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Treating Agitation Without Sedation

Announcer:
You're listening to ReachMD. This program, titled "Treating Agitation Without Sedation," is sponsored by Otsuka and Lundbeck. And now, here's Dr. Jared Stroud, Dr. Clay Jackson, and Dr. Anton Porsteinsson.

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

Dr. Porsteinsson:
Welcome to ReachMD. I'm Dr. Anton Thorstensson, and I'm a professor of psychiatry, neurology, neuroscience, and medicine at University of Rochester in Rochester, New York. I'm joined by my colleagues, Dr. Clay Jackson and Dr. Jared Stroud, and today we'll be discussing sedation and its relevance when managing and treating agitation associated with dementia due to Alzheimer's disease.

Dr. Stroud:
I'm Dr. Jared Stroud, and I'm a clinical assistant professor of geriatrics and internal medicine at The Ohio State University Wexner Medical Center in Columbus, Ohio.

Dr. Jackson:
And I'm Dr. Clay Jackson, clinical assistant professor of family medicine and psychiatry at the University of Tennessee College of Medicine in Memphis, Tennessee. I'm excited to be part of this discussion. Before we begin, let me put the importance of sedation into perspective: psychotropic medications are often used off-label to treat agitation, but with some psychotropic medications as many as one in four patients treated may experience persistent sedation.[1-3]

Dr. Porsteinsson:
That's right, Dr. Jackson. Sedation is more common than people may think and is often used as a proxy for efficacy. That's why these conversations are so important—so we can raise awareness and help navigate agitation treatment in an effective, patient-centered way.[2-5]

Taking a step back, though, agitation itself can be underrecognized. Many caregivers, and even clinicians, tend to associate agitation as an inherent part of Alzheimer's dementia and primarily with physically aggressive behaviors, however agitation can present in a variety of ways, including restlessness, pacing, repetitive behaviors, verbal outbursts, or physically non-aggressive actions.[6-8]

So, symptoms of agitation are a collection of behaviors that can vary widely in presentation and severity depending on the patient. And that variability is important to recognize and understand because these behaviors take a real toll on caregivers.[8,9]

When you look at the data, agitated patients received more care from a nonprofessional caregiver per week, needed more healthcare provider consultations in a year, and had higher all-cause healthcare costs per year compared to non-agitated patients.[9,10]

And for the patients, agitation has been associated with a number of negative consequences like accelerated disease progression, functional decline, decreased quality of life, and more medical issues—things like falls, fractures, or infections—which can further complicate care. On top of that, data has shown these patients were more likely to require additional medications, experienced higher rates of hospitalization or institutionalization, and ultimately had a higher risk of earlier mortality.[9,11-16]

Dr. Jackson:
I couldn't agree more, Dr. Porsteinsson. It's important that both the caregivers and clinical community recognize a broad range of

agitation symptoms, because earlier recognition may help improve patient outcomes and minimize distress for both the patient and the caregiver. And building on that, it's important to understand our current treatment approach—so let's talk about that. Overall, the primary treatment goal should be reducing agitation symptoms while maintaining alertness, engagement, and function.[5,17]

Nonpharmacological intervention is the first-line treatment approach for agitation, because agitation can be influenced by external triggers like environment, stress, or pain.[2,18]

But if nonpharmacological measures are ineffective, or if symptoms are more severe, dangerous, or particularly distressing, pharmacologic treatment may be considered.[2,18]

Recall we mentioned psychotropic medications have been used off-label to treat agitation. This includes agents like antipsychotics, antidepressants, and anxiolytics, but psychotropic agents are defined as any drug that affects brain activities associated with mental processes or behaviors.[1,2]

And while these can help manage symptoms, they also come with a range of potential adverse effects, such as movement-related issues, orthostatic hypotension, worsening cognition, and an increased risk of falls and fractures. And one of the most important to keep in mind is sedation.19-22 It's something we see frequently with these medications and can be misinterpreted as improvement. But sedation isn't treating agitation—it's an adverse effect.[2,5,22,23]

Announcer:
For those just tuning in, you're listening to ReachMD. Today, Drs. Jared Stroud, Clay Jackson, and Anton Porsteinsson are discussing sedation in the treatment of agitation associated with dementia due to Alzheimer's disease.

Dr. Stroud:
You're exactly right, Dr. Jackson—while a sedated patient may appear calmer, we have to ask whether we're truly improving their agitation symptoms or simply suppressing them at the expense of their function and quality of life.[17,23]
Now, let's talk about what's actually driving these behaviors beneath the surface and why treatment approaches should move beyond sedation. At its core, sedation is a calm, subdued state with reduced alertness and may present as excessive sleepiness or drowsiness, decreased activity or withdrawal, and impaired cognition and coordination.[24]

Sedation can be an intended or unintended effect of psychotropic agents, and the degree of sedation is dose- and duration-dependent. Historically, sedation was leveraged to help manage agitation behaviors, but now clinicians better understand the risks that come with sedation. Despite those risks, about 25 percent of patients treated with psychotropic medications experienced persistent sedation.[2-5,24]

The challenge is that while sedation might make agitation appear improved, it can come at a cost. Patients may become less alert during the day, withdrawn from activities, and experience declines in both physical functioning and overall quality of life.[2,22,25] Sedation has also been associated with an increased risk of injury-causing falls, as well as a higher risk of cognitive decline compared to patients not taking these medications.[26,27] It can also further impair a patient's ability to perform daily tasks and, in some cases, has been linked to an increased risk of mortality.[2,22,25]

And because many of the risks of sedation overlap with the adverse outcomes associated with agitation, sedation may actually compound—rather than alleviate—the consequences of agitation.[2,9,11-16,22,25]

Dr. Porsteinsson:
Yes, those limitations make it clear that simply dampening symptoms with sedation doesn't address what's actually driving agitation. And as we move toward more effective and targeted approaches, it's important to understand the underlying neurobiology—specifically, the brain changes that contribute to agitation in the first place. Agitation may reflect underlying changes in the brain's chemistry—an imbalance between the parts of the brain that regulate emotion and those responsible for executive control.[28,29]

Patients may have impaired function from the prefrontal cortex, or PFC, which plays a key role in decision-making and impulse control, along with increased activity in the amygdala, the region associated with emotional drive.[28,30,31]

This imbalance is thought to be driven, at least in part, by disruptions across key neurotransmitter systems—specifically increased norepinephrine activity, decreased serotonin activity, and dysregulated dopamine signaling.[28,32-34]

Together, those changes suggest that broader monoaminergic dysfunction may play an important role in the development of agitation in patients with dementia due to Alzheimer's disease.[28]

So, with all that being said, when we talk about pharmacological treatments for agitation, the goal is to restore balance in the monoaminergic system—helping rebalance executive control and emotional overdrive while preserving the patient's alertness and overall function.[4,5,28]

Dr. Jackson:
Talking about the risk of sedation with psychotropic medications often raises an important question—are all psychotropic medications equally likely to cause sedation? And the answer is no; they can differ quite a bit.

There are FDA-approved treatments for agitation in Alzheimer's dementia, including one drug classified as an atypical antipsychotic. But as I mentioned before, clinicians often use a range of psychotropic agents off-label to manage agitation.[1,28] Many of these medications interact with multiple neurotransmitter systems, including monoaminergic pathways, which may help address symptoms of agitation in patients with Alzheimer's dementia.[1,2,4,35]

But although these medications are often grouped together, they are not all the same. Several factors help determine how a medication performs in practice, including receptor affinity, potency, dose, and duration of treatment. These differences can influence not only the potential benefit for agitation, but also the likelihood of adverse effects.[2,4]

For example, medications within the same therapeutic class do not necessarily bind to the same receptors—or bind with the same degree of affinity. As a result, two atypical antipsychotics may have different pharmacologic profiles, which can contribute to differences in their clinical effects and side-effect profiles.[4]

One important clinical consequence of these receptor-binding differences is the propensity to induce sedation. Sedation is thought to be driven primarily by activity at histamine receptor, H_1.[4]

Because medications vary in their affinity for H_1 receptors, they may also differ in their potential to cause sedation. In general, agents with greater H_1 receptor affinity may be more likely to cause sedation, whereas those with lower H_1 receptor affinity may potentially pose a lower sedation risk.[4]

So the key takeaway is that psychotropic agents are not interchangeable when it comes to sedation, and differences in receptor-binding profiles may be an important consideration when balancing the treatment of agitation with the potential for sedative effects.[4]

Dr. Stroud:
That's a great summary, Dr. Jackson. And taking a step back, these are the things that clinicians should understand and consider when choosing a treatment. Because our goal is to treat agitation while also minimizing any unintended adverse effects and maintaining alertness.[5,17]

As Dr. Jackson mentioned earlier, certain psychotropic medications have been used to manage agitation through sedative effects; however, when sedation is used primarily for behavioral control or staff convenience, it may be considered a form of chemical restraint.[1,2,36]

Current guidelines from the American Psychiatric Association, or APA, and the Centers for Medicare and Medicaid Services, or CMS, recommend a stepwise, individualized approach to managing agitation: identify underlying causes and patient-specific triggers, prioritize nonpharmacologic interventions, and use psychotropic medications only when clearly indicated and at the lowest effective dose.[2,36] These recommendations are intended to help mitigate the risk of sedation, and prevent the use of sedation for convenience or behavioral control in vulnerable patient populations.

Remember, the goal of treatment is to reduce symptoms of agitation while maintaining patient engagement, alertness, and overall function.[5,17]

When medication is needed though, there are FDA-approved treatments for agitation in patients with Alzheimer's dementia, including one drug classified as an atypical antipsychotic. However, clinicians may prescribe other unapproved medications.[1,28]

Dr. Jackson:
Now, we're just about at time for today, but before we come to a close, do you have any key takeaways you'd like to leave with our listeners, Dr. Stroud?

Dr. Stroud:
Yes, I want to reiterate that even though agitation can happen with dementia due to Alzheimer's disease, it's also a separate and

treatable condition in its own right.[18] And when it comes to pharmacological interventions, sedation may make patients appear calmer, but it doesn't address what's really driving the agitation and should not be seen as a sign of efficacy.[2,5,23,28] In many cases, it can actually worsen outcomes.[25-27] Our goal should be to treat agitation thoughtfully, focusing not just on reducing symptoms, but on preserving a patient's alertness, function, and overall engagement.[5,28]

Dr. Porsteinsson:
Agitation associated with dementia due to Alzheimer's disease is often underrecognized.[7] It has a wide range of behavioral presentations, and it's associated with serious consequences, like accelerated disease progression, increased risk of falls, increased healthcare utilization, and higher mortality.[7-14] So effective treatment requires moving beyond symptom suppression and toward approaches that address the underlying drivers.[28] Dr. Jackson—what final thoughts would you like to share?

Dr. Jackson:
I think the most important takeaway is that managing agitation really comes down to taking an individualized approach.[2,36] When medications are needed, it's critical to recognize that not all options are created equal—differences in receptor activity, dosing, and duration can all impact both effectiveness and the risk of side effects like sedation. And keeping that in mind when selecting a medication can contribute to ensuring a patient's agitation is treated while maintaining alertness.[2,4]
So ultimately, it's about making more intentional treatment decisions to manage agitation effectively while minimizing those risks and preserving the patient's quality of life.[4,5,28]
Lastly, there are FDA-approved treatments for agitation in Alzheimer's dementia, including one drug classified as an atypical antipsychotic.[1,28]

And with those final thoughts in mind, I'd like to thank Drs. Jared Stroud and Anton Porsteinsson for sharing their insights on distinguishing sedation from therapeutic efficacy in agitation associated with dementia due to Alzheimer's disease. Thank you both for joining me.

Dr. Stroud:
Thanks Dr. Jackson. I've really enjoyed our conversation today. And thanks as well for sharing your perspective on this important topic.

Dr. Porsteinsson:
I agree, it's been a great conversation. Thanks for having me!

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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