 2022 Alzheimer's disease facts and figures. *Alzheimers Dement*. 2022;18(4):700-789. doi:10.1002/alz.12638
2. Lyketsos CG, Lopez O, Jones B, Fitzpatrick AL, Breitner J, DeKosky S. Prevalence of neuropsychiatric symptoms in dementia and mild cognitive impairment: results from the cardiovascular health study. *JAMA*. 2002;288(12):1475-1483. doi:10.1001/jama.288.12.1475
3. Deardorff WJ, Grossberg GT. Behavioral and psychological symptoms in Alzheimer's dementia and vascular dementia. *Handb Clin Neurol*. 2019;165:5-32. doi:10.1016/B978-0-444-64012-3.00002-2
4. Murphy S, Roberts R. "Black box" 101: How the Food and Drug Administration evaluates, communicates, and manages drug benefit/risk. *Journal of Allergy and Clinical Immunology*. 2006;117(1):34-39. doi:10.1016/j.jaci.2005.10.031

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