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Case Report | Olgu Sunumu

EXPERIENCE WITH ADJUNCTIVE BREXPIPRAZOLE TREATMENT IN PATIENTS WITH TREATMENT-RESISTANT MAJOR DEPRESSIVE DISORDER AT A UNIVERSITY CLINIC: A CASE SERIES

BİR ÜNİVERSİTE KLİNİĞİNDE İZLENEN TEDAVİYE DİRENÇLİ MAJÖR DEPRESİF BOZUKLUK HASTALARINDA BREKSİPİPRAZOL EKLEME TEDAVİSİ DENEYİMİ: OLGU SERİSİ

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ABSTRACT

This case series aims to evaluate the efficacy and tolerability of brexpiprazole as an adjunctive treatment in patients with treatment-resistant major depressive disorder (TRD) at a university clinic. Nine cases diagnosed with TRD, defined as insufficient response to at least two antidepressant therapies, were included. Patients were treated with brexpiprazole (0.5–3 mg/day) in combination with ongoing antidepressants. Treatment responses were assessed based on improvements in depressive symptoms, functionality, and tolerability. Brexpiprazole addition resulted in significant symptomatic improvement in seven cases, with reductions in depressive symptoms such as anhedonia, guilt, and psychomotor agitation. Specific cases highlighted brexpiprazole's potential in managing complex conditions such as borderline personality disorder and post-traumatic stress disorder. Most patients experienced enhanced daily functionality and social interactions. Mild weight gain and transient dizziness were the only side effects reported, with no treatment discontinuation due to adverse effects. Brexpiprazole demonstrates efficacy and tolerability in managing TRD, particularly as part of a personalized treatment approach. These findings align with existing literature, underscoring brexpiprazole's role in improving outcomes in resistant and comorbid depressive syndromes. Further studies are needed to confirm these results in larger patient populations.

Keywords: Major depressive disorder, treatment resistent, brexpiprazole

ÖZ

Bu olgu serisi, bir üniversite kliniğinde tedaviye dirençli majör depresif bozukluk (TR-MDB) hastalarında breksipiprazolün ek tedavi olarak etkinliğini ve tolere edilebilirliğini değerlendirmeyi amaçlamaktadır. En az iki antidepresan tedavisine yetersiz yanıt veren TR-MDB tanılı dokuz hasta çalışmaya dahil edilmiştir. Hastalara, mevcut antidepresan tedavilerine ek olarak breksipiprazol (0.5–3 mg/gün) uygulanmıştır. Tedavi yanıtları, depresif semptomlarda iyileşme, işlevsellik artışı ve tolere edilebilirlik açısından değerlendirilmiştir. Breksipiprazol ek tedavisi, yedi vakada belirgin semptomatik iyileşme sağlamış, anhedoni, suçluluk ve psikomotor ajitasyon gibi depresif semptomların azalmasına katkıda bulunmuştur. Özellikle, breksipiprazolün borderline kişilik bozukluğu ve travma sonrası stres bozukluğu gibi karmaşık durumlarda da etkili olduğu gözlenmiştir. Çoğu hastada günlük işlevsellik ve sosyal etkileşimlerde artış rapor edilmiştir. Hafif kilo artışı ve geçici baş dönmesi dışında kayda değer bir yan etki görülmemiş, tedaviye bağlı bırakma olmamıştır. Breksipiprazol, TR-MDB'nin yönetiminde, özellikle bireyselleştirilmiş tedavi yaklaşımlarının bir parçası olarak etkili ve tolere edilebilir bir seçenek sunmaktadır. Bu bulgular, breksipiprazolün dirençli ve eşlik eden depresif sendromlarda sonuçları iyileştirmedeki rolünü desteklemekte olup, daha geniş hasta popülasyonlarında doğrulayıcı çalışmalar gereklidir.

Anahtar Kelimeler: Majör depresif bozukluk, tedavi direnci, breksipiprazol

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Introduction

Major Depressive Disorder (MDD) is a psychiatric condition characterized by persistent depressive mood, anhedonia (inability to experience pleasure), lack of energy, impaired concentration, feelings of guilt or worthlessness, and changes in sleep and appetite. According to the DSM-5, a diagnosis requires the presence of at least five of these symptoms for a minimum of two weeks, with one of them being either a depressed mood or anhedonia. If left untreated, MDD can persist for 6-12 months and lead to serious complications, including a high risk of suicide. Effective management of the disorder requires an interdisciplinary healthcare team approach and the inclusion of patient and family education.[1] According to the World Health Organization (WHO), MDD ranked third in the global disease burden in 2008 and is projected to rise to the top position by 2030.[2]

There is no universal consensus on the definition of treatment-resistant depression (TRD); however, it is generally described as the lack of response to two or more adequate antidepressant treatments.[3] In the literature, Thase and Rush proposed a classification system for TRD based on different stages. According to this system, Stage 0 represents the absence of any adequate antidepressant trial in terms of dose and duration. Stage 1 involves the failure of one antidepressant from a primary class, such as SSRIs, despite sufficient dose and duration. Stage 2 is defined by the failure of two antidepressants from different classes, such as an SSRI and a TCA. Stage 3 includes the failure of a tricyclic antidepressant (TCA) in addition to Stage 2. Stage 4 adds the failure of a monoamine oxidase inhibitor (MAOI), and Stage 5 includes the failure of bilateral electroconvulsive therapy (ECT) beyond Stage 4. Notably, this model does not incorporate mood stabilizers or antipsychotics in adjunctive treatments. However, a recent meta-analysis indicates that antipsychotics and mood stabilizers play a significant role in the management of TRD, demonstrating efficacy superior to placebo.[4]

Brexpiprazole has been approved by the U.S. Food and Drug Administration (FDA) since 2015 for use as an adjunctive treatment in treatment-resistant depression. According to the prescribing information, the starting dose is 0.5-1 mg/day, the recommended dose is 2 mg/day, and the maximum dose is 3 mg/day. A meta-analysis revealed that brexpiprazole treatment resulted in a significant improvement in Montgomery-Asberg Depression Rating Scale (MADRS) scores within the first week of initiation. From the second week onward, there was a statistically significant difference in response rates between treatment groups, and by the third week, a notable increase in remission rates was observed. These findings indicate that brexpiprazole effectively alleviates symptoms of Major Depressive Disorder (MDD) at an early stage.[5]

In this case series, we aimed to summarize the outcomes of brexpiprazole treatment applied in our clinic to patients with treatment-resistant depression who had received at least two different antidepressant treatments but did not achieve significant improvement in their depressive symptoms. To the best of our knowledge, no such case series has been reported following the introduction of brexpiprazole in our country. Therefore, through this case series, we aimed to contribute to the existing literature.

Case 1

A 39-year-old female patient, a primary school graduate, housewife, married, and mother of four, presented to the clinic nine years ago with complaints of irritability, unhappiness, inability to enjoy life, and frequent crying episodes. Her psychiatric symptoms were associated with her husband's extramarital affair and domestic violence, during which she had also attempted suicide. The patient did not benefit from previous interventions due to irregular medication use.

She was diagnosed with Major Depressive Disorder (MDD) in our clinic and treated with sertraline 50 mg/day, which was titrated to the maximum dose, but no sufficient response was achieved. Subsequently, fluoxetine was prescribed, but the patient discontinued it due to side effects. Duloxetine was started at 30 mg/day and increased to 60 mg/day, with alprazolam 1 mg/day added as an adjunct. However, since adequate improvement was not observed, duloxetine was tapered off and replaced with venlafaxine at 75 mg/day, gradually increased to 300 mg/day. Aripiprazole 5 mg/day was added as a supportive therapy. Despite regular use for one year, the patient reported only partial improvement and discontinued follow-up and treatment.

Three years later, the patient returned to our outpatient clinic with the same complaints, stating that none of the previous treatments had been effective. Paroxetine 20 mg/day and brexpiprazole 1 mg/day were initiated, with brexpiprazole increased to 2 mg/day as recommended after one week.

At the one-month follow-up, despite undergoing a divorce, the patient's depressive symptoms had subsided, and she reported no thoughts of self-harm or harm to others. The treatment was continued with paroxetine 20 mg/day and brexpiprazole 2 mg/day.

Case 2

A 58-year-old illiterate, married housewife presented nine years ago with complaints of reluctance to get out of bed, restlessness, and lack of motivation. Her first psychiatric consultation occurred in 1999 after she lost her husband and son in the Gölcük earthquake. She had been diagnosed with depression and received various treatments; however, her symptoms persisted and became resistant.

Following a one-month hospitalization with a diagnosis of MDD, her treatment regimen included paroxetine 60 mg/day, pregabalin 150 mg/day, and quetiapine 25 mg/day. During outpatient follow-ups, her symptoms worsened, leading to trials of different medication combinations (venlafaxine, aripiprazole, fluoxetine,

mirtazapine, lithium, bupropion, alprazolam). Despite irregular attendance at follow-ups, the patient claimed she used her medications regularly but never experienced complete symptom resolution.

During her most recent consultation, while on venlafaxine 150 mg/day, her lack of full recovery prompted an increase in venlafaxine to 225 mg/day, with brexpiprazole 1 mg/day added. At a one-week follow-up, brexpiprazole was titrated to 2 mg/day. The patient showed significant improvement in her symptoms, better self-care, and increased participation in household activities. Apart from weight gain following the addition of brexpiprazole, no side effects were reported. The final treatment regimen was adjusted to venlafaxine 225 mg/day and brexpiprazole 2 mg/day.

Case 3

A 24-year-old single female patient, a university graduate working as a makeup artist, presented five years ago with complaints of shortness of breath, heart palpitations, numbness, and loss of appetite. She was diagnosed with an anxiety disorder and started on paroxetine 20 mg/day, but due to side effects, her treatment was switched to sertraline 50 mg/day. Her history revealed impulsivity, sudden mood swings, social relationship losses, and a self-harm attempt two years earlier. Based on these findings, borderline personality disorder and major depressive disorder (MDD) were considered, and sertraline was increased to 100 mg/day with aripiprazole 5 mg/day added to the regimen.

During follow-ups, sertraline was further increased to 200 mg/day, while aripiprazole 5 mg/day was maintained. Although partial improvement in depressive symptoms was noted, self-harming behaviors and gambling addiction emerged. Lamotrigine 25 mg/day was added to the treatment; however, it had to be discontinued in the second week due to a skin rash.

As the patient's symptoms persisted, aripiprazole was replaced with brexpiprazole 1 mg/day, which was increased to 2 mg/day after one week, while sertraline 200 mg/day was continued.

At the latest follow-up, a significant reduction in depressive symptoms and gambling behavior was observed, although self-harming behaviors had not completely ceased. As the treatment was well-tolerated without side effects, brexpiprazole was increased to 3 mg/day, alongside sertraline 200 mg/day. The patient was monitored, and follow-ups revealed a marked decrease in self-harming behaviors.

Case 4

A 22-year-old single female university student presented four years ago with depressive complaints, including lack of motivation, loss of appetite, difficulty falling asleep, anhedonia, low self-confidence, and feelings of worthlessness. Since the age of 12, she had been under the care of child and adolescent mental health services, but her symptoms had not improved with previous treatments.

Her history revealed that at the age of five, following her parents' divorce, she moved to live with her father after her mother remarried. Initial treatment with fluoxetine 20 mg/day was started and titrated up to 60 mg/day, but no improvement was observed. Bupropion 150 mg/day was added but discontinued after triggering an epileptic seizure. Subsequently, venlafaxine was initiated and gradually increased to 300 mg/day; however, complete recovery was not achieved. Aripiprazole 10 mg/day, mirtazapine 15 mg/day, quetiapine 300 mg/day, and medazepam 10 mg/day were sequentially added, but the combination failed to produce sufficient benefits, and suicidal ideation emerged.

The patient was hospitalized in a psychiatric unit and received eight sessions of electroconvulsive therapy (ECT), resulting in improvement. She was discharged on venlafaxine 300 mg/day and quetiapine XR 300 mg/day.

After discharge, she resumed university but discontinued her medications due to weight gain despite feeling well. Two months later, her symptoms recurred, prompting her return to our clinic. Since she refused venlafaxine and quetiapine due to weight concerns, duloxetine 30 mg/day and brexpiprazole 1 mg/day were initiated. Duloxetine was discontinued due to daytime sedation, and sertraline 50 mg/day was started and gradually increased to 200 mg/day. Brexpiprazole, initiated as an adjunct, was titrated to 2 mg/day.

This treatment led to significant improvement, with no reported side effects. The patient has been stable on this regimen for six months.

Case 5

A 25-year-old married woman, a university graduate and housewife, presented to the clinic with complaints of inner distress, panic, persistent unhappiness, inability to experience pleasure, and feelings of guilt. Five months prior to her presentation, she was involved in a traffic accident, which, despite causing no physical injuries, resulted in re-experiencing the event and a fear of getting into a car.

The patient had been started on paroxetine 10 mg/day at an external center but experienced no improvement, leading her to seek treatment at our clinic. Diagnosed with Major Depressive Disorder (MDD) and Post-Traumatic Stress Disorder (PTSD), her paroxetine dose was gradually increased to 40 mg/day. Trazodone 50 mg/day was added to address her insomnia, but her depressive symptoms did not fully resolve. Subsequently, paroxetine and trazodone were discontinued, and treatment was switched to sertraline 50 mg/day and brexpiprazole 0.5 mg/day. Follow-up evaluations resulted in adjustments to sertraline 100 mg/day and brexpiprazole 1 mg/day.

At the next follow-up, the patient reported a reduction in crying spells, psychomotor agitation, and insomnia. Given her partial response, brexpiprazole was increased to 2 mg/day, and sertraline was titrated to 150 mg/day. The patient did not report any side effects with this treatment.

Case 6

A 63-year-old widowed male, a retired laborer with a primary school education, presented with complaints of fear of death, feelings of worthlessness, social withdrawal, being unwanted by others, difficulty falling asleep, loss of appetite, and passive thoughts of death. He reported no benefit from previous treatments with various antidepressants and antipsychotics, including sertraline, valproic acid, carbamazepine, aripiprazole, risperidone, quetiapine, fluoxetine, olanzapine, and alprazolam, prescribed at an external center.

To rule out dementia, a Mini-Mental State Examination (MMSE) was performed, yielding a normal score of 29, and a neurology consultation also excluded dementia. His symptoms were considered related to treatment-resistant depression. Sertraline 50 mg/day and brexpiprazole 0.5 mg/day were initiated. Follow-ups led to dose adjustments to sertraline 100 mg/day and brexpiprazole 2 mg/day.

The patient reported dizziness after the increase in brexpiprazole dose, which resolved when the dose was reduced to 1 mg/day. During subsequent visits, the patient, who adhered to his medications, reported no side effects, showed improved appetite, and no longer experienced active or passive thoughts of death. Furthermore, his relationships with relatives improved. The final treatment regimen consisted of sertraline 100 mg/day and brexpiprazole 1 mg/day.

Case 7

A 56-year-old single woman, a primary school graduate who previously worked as a cleaner but had been unemployed for the past eight years, presented to the clinic with complaints of inner distress, restlessness, shortness of breath, and hearing voices. She had a prior diagnosis of psychotic major depressive disorder at an external center, had been hospitalized once, and had attempted suicide by jumping from a height.

At the time of her clinic visit, the patient was on venlafaxine 150 mg/day, lamotrigine 100 mg/day, quetiapine 400 mg/day, aripiprazole 10 mg/day, and diazepam 5 mg/day, but reported no benefit from these treatments. During her outpatient consultation, she described low mood, unhappiness, lack of pleasure in life, inner restlessness, and occasional urges to scream. She also reported pseudohallucinations, such as hearing her name being called. A diagnosis of major depressive disorder with pseudohallucinations was made. Her treatment was simplified to venlafaxine 300 mg/day and quetiapine 400 mg/day, with the addition of brexpiprazole 1 mg/day. A planned cross-tapering between quetiapine and brexpiprazole was implemented during follow-ups.

At subsequent check-ups, her screaming episodes and pseudohallucinations had decreased, and no self-harm behaviors were observed. Brexpiprazole was increased to 2 mg/day. At later follow-ups, her sleep patterns had normalized, and self-harm thoughts were absent. Her final treatment consisted of venlafaxine 300 mg/day, quetiapine 200 mg/day, and brexpiprazole 3 mg/day, with no reported side effects.

Case 8

A 31-year-old single male, a university graduate and computer engineer, presented with complaints of unhappiness, lack of motivation, inability to enjoy life, and difficulty falling asleep. He reported no benefit from previous treatments, including fluoxetine 40 mg/day and olanzapine 2.5 mg/day. His symptoms persisted despite being on venlafaxine 150 mg/day.

In our clinic, his treatment was adjusted to venlafaxine 225 mg/day, and brexpiprazole 0.5 mg/day was added, which was increased to 1 mg/day after one week. At follow-up, he reported a reduction in active symptoms but persistent insomnia, with no side effects. Mirtazapine 7.5 mg/day was added to his treatment alongside venlafaxine 225 mg/day and brexpiprazole 1 mg/day. With improvements in his sleep disturbances, the patient continued on this regimen during follow-up.

Case 9

A 31-year-old single female teacher with a university degree presented with complaints of lack of motivation, social withdrawal, difficulty concentrating, and chronic insomnia. She had previously been diagnosed with major depressive disorder at an external center and initially treated with sertraline 100 mg/day. After experiencing no benefit, her treatment was switched to paroxetine 30 mg/day and olanzapine 5 mg/day. Although her depressive symptoms improved, she experienced side effects such as increased sleep and appetite.

At our clinic, her treatment was adjusted by maintaining paroxetine 30 mg/day while discontinuing olanzapine. Brexpiprazole 1 mg/day was added to her regimen. At her follow-up, the patient reported satisfaction with the treatment, no side effects, increased social engagement with her family, and enjoyment from social activities. Her final treatment was continued as paroxetine 30 mg/day and brexpiprazole 1 mg/day.

A summary of the cases is given in Table 1.

Discussion

According to the World Health Organization (WHO) assessment report on the global burden of disease, depression was the second leading cause of disease burden and disability among all diseases as of 2020. Furthermore, it is projected to become the leading cause of global disease burden by 2030. A large meta-analysis indicates that only 50% of all depression cases achieve remission with antidepressant treatment.[6] Even when appropriate treatment is provided and remission is achieved, 25–40% of patients may experience a depressive episode within 2 years, 60% within 5 years, and 85% within 15 years.[7] Considering these statistics, the significance of incorporating options like brexpiprazole as an adjunctive treatment in managing a

condition that causes such substantial disability cannot be overstated.

Brexpiprazole acts as a partial agonist at D2 receptors rather than as an antagonist and also exhibits high affinity for 5HT2A, 5HT1A, and α1 receptors. Its antidepressant effect is based on its ability to modulate the balance of dopamine and serotonin through partial agonist activity at dopamine D2 and serotonin 5-HT1A receptors, as well as antagonist activity at 5-HT2A receptors.[3] Studies indicate that brexpiprazole does not have significant effects on receptors typically associated with sedation, weight gain, or increased cardiometabolic risk.

Table 1. Summary of the Cases

Case	Diagnosis	Complaints	Treatment	Side Effects
Case 1	Major depressive disorder	Irritability, unhappiness, crying, anhedonia	Brexpiprazole 2 mg/day, paroxetine 20 mg/day	Not reported
Case 2	Major depressive disorder	Inability to get out of bed, restlessness, lack of motivation	Brexpiprazole 2 mg/day, venlafaxine 225 mg/day	Weight gain
Case 3	Major depressive disorder + Borderline personality disorder	Impulsivity, sudden mood changes, gambling	Brexpiprazole 3 mg/day, sertraline 200 mg/day	Not reported
Case 4	Major depressive disorder	Lack of motivation, loss of appetite, difficulty falling asleep	Brexpiprazole 2 mg/day, sertraline 200 mg/day	Not reported
Case 5	PTSD + Major depressive disorder	Inner distress, panic, guilt feelings	Brexpiprazole 2 mg/day, sertraline 150 mg/day	Not reported
Case 6	Major depressive disorder	Fear of death, worthlessness, social withdrawal	Brexpiprazole 1 mg/day, sertraline 100 mg/day	Dizziness
Case 7	Major depressive disorder	Inner distress, restlessness, pseudohallucinations	Brexpiprazole 3 mg/day, venlafaxine 300 mg/day, quetiapine 200 mg/day	Not reported
Case 8	Major depressive disorder	Unhappiness, lack of motivation, insomnia	Brexpiprazole 1 mg/day, venlafaxine 225 mg/day, mirtazapine 7.5 mg/day	Not reported
Case 9	Major depressive disorder	Lack of motivation, social withdrawal, excessive sleep	Brexpiprazole 1 mg/day, paroxetine 30 mg/day	Not reported

The efficacy of brexpiprazole as an adjunctive treatment in cases of treatment-resistant depression has been demonstrated in various studies. Similarly, in our cases, the addition of brexpiprazole at varying doses to the treatment regimens of patients who had not responded or had shown insufficient response to at least two antidepressant treatments resulted in an increase in treatment response rates. As observed in Cases 1, 2, 4, 6, 7, 8, and 9, patients whose depressive symptoms persisted despite the use of multiple medications benefited from adjunctive brexpiprazole therapy. This finding is consistent with other brexpiprazole studies in the literature.[3,4,5]

A case series in the literature highlights the use of brexpiprazole in patients with borderline personality disorder. According to these findings, brexpiprazole reduces aggression, self-harming behaviors, and substance abuse in patients with borderline personality disorder.[8] In Case 3, a diagnosis of borderline personality disorder co-occurring with major depressive disorder was considered, and following treatment with brexpiprazole at 2 mg/day, the patient showed improvement in self-harming behaviors and gambling addiction.

According to a recently published study, the combination of sertraline and brexpiprazole has shown beneficial results in the treatment of post-traumatic stress disorder (PTSD).[9] In Case 5, a diagnosis of PTSD co-occurring with major depressive disorder was considered, and brexpiprazole 2 mg/day was added to sertraline 150 mg/day. Follow-up evaluations indicated that the patient benefited from the treatment.

In the literature, the most common side effects of brexpiprazole, such as weight gain and akathisia, are generally described as mild to moderate in severity.[10] Among our cases, no significant side effects were reported, except for mild weight gain in one case, which did not lead to treatment discontinuation, and dizziness in another case, which resolved with dose adjustment.

In conclusion, this case series demonstrates that brexpiprazole may be considered as an effective and well-tolerated option not only for treatment-resistant depression but also for the management of borderline personality disorder and post-traumatic stress disorder. In our cases, positive outcomes were achieved, including improvements in depressive symptoms, enhanced functionality, and reductions in aggression, self-harming behaviors, and pseudohallucinations. The efficacy and safety of brexpiprazole in various clinical conditions are supported by the literature, and our findings align with these results. The absence of severe side effects during the treatment process suggests that brexpiprazole offers an advantage in terms of patient adherence. Further exploration of brexpiprazole's role in individualized treatment approaches for depression and co-occurring psychiatric symptoms is warranted through larger case series and controlled studies.

Compliance with Ethical Standards

Ethical considerations have been observed while ensuring the patient's confidentiality.

Conflict of Interest

There is no conflict of interest among the authors. Informed consent was obtained from the patients before this case series was prepared.

Author Contributions

AG, EŞ, AP: Study idea; AG, EŞ, AP: Design; MT: Data collection; AG, EŞ, MT, AP Analysis; AG, EŞ: Literature review; AG, AP: Writing; AG, AP: Critical review.

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