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Treating Agitation With Co-Occurring Psychosis: A Post Hoc Analysis

Announcer:

You're listening to ReachMD. This program, titled "Treating Agitation With Co-Occurring Psychosis: A Post Hoc Analysis," is sponsored by Otsuka and Lundbeck.

Drs. Tariot and Montano are paid consultants of Otsuka Pharmaceutical Development & Commercialization, Inc and Lundbeck.

Dr. Tariot:

Welcome to ReachMD. I'm Dr. Pierre Tariot, and I'm the Director for Banner Alzheimer's Institute in Phoenix, Arizona with a clinical and research background in psychiatry.

Joining me today is Brendan Montano. Dr. Montano, thanks for being here.

Dr. Montano:

Thanks, Dr. Tariot, I'm happy to be here. I'm Dr. Brendan Montano, and I'm the Director and Principal Investigator of CT Clinical Research in Cromwell, Connecticut. In this program, we'll focus on a clinically relevant group of patients with agitation associated with dementia due to Alzheimer's disease by reviewing the brexpiprazole data in those with and without co-occurring psychosis.

Agitation is commonly experienced in people living with Alzheimer's dementia.¹ Many of these patients also experience psychosis, including delusions and hallucinations. In fact, psychosis affects roughly 40 percent of patients with Alzheimer's dementia and is associated with functional impairment, faster disease progression, increased caregiver burden, and higher rates of institutionalization.² Because clinicians commonly care for patients who present with both agitation and psychosis, an important question is whether treatment outcomes differ in these more clinically complex patients. The post hoc analyses we'll review today offer additional insights into the use of brexpiprazole for agitation associated with dementia due to Alzheimer's disease in patients who also have co-occurring psychosis. Before we move on, let's review the FDA-approved indication and important safety information for brexpiprazole.

Announcer:

Indication and Important Safety Information

INDICATION

Brexpiprazole is indicated for treatment of agitation associated with dementia due to Alzheimer's disease.

Limitations of Use: Brexpiprazole is not indicated as an as needed ("prn") treatment for agitation associated with dementia due to Alzheimer's disease.

Contraindication

In patients with known hypersensitivity to brexpiprazole or any of its components. Reactions have included: rash, facial swelling, urticaria, and anaphylaxis.

IMPORTANT SAFETY INFORMATION

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at increased risk of death. Brexpiprazole is not approved for the treatment of patients with dementia-related psychosis without agitation associated with dementia due to Alzheimer's disease.

Stay tuned for additional Important Safety Information later in this program.

Dr. Montano:

Now, with that in mind, Dr. Tariot, many clinicians remain cautious about using antipsychotics in patients with dementia-related psychosis because of longstanding safety concerns.² In fact, in my experience, providers may hesitate to use antipsychotics or titrate to a therapeutic dose due to

safety concerns.

Before we discuss the findings from this analysis, can you help clarify how the brexpiprazole boxed warning differs from the traditional antipsychotic class warning?

Dr. Tariot:

Absolutely. Psychosis itself can be treated with antipsychotics, but dementia-related psychosis has historically raised important safety concerns in older adults. The FDA issued a Public Health Advisory in 2005 after finding that 15 of 17 studies of atypical antipsychotics in elderly demented patients with behavioral disorders showed numerical increases in mortality.

The agency concluded this to be related to the pharmacology of atypical antipsychotics and asked the manufacturers to include a Boxed Warning describing this risk.³ And, as a result, antipsychotic use in this population has been approached cautiously.²

But brexpiprazole's boxed warning has been modified to clarify that it's approved for the treatment of agitation associated with dementia due to Alzheimer's disease, even when a patient also has co-occurring psychosis. The boxed warning simply clarifies that it isn't approved to treat dementia-related psychosis on its own, in the absence of agitation.⁴

And that sets it apart from other antipsychotic boxed warnings which indicate they're not approved for the treatment of dementia-related psychosis and still carry a class boxed warning.^{5,6}

That distinction is key, because clinicians frequently care for patients who present with both agitation and psychosis. Given historical concerns about antipsychotic use in patients with dementia-related psychosis, understanding the efficacy and safety of brexpiprazole in these patients is particularly important.²

Dr. Montano:

Exactly. And that's really the question these post hoc analyses were designed to address.

Now, let's get into the data.

Researchers evaluated brexpiprazole at doses of two and three milligrams per day versus placebo in patients with agitation associated with dementia due to Alzheimer's disease, comparing outcomes in those with and without co-occurring psychosis.²

The primary post-hoc analysis pooled data from two Phase three, 12-week, randomized, placebo-controlled trials that included patients from both community and long-term care settings aged 55 to 99 years. Patients with clinically significant or uncontrolled medical conditions or other psychotic disorders were excluded from the study.²

In addition to the short-term 12-week analyses, researchers also evaluated outcomes over 24 weeks to better understand the durability of treatment effects. This long-term analysis followed participants who continued receiving brexpiprazole and assessed whether improvements in agitation were maintained over time.^{2,7}

Efficacy was assessed using the Cohen-Mansfield Agitation Inventory, or CMAI, a validated measure that captures the frequency of agitation symptoms across a broad range of behaviors. This includes physically non-aggressive behaviors, verbally agitated behaviors, and aggressive behaviors.^{8,9} Data was collected at two-week intervals by the clinicians based on caregiver feedback.²

Safety was monitored throughout the studies, including adverse events of special interest such as falls, cerebrovascular events, and somnolence or sedation.²

Before reviewing the results, it's important to understand the patient population. Approximately one-quarter of participants had co-occurring psychosis at baseline, defined by clinically significant delusions or hallucinations on the Neuropsychiatric Inventory, or NPI.² Antipsychotic medications other than brexpiprazole were prohibited during the randomized trials, and prohibited medications underwent a washout period of up to 42 days before randomization.¹⁰

One thing that's important to note is that patients with co-occurring psychosis tended to have more severe agitation at baseline than those without psychosis. And trial completion rates were similar in patients with and without psychosis. This provided an opportunity to evaluate how brexpiprazole performed in a more clinically complex population.²

Now, with all of that being said, Dr. Tariot, will you walk us through the results of these analyses?

Dr. Tariot:

Of course.

Looking at the short-term analysis, brexpiprazole was associated with statistically significant improvements in agitation symptoms with co-occurring psychosis compared with placebo based on the change from baseline in CMAI total score. A similar pattern was seen in participants without co-occurring psychosis, although statistical significance of the improvements was observed a bit earlier, beginning at week six.²

Interestingly, it's also worth highlighting that patients with co-occurring psychosis experienced greater improvements with brexpiprazole compared to

those without psychosis, even though they entered the study with more severe agitation at baseline which suggests that the presence of psychosis did not diminish treatment response.²

These findings were consistent in the sensitivity analysis. Patients with and without co-occurring psychosis continued to show greater improvements in agitation with brexpiprazole compared with placebo—similar to what was seen in the primary analysis.⁷

Moving on to the long-term analysis, improvements in agitation symptoms were maintained through 24 weeks of brexpiprazole. Participants receiving brexpiprazole—both with and without co-occurring psychosis—showed ongoing reductions in agitation symptoms throughout the course of treatment.⁷

Dr. Montano:

Thanks for reviewing that, Dr. Tariot. Now that we've covered efficacy, let's talk about safety.

Looking first at the short-term analysis, the overall safety profile was generally consistent in patients with and without co-occurring psychosis.²

About half of patients receiving brexpiprazole experienced an adverse event, while serious adverse events remained relatively uncommon in both groups. Discontinuations due to adverse events were also infrequent, and there were no deaths among patients with co-occurring psychosis.²

Adverse events of special interest, which included cerebrovascular events, cardiovascular events, falls, orthostatic hypotension, and somnolence or sedation were generally uncommon. Extrapyramidal symptoms occurred more frequently in patients with co-occurring psychosis receiving brexpiprazole than placebo, but overall, no new safety signals emerged.²

So taken together, the authors concluded that brexpiprazole was generally tolerated in patients with co-occurring psychosis.²

Dr. Tariot, could you tell us about long-term safety?

Dr. Tariot:

Absolutely. The 24-week analysis suggested there were no new long-term safety signals, which is reassuring.² In fact, the incidence of adverse events was numerically lower in patients with co-occurring psychosis compared with those without psychosis—31.4 percent versus 39.3 percent.⁷

Serious adverse events were uncommon, with only one serious adverse event reported in the subgroup without co-occurring psychosis. And importantly, there were no deaths or discontinuations due to adverse events in patients with or without psychosis at 24-weeks.⁷

It's important to note, though, that the 24-week safety analysis was limited by small subgroup sizes and did not have a placebo group for comparison.⁷

So taken together, it seems like both the short-term and long-term data analyses suggest that brexpiprazole maintained a consistent safety profile in patients with agitation associated with dementia due to Alzheimer's disease, including those with the added clinical complexity of co-occurring psychosis.^{2,7}

Dr. Montano:

I agree, Dr. Tariot. This analysis may provide valuable information for clinicians treating patients with co-occurring psychosis.²

So, as we come to the end of our program, what do you think these findings mean for clinicians caring for patients with agitation associated with Alzheimer's dementia, especially those with co-occurring psychosis?

Dr. Tariot:

In my experience, clinicians have been understandably cautious when treating patients with agitation who also present with dementia-related psychosis, because these patients are often more complex and difficult to manage. So, like we mentioned before, these findings may be helpful to clinicians who are actually seeing these patients in practice.

So those are my thoughts. But what do you think, Dr. Montano?

Dr. Montano:

Well, I agree with you—what these analyses suggest is that brexpiprazole may improve agitation symptoms, even in patients with co-occurring psychosis, while maintaining a generally consistent safety profile.^{2,7} Although these findings are exploratory, they suggest that brexpiprazole may be a valuable option for patients who present with both agitation and psychosis in clinical practice.²

And with those final thoughts in mind, I want to thank Dr. Pierre Tariot, for joining me today to talk about treating agitation in Alzheimer's dementia with brexpiprazole in patients with co-occurring psychosis. Dr. Tariot, it was great speaking with you.

Dr. Tariot:

Thank you, Dr. Montano! I really enjoyed our conversation.

Before we close, let's take a moment to review some Important Safety Information.

Announcer:

IMPORTANT SAFETY INFORMATION continued

Contraindication: In patients with known hypersensitivity to brexpiprazole or any of its components. Reactions have included: rash, facial swelling, urticaria, and anaphylaxis.

Cerebrovascular Adverse Events, Including Stroke: In clinical trials, elderly patients with dementia randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. Brexpiprazole is not approved for the treatment of patients with dementia-related psychosis without agitation associated with dementia due to Alzheimer's disease.

Neuroleptic Malignant Syndrome (NMS): NMS is a potentially fatal symptom complex reported in association with administration of antipsychotic drugs, including brexpiprazole. Clinical signs of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Manage NMS with immediate discontinuation of brexpiprazole, intensive symptomatic treatment, and monitoring.

Tardive Dyskinesia (TD): Risk of TD, and the potential to become irreversible, appear to increase with duration of treatment and total cumulative dose of antipsychotic drugs. TD can develop after relatively brief treatment periods, at low doses, or after discontinuation of treatment. For chronic treatment, use the lowest dose and shortest duration of brexpiprazole needed to produce a clinical response. If signs and symptoms of TD appear, drug discontinuation should be considered.

Metabolic Changes: Atypical antipsychotic drugs, including brexpiprazole, have caused metabolic changes including:

- **Hyperglycemia/Diabetes Mellitus:** Hyperglycemia and diabetes mellitus, in some cases extreme and associated with diabetic ketoacidosis, hyperosmolar coma, or death, have been reported in patients treated with atypical antipsychotics. Assess fasting plasma glucose before or soon after initiation of antipsychotic medication and monitor periodically during long-term treatment.
- **Dyslipidemia:** Atypical antipsychotics cause adverse alterations in lipids. Before or soon after initiation of antipsychotic medication, obtain a fasting lipid profile at baseline and monitor periodically during treatment.
- **Weight Gain:** Weight gain has been observed in patients treated with brexpiprazole. Monitor weight at baseline and frequently thereafter.

Pathological Gambling and Other Compulsive Behaviors: Intense urges, particularly for gambling, and the inability to control these urges have been reported while taking brexpiprazole. Other compulsive urges have been reported less frequently. Prescribers should ask patients or their caregivers about the development of new or intense compulsive urges. Consider dose reduction or stopping brexpiprazole if such urges develop.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia and neutropenia have been reported with antipsychotics. Agranulocytosis (including fatal cases) has been reported with other agents in this class. Monitor complete blood count in patients with pre-existing low white blood cell count (WBC)/absolute neutrophil count or history of drug-induced leukopenia/neutropenia. Discontinue brexpiprazole at the first sign of a clinically significant decline in WBC and in patients with severe neutropenia.

Orthostatic Hypotension and Syncope: Atypical antipsychotics cause orthostatic hypotension and syncope. Generally, the risk is greatest during initial dose titration and when increasing the dose. Monitor in patients vulnerable to hypotension and those with cardiovascular and cerebrovascular diseases.

Falls: Antipsychotics may cause somnolence, postural hypotension, and motor and sensory instability, which may lead to falls causing fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating treatment and recurrently during treatment.

Seizures: Brexpiprazole may cause seizures and should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold.

Body Temperature Dysregulation: Use brexpiprazole with caution in patients who may experience conditions that increase body temperature (eg, strenuous exercise, extreme heat, dehydration, or concomitant use with anticholinergics).

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotics, including brexpiprazole, and should be used with caution in patients at risk for aspiration.

Potential for Cognitive and Motor Impairment: Brexpiprazole may cause somnolence and has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including operating motor vehicles, until they are reasonably certain brexpiprazole does not affect them adversely.

Concomitant Medication: Dosage adjustments are recommended in patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers.

Most commonly observed adverse reactions: In clinical trials of adults, the most common adverse reactions were:

- **Agitation associated with dementia due to Alzheimer's disease** ($\geq 4\%$ incidence and at least twice the rate of placebo for brexpiprazole vs placebo): nasopharyngitis and dizziness.

Dystonia: Symptoms of dystonia may occur in susceptible individuals during the first days of treatment and at low doses.

Pregnancy: Adequate and well-controlled studies to assess the risks of brexpiprazole during pregnancy have not been conducted. Brexpiprazole should be used during pregnancy only if the benefit justifies the risk to the fetus.

Lactation: It is not known if brexpiprazole is excreted in human breast milk. A decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

Please see **FULL PRESCRIBING INFORMATION**, including **BOXED WARNING**.

Announcer:

This program was sponsored by Otsuka and Lundbeck. If you missed any part of this discussion, visit ReachMD.com, where you can Be Part of the Knowledge.

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