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Treating Agitation in Patients on Antidepressants: A Post Hoc Analysis

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

Dr. Montano:
Welcome to ReachMD. I'm Dr. Brendan Montano, and I'm Director and Principal Investigator of Connecticut Clinical Research in Cromwell, Connecticut. Joining me today is my colleague Dr. Anton Porsteinsson.

Dr. Porsteinsson:
Thanks, Brendan.

I'm Dr. Anton Porsteinsson, and I'm a Professor of Psychiatry, Neurology, Neuroscience, and Medicine at the University of Rochester in Rochester, New York.

Today, we'll be talking about treatment of agitation in patients with agitation associated with dementia due to Alzheimer's disease who are also receiving concomitant antidepressant therapy.

Now, to understand why this subgroup is important, it's helpful to consider how often clinicians see these patients in practice.

Agitation is commonly experienced in people living with Alzheimer's dementia, affecting approximately 76 percent of patients.[1] But, importantly, agitation associated with dementia due to Alzheimer's disease is a distinct clinical condition with its own FDA-approved treatment indication, separate from Alzheimer's dementia itself.[2-4]

Concomitant antidepressants are often used by people with agitation in Alzheimer's dementia. These medications are prescribed both on- and off-label for conditions like depression, insomnia, agitation, apathy, and pain.[5,6] In fact, real-world studies suggest that approximately one in two people with dementia in the United States receive antidepressants, highlighting the importance of understanding medication use and risk in this population.[7]

Dr. Montano:
I agree, Anton. Historically, there has been limited evidence supporting the off-label use of antidepressants for the treatment of agitation in Alzheimer's dementia, but it's common for patients to remain on an antidepressant for another indication, like depression, while receiving treatment for agitation.[6] So understanding the efficacy and safety of concomitant treatment may help inform clinical decision-making.

The post hoc analysis we'll review today evaluates short- and long-term clinical trial data on the efficacy and safety of brexpiprazole in patients with agitation associated with dementia due to Alzheimer's disease who are receiving concomitant antidepressant therapy.[6,8]

But before we move on, let's review the FDA-approved indication and important safety information for brexpiprazole.

Announcer:

Indication and Important Safety Information

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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:
With that in mind, let's get into the data.

We evaluated brexpiprazole in patients with agitation associated with dementia due to Alzheimer's disease, comparing outcomes in those who were and were not receiving concomitant antidepressant therapy. The analysis pooled data from two Phase three, short-term 12-week, randomized, double-blind, placebo-controlled trials that included adults aged 55 to 90 years from both community and long-term care settings.[6]

Researchers also examined long-term outcomes over 24 weeks among participants who continued brexpiprazole treatment to determine whether improvements in agitation were sustained over time.[6]

Efficacy was evaluated using the Cohen-Mansfield Agitation Inventory, or CMAI, to capture the broad range of behaviors that characterize agitation and their frequency—this includes physically non-aggressive behaviors, verbally agitated behaviors, and aggressive behaviors.[9] Data was collected at two-week intervals by the clinicians based on caregiver feedback.[5,6]

For safety, adverse events were monitored, including discontinuations and other adverse events of special interest, like cerebrovascular events, dizziness, falls, somnolence, and sedation.[6]

Dr. Porsteinsson:
Thanks, Brendan. It's also important to understand the patient population.

Among participants with both baseline and post-baseline CMAI assessments, 15.9 percent were taking an antidepressant. Antidepressants were used for depression, insomnia, anxiety, agitation, sleep disorder, and other conditions or unspecified reasons.[6]

Another thing that's important to note is that trial completion rates were similar across subgroups.[6]

And based on baseline mean CMAI and CGI-S scores, agitation frequency and severity were similar across patients receiving brexpiprazole and placebo.[6]

Knowing all of that, Brendan, will you walk us through the efficacy results?

Dr. Montano:
Of course.

In the short-term analysis, brexpiprazole demonstrated greater improvement in CMAI total score compared to placebo starting at week eight in patients both with and without concomitant antidepressants use.[6]

Notably, a sensitivity analysis including data from an additional Phase 3 trial, separate from the main analysis, showed results consistent with the primary findings.[8]

And we saw that pattern continue long-term. Both patients receiving and not receiving concomitant antidepressants showed continued

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reductions in agitation symptoms with brexpiprazole over 24 weeks.[8]

Now that we've covered efficacy, Anton, can you tell us about the safety?

Dr. Porsteinsson:
Absolutely. The short-term analysis was generally consistent regardless of whether patients were receiving concomitant antidepressant therapy or not.[6]

Reported adverse events were slightly lower in patients receiving concomitant antidepressants, at just under 40 percent, compared to just over half of those not receiving antidepressant therapy. Serious adverse events and discontinuations due to adverse events were relatively uncommon across both subgroups.[6]

Adverse events of special interest were also infrequent across subgroups, and no new safety signals were identified, although events were reported more frequently in patients without concomitant antidepressants. That included cerebrovascular events, extrapyramidal symptoms, akathisia, orthostatic hypotension or dizziness, insomnia, and somnolence including sedation.[6]

The long-term safety analysis showed similar signals. Brexpiprazole was generally well tolerated in patients both with and without concomitant antidepressant therapy.[8]

Adverse events continued to be reported less frequently among patients receiving concomitant antidepressants than among those who were not, with a more meaningful gap in the long-term analysis than short-term. No serious adverse events or discontinuations due to adverse events were reported in the concomitant antidepressant subgroup, and only one serious adverse event occurred in patients who were not receiving antidepressants.[8]

Once again, adverse events of special interest were reported more frequently in patients not taking concomitant antidepressants, but overall uncommon with no new safety signals observed.[8]

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.[8]

So, taken together, the short and long-term analyses suggest that brexpiprazole maintained a generally consistent and manageable efficacy and safety profile in patients with agitation associated with dementia due to Alzheimer's disease, regardless of whether they were receiving concomitant antidepressant therapy.[6,8]

Dr. Montano:
I agree, Anton. I think one of the advantages of this analysis is that it reflects a common clinical scenario, where patients with agitation associated with dementia due to Alzheimer's disease are already taking antidepressants for other conditions.[5-7]

So understanding how brexpiprazole performs in that setting is highly relevant to everyday practice.[6]

As we wrap up, what do you see as the biggest clinical takeaway from these findings?

Dr. Porsteinsson:
For me, it's the consistency of the results. Patients receiving concomitant antidepressants experienced reductions in agitation symptoms that were similar to those seen in patients who were not taking antidepressants, and the overall safety profile remained generally consistent across both groups.[6,8]

While these findings should be interpreted within the context of an exploratory post hoc analysis, the results may help clinicians when treating patients who are already receiving antidepressant therapy.

Brendan, what stands out most to you?

Dr. Montano:
Well, what stands out to me is the clinical relevance. The patients included in this analysis closely resemble the individuals many of us care for every day—patients with multiple symptoms who are already receiving ongoing therapies.[5-7]

As you mentioned, this was an exploratory post hoc analysis. With that consideration in mind, these results suggest brexpiprazole was generally well tolerated in patients on concomitant antidepressant therapy, and the overall efficacy or safety profile was not meaningfully altered.[6,8] And that additional context may be helpful when considering treatment options in practice.

And as that brings us to the end of our program, I want to thank Dr. Anton Porsteinsson for joining me today to talk about treating

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agitation in dementia due to Alzheimer's disease with brexpiprazole in patients who are also receiving concomitant antidepressants. Anton, it was great speaking with you.

Dr. Porsteinsson:
Thank you, Brendan! 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.

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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** (≥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**.

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