doi: 10.30934/kusbed.1617807 **e-ISSN:** 2149-8571

Kocaeli Üniversitesi Sağlık Bilimleri Dergisi

Olgu Sunumu / Case Report

http://dergipark.org.tr/kusbed

EXPERIENCES WITH BREXPIPRAZOLE IN THE MANAGEMENT OF AGITATION DUE TO DEMENTIA IN A UNIVERSTIY CLINIC: A CASE SERIES

Aila Gareayaghi[*1], Ezgi Şişman[2], Mert Türksoy[1], Aslıhan Polat[1]

[1]Kocaeli University, Faculty of Medicine, Department of Psychiatry, Kocaeli, Türkiye; [2]Kocaeli City Hospital, Department of Psychiatry, Kocaeli, Türkiye.

ORCID ID: Aila Gareayaghi: 0000-0001-8453-0321; Ezgi Şişman: 0000-0001-9496-991X; Mert Türksoy: 0009-0006-4989-0528; Aslıhan Polat: 0000-0001-9649-8701

***Sorumlu Yazar / Corresponding Author:** Aila Gareayaghi, **e-posta / e-mail:** aylingare@gmail.com

Geliş Tarihi / Received: 11.01.2025 **Kabul Tarihi / Accepted:** 19.02.2025 **Yayım Tarihi / Published:** 21.03.2025

Abstract

This case series focuses on the use of brexpiprazole in the management of agitation associated with dementia. Dementia is characterized by cognitive and functional impairments, as well as behavioral symptoms such as agitation, anxiety, and depression. A multidisciplinary approach is required for treatment, with pharmacological interventions carefully evaluated.

The effects of brexpiprazole were examined in patients with three different types of dementia (vascular, frontotemporal, and Alzheimer's). Treatment was administered in doses ranging from 0.5 to 2 mg/day, and a reduction in agitation symptoms was observed in all cases. In Case 1 (vascular dementia), agitation markedly decreased, while in Case 2 (frontotemporal dementia), the patient's social and daily functionality improved. In Case 3 (Alzheimer's dementia), sleep disturbances were alleviated, although dizziness and falls necessitated dose reduction.

The findings suggest that brexpiprazole may be an effective option for treating agitation associated with dementia. The drug's multi-receptor effects contribute to symptom improvement, while its side effects may vary among individuals. These results support the use of brexpiprazole as part of personalized treatment plans.

Keywords: *Dementia, Alzheimer's disease, agitation, brexipiprazole.*

Introduction

Dementia is a syndrome characterized by a progressive decline in cognitive functions such as memory, thinking, reasoning, and problem-solving, significantly impacting daily activities and quality of life. It often includes challenges related to mood, behavior, and personality changes, as well as difficulties with language, attention, and visual perception.[1] The most common cause of dementia, Alzheimer's disease, accounts for 60-70% of cases. While age is the strongest risk factor, dementia is not a normal part of aging, and many individuals can live to advanced ages without exhibiting symptoms of dementia. Other risk factors include genetic predisposition, cardiovascular issues, smoking, and physical inactivity. Although no structured treatment exists for dementia, early diagnosis, pharmacological treatments that slow progression, supportive care, regular exercise, a healthy diet, and social interaction can improve the process and reduce the risk of progression.[2]
The behavioral and psychological symptoms of dementia include agitation, depression, apathy, repetitive questioning, psychosis, aggression, sleep disturbances, wandering, and various inappropriate behaviors. These symptoms affect almost all dementia patients during the course of the disease and are among the most complex, stressful, and costly aspects of care.[3] Considering the wide range of symptoms and the additional comorbidities expected in advanced age, finding a single algorithm applicable to all patients is challenging, necessitating individualized approaches tailored to each patient. In 2016, the American Psychiatric Association (APA) published a 15-point guideline on the pharmacological management of patients with agitation due to dementia. According to this guideline, patients' symptoms should be carefully evaluated for pain and other modifiable factors. Treatment plans should be comprehensive, incorporating person-centered and non-pharmacological interventions. Antipsychotic medications should only be considered in cases of severe symptoms, and the effectiveness of non-pharmacological interventions should be assessed prior to use. Treatment should start with low doses, maintain the lowest effective dose, and monitor for side effects. If no response is observed after a 4-week trial, the medication should be discontinued. For effective treatments, medication should be tapered and discontinued within four months. Agents such as haloperidol should not be a first-line choice unless delirium is present, and long-acting injections should only be used in chronic psychotic disorders. Throughout the process, risks and benefits should be discussed with the patient, their family, and caregivers.[4]
In 2015, the U.S. Food and Drug Administration (FDA) approved brexpiprazole for adjunctive treatment of schizophrenia and depression, and in 2023, it was approved for the treatment of agitation associated with Alzheimer's dementia.[5] Although antipsychotic use is generally avoided in dementia-related agitation, brexpiprazole has emerged as a promising option. Brexpiprazole acts as an antagonist at noradrenergic α1B and α2C receptors and serotonergic 5-HT2A receptors, and as a partial agonist at 5-HT1A and dopaminergic D2 receptors. It affects various receptors associated with agitation, aggression, impulsivity, arousal, and psychosis in the brain. Additionally, brexpiprazole shows moderate binding affinity for histamine H1 receptors, suggesting that its effects on agitation are less likely to stem from sedation.[6] Furthermore, as a partial dopamine D2 agonist, brexpiprazole is not expected to increase the risk of drug-induced parkinsonism.[7]

Case 1

A 64-year-old married female, a primary school graduate and housewife, was hospitalized in the neurology department with a diagnosis of vascular dementia. She exhibited behaviors such as wanting to constantly get out of bed, pulling at her hands and chin, restlessness, and a desire to jump out of the window. According to her relatives, she behaved like a mischievous child, was constantly restless, and resisted instructions from her caregiver. Memantine hydrochloride 5 mg/day was initiated for dementia management by neurology, but the patient refused the medication, claiming it increased her sense of restlessness.
The patient had a history of major depressive disorder and psychiatric hospitalizations. Her psychiatric treatment, arranged 10 days before hospitalization, included quetiapine IR 200 mg/day, quetiapine XR 150 mg/day, and citalopram 20 mg/day. She was challenging to manage at home due to persistent self-harm ideation, requiring her caregiver's constant presence. Other comorbidities included type 2 diabetes mellitus, obstructive sleep apnea syndrome, cataracts, and hypertension, all managed with regular follow-ups.
Mental status examination revealed inappropriate responses to questions, continuous anxiety, and agitation during the interview. Given her history of dementia and agitation, brexpiprazole 0.5 mg/day was added to her treatment. After one week, no side effects were reported, and the dose was increased to 1 mg/day for greater efficacy. However, after two weeks, it was found that she had not increased the dose as recommended, and her anxiety and agitation symptoms persisted. She was instructed to follow the dosing schedule and was re-evaluated a month later. Following three weeks of brexpiprazole 0.5 mg/day and one month at 1 mg/day, her caregivers reported a marked reduction in agitation. The patient expressed a willingness to assist with household chores and was noted to be more cooperative.

Case 2

A 65-year-old widow, a primary school graduate and housewife, was evaluated in the psychiatry outpatient clinic. She had been followed for depressive symptoms for three years and was diagnosed with frontotemporal dementia. Two years before her psychiatric follow-up, her daughter had died by hanging, leading to symptoms of depressed mood, lack of interest, insomnia, fatigue, and suicidal thoughts.
Her psychiatric treatment was adjusted to escitalopram 20 mg/day and risperidone 1 mg/day, which provided partial benefit. Later, she was diagnosed with frontotemporal dementia, and her neurological treatment was arranged as ginkgo biloba 80 mg/day and rivastigmine patch 4.6 mg/day. At the clinic, she presented with agitation, reluctance to leave the house, avoidance of tasks, severe anxiety, restlessness, and a compulsion to wander around the house. Due to the limited effectiveness of her current treatments and the extrapyramidal symptoms (EPS) caused by risperidone, it was discontinued, and brexpiprazole at a dosage of 0.5 mg per day was started. After two weeks, as no side effects were observed, the dose was increased to 1 mg/day. Follow-up revealed improvements in her willingness to leave the house, reduced affective flattening, and increased participation in daily activities. Her treatment was maintained at a dosage of 2 mg per day, with no reported side effects and notable improvement in her symptoms.

Case 3

An 84-year-old illiterate widow diagnosed with Alzheimer's disease presented with complaints of insomnia. She reported sleeping only four hours at night, with no daytime sleep, and often followed her caregiver around the house. She experienced frequent crying episodes and repetitive, ruminative conversations about the future.

Previous treatment included quetiapine IR 200 mg/day, escitalopram 10 mg/day, and ginkgo biloba 80 mg/day. In our clinic, she exhibited prominent agitation, difficulty expressing herself, and persistent insomnia. Quetiapine IR was increased to 300 mg/day and scheduled for evening use. Laboratory tests showed a glomerular filtration rate of 19 mL/min and creatinine of 2.2 mg/dL, indicating renal insufficiency. Escitalopram was adjusted to 5 mg/day, and brexpiprazole 0.5 mg/day was added.

After two weeks, brexpiprazole was increased to 1 mg/day. Follow-up showed reduced crying and agitation, along with some improvement in insomnia. However, the patient began experiencing dizziness, falls, and difficulty standing after using the toilet. These symptoms were associated with brexpiprazole 1 mg/day, and at the patient's and caregivers' request, the dose was reduced to 0.5 mg/day. At this dose, her dizziness and fall episodes resolved, and the treatment was continued without further issues.

The summary of the cases is given in Table 1.

Table 1. Summary of the cases

Case	Diagnosis	Complaints	Treatment	Side effects
Case 1	Vascular dementia	Restlessness, a constant urge to walk, and self-harming behavior such as pulling at the hands and face	Brexpiprazole 1 mg/day, quetiapine IR 200 mg/day, quetiapine XR 150 mg/day, citalopram 20 mg/day	None
Case 2	Frontotemporal dementia	agitation, lack of motivation, and inability to stay still	Brexpiprazole 2 mg/day, escitalopram 20 mg/day, ginkgo biloba 80 mg/day, rivastigmine patch 4.6 mg/day	None
Case 3	Alzheimer's dementia	Insomnia, constant crying, anxiety, and inability to stay still	Brexpiprazole 0.5 mg/day, quetiapine IR 300 mg/day, escitalopram 5 mg/day, ginkgo biloba 80 mg/day	Dizziness, fall

Discussion

Dementia leads to cognitive and functional losses for the patient while imposing physical, emotional, and financial burdens on family members. Additionally, the behavioral and psychological symptoms of the patient can further complicate caregiving for family members, potentially leading to feelings of burnout. The management of agitation caused by dementia often carries specific pharmacological side effects, which is why guidelines generally recommend delaying their use.[4] A study reported that risperidone was the most effective neuroleptic drug for dementia-related agitation, with its rapid onset of action enhancing its benefits, although its tolerability was poor. Gabapentin was found to be the best-tolerated medication, but its effectiveness was limited. In terms of ease of use, citalopram was highlighted; however, it is less commonly preferred due to its delayed onset of action.[8]

Brexpiprazole is an antagonist/partial agonist with multiple effects on the serotonin, dopamine, and norepinephrine systems and was approved by the FDA in 2023 for the treatment of agitation associated with Alzheimer's disease (AD).[5] It exerts synergistic effects in calming the hyperactivity of agitation pathways in AD through mechanisms such as partial agonism at dopamine D2 receptors, partial agonism at 5-HT1A receptors, antagonism at 5-HT2A receptors, and blockade of α1- and α2-adrenergic receptors. Brexpiprazole reduces dopamine release from the ventral tegmental area (VTA) triggered by amygdala activation, improving the thalamic filtering of emotional information. Additionally, it suppresses norepinephrine-induced arousal by blocking α1- and α2-adrenergic receptors. Within the serotonergic system, brexpiprazole decreases excitatory signals via antagonism at 5-HT2A receptors and increases inhibitory signals through partial agonism at 5-HT1A receptors. These various effects help decrease both motor and emotional agitation arising from limbic and cortical sources. Brexpiprazole has long been approved for the treatment of schizophrenia and depression, and its use at lower doses for AD-related agitation is considered a safer option. These effects are thought to arise from the drug's ability to act simultaneously on multiple mechanisms.[9]

Studies have shown that the use of brexpiprazole provides a significant reduction in the total score of the Cohen-Mansfield Agitation Inventory (CMAI) compared to placebo. It has been reported that patients experienced a reduction in agitation symptoms, leading to clinically meaningful improvements. Improvement scores were observed as 3.7 with brexpiprazole at 1 mg/day and 7.2 with 2 mg/day.[10] In our cases, it was observed that all patients, including Case 3 who discontinued the treatment, benefited to varying degrees. Notably, there was a reduction in agitation complaints, which positively impacted both the patients and their caregivers.

The development of extrapyramidal side effects associated with antipsychotic use in dementia patients is a concerning issue and often leads to the avoidance of such medications. However, according to the literature, these side effects are very rare with brexpiprazole.[7] Reported side effects of brexpiprazole include somnolence, dizziness, diarrhea, falls, akathisia, and, rarely, extrapyramidal symptoms. The drug is generally well tolerated, and the rate of discontinuation is similar to that of a placebo.[6] In our cases, dizziness and falls led to treatment discontinuation in Case 3. In contrast, no side effects associated with the medication were reported in Cases 1 and 2. When the literature data presented and the patients monitored in our clinic are evaluated together, the potential efficacy of brexpiprazole in treating agitation associated with dementia becomes clear. Positive outcomes such as reductions in agitation and anxiety symptoms, improvements in daily functionality, and relief of caregiver burden have been observed in the cases. However, it is also understood that treatment-related side effects may vary individually, particularly with the contribution of advanced age and comorbid conditions. Compared to the reported efficacy and side effect profiles in the literature, this case series reaffirms the need for personalized approaches in the application of brexpiprazole. Careful monitoring of both clinical benefits and side effects will enable safer and more effective use of this drug in

managing dementia-related agitation. These cases not only highlight the role of brexpiprazole in multidisciplinary treatment approaches but also underscore the importance of dynamic planning in individualized patient management.

Financial Support
The authors recieved no financial support for the research, authorship and/or publication of this article.

Authors' Contributions
A.G., E.Ş., A.P: Study idea; A.G., E.Ş., A.P: Design; M.T.: Daha collection; A.G., E.Ş., M.T., A.P: Analysis; A.G., E.Ş.: Literature review; A.G., A.P.: Writing; A.G., A.P: Critical review

References

1. Dementia. Accessed January 7, 2025. https://www.who.int/news-room/fact-sheets/detail/dementia
2. Dementias | National Institute of Neurological Disorders and Stroke. Accessed January 7, 2025. https://www.ninds.nih.gov/health-information/disorders/dementias
3. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ*. 2015;350:h369. doi:10.1136/BMJ.H369.
4. Reus VI, Fochtmann LJ, Eyler AE, et al. The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia. *Am J Psychiatry*. 2016;173(5):543-546. doi:10.1176/APPI.AJP.2015.173501.
5. FDA Approves First Drug to Treat Agitation Symptoms Associated with Dementia due to Alzheimer's Disease | FDA. Accessed January 7, 2025. https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-treat-agitation-symptoms-associated-dementia-due-alzheimers-disease
6. Lee D, Slomkowski M, Hefting N, et al. Brexpiprazole for the Treatment of Agitation in Alzheimer Dementia: A Randomized Clinical Trial. *JAMA Neurol*. 2023;80(12):1307. doi:10.1001/JAMANEUROL.2023.3810.
7. Hope J, Castle D, Keks NA. Brexpiprazole: a new leaf on the partial dopamine agonist branch. https://doi.org/101177/1039856217732473. 2017;26(1):92-94. doi:10.1177/1039856217732473.
8. Davies SJ, Burhan AM, Kim D, et al. Sequential drug treatment algorithm for agitation and aggression in Alzheimer's and mixed dementia. *Journal of Psychopharmacology*. 2018;32(5):509-523. doi:10.1177/0269881117744996.
9. Stahl SM. Stahl's Essential Psychopharmacology. *Cambridge University Press*; 2021. doi:10.1017/9781108975292.
10. Nakamura Y, Adachi J, Hirota N, et al. Brexpiprazole treatment for agitation in Alzheimer's dementia: A randomized study. *Alzheimer's & Dementia*. 2024;20(11):8002-8011. doi:10.1002/alz.14282.