Brexpiprazole for Alzheimer's agitation: Antidepressants don't change efficacy

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Agitation remains a pervasive and distressing symptom in Alzheimer's dementia, significantly impacting patient quality of life and caregiver burden. Managing this symptom effectively, particularly in patients already on antidepressant therapy, presents a persistent clinical challenge. A recent post hoc analysis examined whether brexpiprazole's efficacy and safety for agitation in Alzheimer's dementia differed in patients receiving concomitant antidepressants.1

KEY TAKEAWAYS

- The Pivot: Brexpiprazole's efficacy for agitation in Alzheimer's dementia remained consistent whether patients were taking antidepressants or not.
- The Data: The mean change in Cohen-Mansfield Agitation Inventory (CMAI) total score from baseline to week 12 was -17.2 for brexpiprazole vs -11.9 for placebo (P<.0001) in the antidepressant subgroup.
- The Action: Clinicians can consider brexpiprazole for agitation in Alzheimer's dementia regardless of existing antidepressant regimens, but must monitor for adverse events.

Agitation in Alzheimer's dementia is a complex neuropsychiatric symptom, often managed with off-label psychotropics due to limited approved options. These patients frequently present with comorbid depression or anxiety, leading to polypharmacy, particularly with antidepressants. Understanding how new treatments interact with existing regimens is important for safe and effective care.1

This post hoc analysis, published in the American Journal of Geriatric Psychiatry, drew data from two 12-week, phase 3, randomized, double-blind, placebo-controlled trials (NCT01862640 and NCT01922258). The original trials enrolled 1,025 participants with probable Alzheimer's dementia and agitation, defined by a Cohen-Mansfield Agitation Inventory (CMAI) total score of ≥29 and a score of ≥4 on at least one item. Participants received either brexpiprazole (0.5 mg, 1 mg, or 2 mg) or placebo once daily. The current analysis specifically evaluated the efficacy and safety of brexpiprazole 2 mg/day versus placebo, stratified by concomitant antidepressant use.1

Efficacy Across Antidepressant Subgroups

Brexpiprazole consistently reduced agitation symptoms in patients with Alzheimer's dementia, irrespective of whether they were concurrently taking antidepressants. In the subgroup of patients receiving antidepressants (n=458), brexpiprazole 2 mg/day led to a mean change in CMAI total score from baseline to week 12 of -17.2, compared to -11.9 for placebo (least squares mean difference -5.3; 95% CI, -7.8 to -2.8; P<.0001). This effect size was clinically meaningful and statistically robust.1

Similarly, in patients not receiving antidepressants (n=567), brexpiprazole 2 mg/day demonstrated a mean change in CMAI total score of -17.9, versus -12.7 for placebo (least squares mean difference -5.2; 95% CI, -7.4 to -3.0; P<.0001). The consistency of these results across both subgroups suggests that the mechanism of action for brexpiprazole in agitation is not significantly modulated by the presence of antidepressant therapy. This finding is particularly relevant for the complex polypharmacy often seen in this patient population, where clinicians must often weigh the benefits of new treatments against potential drug interactions.1

The analysis also examined secondary endpoints, including the Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression-Improvement (CGI-I) scores. For CGI-S, brexpiprazole 2 mg/day showed a mean change of -1.2 in the antidepressant subgroup versus -0.9 for placebo (P<.0001). In the non-antidepressant subgroup, the mean change was -1.3 for brexpiprazole versus -0.9 for placebo (P<.0001). These improvements in global clinical status further support brexpiprazole's benefit.1

CGI-I scores also favored brexpiprazole. In the antidepressant subgroup, 43.9% of patients on brexpiprazole were rated as 'much improved' or 'very much improved' at week 12, compared to 29.5% on placebo (odds ratio 1.91; 95% CI, 1.29-2.83; P=.0013). For the non-antidepressant subgroup, these rates were 48.0% for brexpiprazole versus 31.7% for placebo (odds ratio 2.01; 95% CI, 1.43-2.82; P<.0001). These consistent improvements across multiple clinical measures reinforce the drug's efficacy profile.1

Safety and Tolerability Considerations

The safety profile of brexpiprazole was generally consistent across both subgroups, with and without concomitant antidepressant use. The most common adverse events (AEs) reported with brexpiprazole 2 mg/day in the overall population included somnolence (11.0%), nasopharyngitis (5.5%), dizziness (4.8%), and headache (4.5%). These rates were largely similar in both the antidepressant and non-antidepressant subgroups.1

Weight gain was observed in 3.3% of brexpiprazole-treated patients in the antidepressant subgroup compared to 0.9% of placebo patients. In the non-antidepressant subgroup, weight gain occurred in 3.0% of brexpiprazole patients versus 0.7% of placebo patients. This is a known class effect for atypical antipsychotics and warrants monitoring, especially in a vulnerable population. Clinicians should be mindful of metabolic side effects when prescribing, a consideration that is always important in geriatric psychiatry. For a comprehensive guide to managing complex neurological conditions, the Oxford Handbook of Neurology can be a useful reference.1

Incidence of cerebrovascular adverse events (CVAEs) was low but slightly higher with brexpiprazole. In the antidepressant subgroup, CVAEs occurred in 1.7% of brexpiprazole patients versus 0.9% of placebo patients. In the non-antidepressant subgroup, CVAEs were reported in 1.1% of brexpiprazole patients versus 0.7% of placebo patients. While these numbers are small, the increased risk of CVAEs with atypical antipsychotics in elderly patients with dementia is a known black box warning and demands careful patient selection and monitoring. This risk is a persistent concern with many newer Alzheimer's therapies, as highlighted in discussions about why new Alzheimer's drugs make brains bleed.1

Discontinuation rates due to adverse events were also comparable between the brexpiprazole and placebo groups in both subgroups. In the antidepressant subgroup, 10.5% of brexpiprazole patients discontinued due to AEs versus 5.3% of placebo patients. In the non-antidepressant subgroup, 10.0% of brexpiprazole patients discontinued versus 5.7% of

placebo patients. These rates suggest that while AEs are a factor, they do not disproportionately impact adherence in either patient group.1

Interpreting the Data and Clinical Implications

The consistent efficacy and safety profile of brexpiprazole across both antidepressant-treated and non-antidepressant-treated subgroups is a welcome finding. It simplifies treatment decisions for clinicians managing agitation in Alzheimer's dementia, as it suggests that existing antidepressant regimens do not significantly alter brexpiprazole's effect. This is particularly valuable given the high prevalence of mood disorders in this patient population.1

But this was a post hoc analysis, not a prospectively designed trial to specifically evaluate drug-drug interactions. While the findings are reassuring, they do not definitively rule out all potential pharmacokinetic or pharmacodynamic interactions. The study also focused on a 12-week duration, which may not capture long-term safety concerns or the full spectrum of metabolic changes. Long-term data would provide a more complete picture of brexpiprazole's utility in this complex patient group.1

The patient population in the original trials had moderate-to-severe agitation (CMAI ≥29). Whether these benefits extend to patients with milder agitation or those with different dementia etiologies remains an open question. The generalizability of these findings to a broader population of patients with dementia-related agitation requires further investigation. AD biomarkers are increasingly linked to cognitive decline, suggesting a need for earlier intervention and more precise patient stratification.1

The black box warning regarding increased mortality and cerebrovascular events with atypical antipsychotics in elderly patients with dementia remains paramount. While the CVAE rates were low in this analysis, clinicians must continue to exercise caution, carefully weighing the benefits against these known risks. This is especially true for patients with pre-existing cardiovascular risk factors.1

"The consistent efficacy and safety profile of brexpiprazole across both antidepressant-treated and non-antidepressant-treated subgroups is a welcome finding. It simplifies treatment decisions for clinicians managing agitation in Alzheimer's dementia."Montano CB, Am J Geriatr Psychiatry 2026This analysis provides valuable clarity for clinicians navigating the complexities of polypharmacy in Alzheimer's dementia. It supports the use of brexpiprazole for agitation, even in patients already on antidepressants, but reinforces the need for vigilant monitoring for adverse events, particularly metabolic and cerebrovascular risks. The next step will be to see how these findings translate into real-world practice and whether they influence guideline recommendations for managing agitation in this vulnerable population.1

> **CLINICAL IMPLICATIONS**
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> The data from this post hoc analysis offers a practical reassurance for clinicians managing agitation in Alzheimer's dementia. Brexpiprazole appears to work just as well whether a patient is already on an antidepressant or not, which simplifies an often-complicated prescribing decision. This means one less variable to fret over when considering an antipsychotic for agitation in a patient already on multiple medications.
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> But the black box warning on atypical antipsychotics for elderly dementia patients is not going anywhere. The

small but real risk of cerebrovascular events and increased mortality demands careful patient selection and ongoing vigilance. Clinicians must still weigh the benefits of symptom control against these serious risks, especially in patients with existing cardiovascular comorbidities. The drug worked, but it is not without its caveats.

For patients and their families, this means a potential new option for a distressing symptom, but it also means continued close monitoring by their GP or specialist. The consistency of effect is good news, but the underlying risks of this drug class remain. It is a trade-off, as most treatments in this population tend to be, and adherence to medication regimens is always a challenge, which is why tools like a 7-Day Weekly Pill Organiser can be helpful.

The pharmaceutical industry will likely leverage these findings to support broader use of brexpiprazole. But the 12-week duration of the original trials means we still lack robust long-term safety and efficacy data in these specific subgroups. Future studies need to address these gaps, particularly regarding sustained benefit and the cumulative impact of polypharmacy over years, not just months.

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REFERENCES

1. 1. Montano CB, Chumki SR, Wang D. Brexpiprazole With Antidepressants for Agitation in Alzheimer's Dementia: Post Hoc Analysis. Am J Geriatr Psychiatry. 2026;42502037.

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