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Understanding Sedation and Somnolence with Brexpiprazole in Agitation: What the Data Show

Announcer:
You're listening to ReachMD.

This program titled "Understanding Sedation and Somnolence with Brexpiprazole in Agitation," is sponsored by Otsuka and Lundbeck. And now, here's Dr. George Grossberg and Dr. Marc Agronin.

Drs. Grossberg and Agronin are paid consultants of Otsuka Pharmaceutical Development & Commercialization, Inc and Lundbeck.

Dr. Grossberg:
Hello, and welcome to ReachMD. I'm Dr. George Grossberg, and I'm the Inaugural Henry and Amelia Nasrallah Endowed Professor at the Saint Louis University School of Medicine in Saint Louis, Missouri. I'm also the Director of the Division of Geriatric Psychiatry in the Department of Psychiatry and Behavioral Neuroscience.

Today, I'm joined by my colleague, Dr. Marc Agronin, and we're discussing an exploratory post hoc analysis of brexpiprazole safety data presented at the 2026 American Association for Geriatric Psychiatry, or AAGP Annual Meeting. The analysis evaluated the incidence and impact of sedation and somnolence from clinical trials of brexpiprazole in patients with agitation associated with dementia due to Alzheimer's disease.[1]

Marc, welcome and thank you for joining me in this important discussion.

Dr. Agronin
Thanks, George. I'm Dr. Marc Agronin, Chief Medical Officer of the MIND Institute at Miami Jewish Health in Miami, Florida.

We'll also discuss what this data means for clinicians making treatment decisions for patients with agitation, so I'm looking forward to the discussion.

Dr. Grossberg:
So let's get started. Before we dive into the data, it's important to set the stage for our listeners.

People living with Alzheimer's dementia often experience neuropsychiatric symptoms, with agitation being one of the most common—affecting approximately 76 percent of these individuals.[2] Agitation is also one of the most distressing symptoms reported by caregivers.[3] That's roughly 5.5 million adults with Alzheimer's disease in the U.S. who are affected by agitation.[2,4]

Importantly, agitation that's associated with dementia due to Alzheimer's disease is a separate condition from Alzheimer's dementia that is treatable.[4,5] And the treatment goal should always be to reduce agitation symptoms and minimize safety risk while maintaining the patient's alertness, engagement, and function.[6,7]

So, Marc, when we think about treating these patients, what are some of the challenges clinicians face?

Dr. Agronin:
Well, when we're treating patients with agitation, one challenge is that pharmacological options—including psychotropic medicines often used, in this case, are off-label—and they may be associated with adverse events like sedation and somnolence.[8-11]

So in some cases, the treatment itself can introduce issues that overlap with, worsen, or even mask the outcomes that we're trying to

address.[8-13] So as an example, sedation may sometimes be used intentionally for symptom control, but it also can emerge as an unintended side effect of treatment.[1]

That being said, sedation and somnolence are often used interchangeably in clinical conversation, even though the terms are clinically distinct.[1]

With that in mind, I think an important distinction we can make for clinicians is the difference between sedation and somnolence.

George, how do you explain that to colleagues?

Dr. Grossberg:
Great question. Sedation is a subdued state with reduced alertness and engagement.[14]

Whereas somnolence is more subjective; it's that feeling of excessive sleepiness or drowsiness during waking hours.[1]

What's important is that either can lead to negative outcomes for patients.[9,15] They can affect daily functioning, engagement, and interactions, and sedation may also increase the risk of falls and cognitive impairment—which is especially concerning in older adults.[1]

So when evaluating a patient's response to a treatment for agitation, we need to monitor for safety consequences such as sedation and somnolence.[6,7]

I'd like to hear your thoughts on this matter as well, Marc.

Dr. Agronin:
You hit the nail on the head. When a patient with agitation becomes quiet after receiving a medication, it can look like improvement. But if that patient is simply too sedated to exhibit agitation symptoms, we haven't treated the underlying condition—we've masked it.[6,7,9,12,13]

The consequences are serious: impaired arousal, withdrawal from activities, decline in physical functioning, and increased mortality risk.[9,12,15]

Now, brexpiprazole is the first FDA-approved treatment for agitation associated with dementia due to Alzheimer's disease. The efficacy and safety of brexpiprazole have been demonstrated in this population in Phase Three trials.[1,16]

Let's now turn to the data presented at the 2026 AAGP Annual Meeting. This post hoc analysis aimed to evaluate the incidence and impact of the adverse events of sedation and somnolence in patients with agitation associated with dementia due to Alzheimer's disease.

As an exploratory analysis, these findings may help us understand patterns and clinical context.[1]

So George, can you walk us through how the study was set up?

Dr. Grossberg:
Of course. The analysis includes safety data from three clinical trials. Two of these were 12-week, fixed-dose, randomized, double-blind, controlled trials, and the third was a 12-week active-treatment extension study.[1]

- In the first fixed-dose clinical trial, patients were randomized one-to-one-to-one to receive brexpiprazole at one or two milligrams per day, or a placebo.[1]
- And in the second fixed-dose clinical trial, patients were randomized two-to-one to receive either two or three milligrams of brexpiprazole per day or a placebo.[1]
- A subset of patients who completed the second fixed-dose trial were then enrolled in the extension study, in which all patients continued on two or three milligrams of brexpiprazole per day.[1]

For this analysis, the pooled sample from the two fixed-dose trials included 754 patients.[1]

Reported outcomes for treatment-emergent adverse events, or TEAEs, of sedation or somnolence included incidence, severity, discontinuation rate, number needed to harm, timing of discontinuation due to these TEAEs, and the incidence of potentially related TEAEs such as falls.[1]

Announcer:

For those just tuning in, you're listening to ReachMD.

Today, Drs. George Grossberg and Marc Agronin are reviewing results from an exploratory post-hoc analysis of clinical trial safety data examining sedation and somnolence with brexpiprazole in patients with agitation associated with dementia due to Alzheimer's disease.

Dr. Grossberg:
So, Marc, now that we have some background on the study, what did the 12-week short-term data show in terms of the incidence of sedation and somnolence?

Dr. Agronin:
Well, over 12 weeks, the combined incidence of sedation or somnolence was three percent for all brexpiprazole doses combined and 0.8 percent for placebo.[1]

Somnolence was reported in 2.8 percent of patients for all brexpiprazole doses and 0.8 percent for placebo. By dose, somnolence rates were 1.5, 3.3, and 3.3 percent across the one-milligram, two-milligram, and three-milligram groups, respectively.[1]

And for sedation, rates were low—reported in 0.2 percent for all brexpiprazole doses and zero percent for placebo.[1]

These findings showed no clear dose dependent increase of somnolence or sedation and indicate that sedation with brexpiprazole was uncommon and generally mild.[1]

No participants taking brexpiprazole or placebo discontinued treatment due to sedation, and only one participant discontinued brexpiprazole due to somnolence in the three-milligram-per-day group.[1]

The number needed to harm helps describe how many patients would need to be treated with an intervention before expecting to encounter one additional safety outcome of interest. A higher number is better.[17,18]

For instance, when comparing psychotropic medications, a number needed to harm of 10 or higher suggests the treatment is well-tolerated. A number of 20 or higher suggests a lower risk.[17,18]

In this case, the number needed to harm for sedation or somnolence with all brexpiprazole doses relative to placebo was 46.[1] That said, these numbers should be interpreted carefully when events are rare.

Dr. Grossberg:
Another interesting finding from this analysis was the prevalence of sedation or somnolence adverse events over time. The poster reported prevalence at two-week intervals over 12 weeks. Marc, what did we see there?

Dr. Agronin:
Over the 12 week period, the prevalence of sedation or somnolence remained low and stable, ranging from approximately 1.2 percent to two percent for brexpiprazole across all doses combined, and from zero to 0.4 percent for placebo.[1]

This means that, at any given two week interval, only a small proportion of patients were experiencing these events.[1]

In addition, the median time to the first event was 24 days with brexpiprazole and 16 days with placebo. Symptoms resolved within three days for brexpiprazole and about one week for placebo.[1]

Now, when we think about sedation or somnolence in our older patients, it's important to consider associated factors such as falls. Falls may also be related to blood pressure drop or orthostatic hypotension.[9,15]

Over 12 weeks, the incidence of any orthostatic hypotension was four percent for all brexpiprazole doses combined and 3.6 percent for placebo.[1]

For falls, the incidence was 1.4 percent for all brexpiprazole doses and 1.6 percent for placebo.[1]

The analysis also noted that safety events associated with some antipsychotics—such as cerebrovascular events, cardiovascular events, extrapyramidal symptoms, and fractures—were generally reported at comparable levels to placebo, and there was no worsening of cognition reported among brexpiprazole-treated patients.[1]

Let's now shift our attention to the longer-term safety data in the 12-week extension study. One subgroup received two or three milligrams of brexpiprazole for a cumulative 24 weeks while the other received 12 weeks of placebo followed by 12 weeks of brexpiprazole.[1]

George, what did those longer-term results look like?

Dr. Grossberg:
There were no reports of sedation across the 24-week sample. Somnolence was infrequent, with an incidence of 4.9 percent in the all-brexpiprazole subgroup and 2.1 percent in the placebo lead-in subgroup.[1]

The prevalence of somnolence in the 24-week sample was between 0.6 percent and 1.9 percent in the all-brexpiprazole subgroup, and zero to 2.3 percent in the placebo lead-in subgroup.[1]

The first event of somnolence occurred at a median of 46 days in the all-brexpiprazole subgroup and 94 days in patients with a placebo lead-in. These events resolved quickly in patients receiving only brexpiprazole at a median duration of two days, compared with 22 days for those with a placebo lead-in.[1]

Adverse events due to somnolence were mostly mild in severity. And only one participant discontinued due to somnolence in the all-brexpiprazole subgroup.[1]

Looking at adverse events potentially related to sedation or somnolence over 24 weeks, the incidence of orthostatic hypotension was 5.5 percent in the all-brexpiprazole subgroup and 5.2 percent in the placebo lead-in subgroup. For falls, it was 3.7 percent in the all-brexpiprazole subgroup and 1.0 percent in the placebo lead-in subgroup. And overall, the analysis noted no specific safety concerns from the 24-week analyses of brexpiprazole treatment.[1]

Before we wrap up, 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. Grossberg:
Now that we've heard that Important Safety Information, Marc, let's bring all of this together. How would you translate this data for clinicians who are managing patients with agitation associated with dementia due to Alzheimer's disease?

Dr. Agronin:
I think the key takeaway is this: when we're treating agitation associated with dementia due to Alzheimer's disease the treatment goal should always be reducing agitation symptoms while minimizing safety risk and maintaining the patient's alertness and engagement—not masking symptoms.[6,7]

These post-hoc analysis results report low rates of sedation and somnolence across multiple Phase Three trials and a pooled safety analysis of brexpiprazole. The adverse events that occurred were mostly mild and rarely led to discontinuation, with no discontinuation due to sedation. Adverse events that are potentially related to sedation, like falls and orthostatic hypotension, also had a low incidence in the trials, confirming long-term tolerability.[1]

These findings may help inform treatment decision-making when considering the risk for, and impact of, sedation and somnolence in this population. While our goal is to help the patient reduce the distress and burden of agitation, we want to do so without compromising their safety or ability to function and engage with their loved ones, caregivers, and environment.[1,6,7]

Dr. Grossberg:
Well, as those final insights bring us to the end of today's program, I'd like to thank Dr. Marc Agronin for joining me today. We've covered a lot of ground, Marc, and I appreciate your insights on the impact of sedation and somnolence in managing agitation associated with dementia due to Alzheimer's disease.

Dr. Agronin:
Well, thank you for a thoughtful discussion, George. I'd also like to thank Dr. George Grossberg for sharing his clinical expertise on this important topic.

Dr. Grossberg:
My pleasure. Please stay tuned to hear additional important safety information for brexpiprazole.

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** (≥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 Close
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July 2026 US.REX.X.26.00002