

Adverse Effect Occurring in the Long-Term Association Multiple Psychotropic Drugs: Priapism in a Child with Autism Spectrum Disorder

Çoklu Psikotrop İlaçların Uzun Süreli Birlikte Kullanımı Sırasında Ortaya Çıkan Yan Etki: Otizm Spektrum Bozukluğu Olan Bir Çocukta Priapizm

Volkan Şahin¹, Feyza Nur Karakaş¹, Esra Hoşoğlu¹, Bahadır Turan^{1,2}

¹Karadeniz Technical University Faculty of Medicine, Department of Child and Adolescent Psychiatry, Trabzon, Türkiye

²Cambridgeshire and Peterborough NHS Foundation Trust, Cambridge, United Kingdom

ABSTRACT

This case report aims to highlight the occurrence of delayed-onset priapism in a child with autism spectrum disorder (ASD) who had been receiving long-term polypharmacy with psychotropic drugs. The objective is to raise awareness about the potential adverse effects associated with the combined use of multiple psychotropic medications in pediatric psychiatric treatment. A clinical case of an 11-year-old boy diagnosed with ASD, attention deficit hyperactivity disorder, and anxiety disorder is presented. The patient had been treated over a year with a combination of atomoxetine, risperidone, and fluoxetine. Clinical observations, patient history, and laboratory evaluations were analyzed to investigate the etiology of priapism. The psychotropic medications were discontinued following the onset of symptoms, and the course of the condition was monitored. The patient developed priapism after approximately one year of stable combination treatment. No organic causes such as infection, hematologic disorders, or trauma were identified. The priapism resolved completely within 24 hours following the discontinuation of all psychotropic drugs. Pharmacodynamic and pharmacokinetic interactions between atomoxetine, risperidone, and fluoxetine were identified as possible contributing factors. Priapism is a rare but potentially serious side effect of psychotropic polypharmacy, especially in pediatric populations with neurodevelopmental disorders. The interaction of psychotropic drugs through α -1 adrenergic blockade and CYP2D6 inhibition may increase the risk, particularly during the hormonally sensitive peripubertal period. Clinicians should remain vigilant for delayed adverse effects, educate caregivers, and carefully evaluate the risk-benefit balance when prescribing combination treatments in children with ASD.

Keywords: Priapism, autism spectrum disorder, psychotropic drugs

ÖZ

Bu olgu sunumu, uzun süreli çoklu psikotrop ilaç tedavisi alan otizm spektrum bozukluğu (OSB) tanılı bir çocukta gecikmiş başlangıçlı priapizm gelişimini vurgulamayı amaçlamaktadır. Amaç, pediatrik psikiyatrik tedavide birden fazla psikotrop ilacın birlikte kullanımıyla ilişkili potansiyel yan etkiler konusunda farkındalık oluşturmaktır. OSB, dikkat eksikliği ve hiperaktivite bozukluğu ve anksiyete bozukluğu tanıları olan 11 yaşındaki bir erkek çocuğa ait klinik olgu sunulmuştur. Hasta, bir yıldan uzun süredir atomoksetin, risperidon ve fluoksetin kombinasyonu ile tedavi edilmiştir. Priapizmin etiyolojisini araştırmak amacıyla klinik gözlemler, hasta öyküsü ve laboratuvar değerlendirmeleri analiz edilmiştir. Semptomların ortaya çıkmasının ardından psikotrop ilaçlar kesilmiş ve durumun seyri izlenmiştir. Hastada yaklaşık bir yıllık stabil kombinasyon tedavisinin ardından priapizm gelişmiştir. Enfeksiyon, hematolojik bozukluklar veya travma gibi organik nedenler saptanmamıştır. Tüm psikotrop ilaçların kesilmesini takiben priapizm 24 saat içinde tamamen düzelmiştir. Atomoksetin, risperidon ve fluoksetin arasındaki farmakodinamik ve farmakokinetik etkileşimler olası katkıda bulunan faktörler olarak değerlendirilmiştir. Priapizm, özellikle nörolojik gelişimsel bozukluğu olan pediatrik popülasyonlarda, psikotrop polifarmasinin nadir ancak potansiyel olarak ciddi bir yan etkisidir. Psikotrop ilaçların α -1 adrenerjik blokaj ve CYP2D6 inhibisyonu yoluyla etkileşimi, özellikle hormonal açıdan duyarlı peripubertal dönemde riski artırabilir. Klinisyenler gecikmiş yan etkiler açısından dikkatli olmalı, bakım verenleri bilgilendirmeli ve OSB'li çocuklarda kombinasyon tedavileri reçete ederken risk-yarar dengesini dikkatle değerlendirmelidir.

Anahtar Kelimeler: Priapizm, otizm spektrum bozukluğu, psikotrop ilaçlar

Address for Correspondence/Yazışma Adresi: Lec, Volkan Şahin, MD, Karadeniz Technical University Faculty of Medicine, Department of Child and Adolescent Psychiatry, Trabzon, Türkiye

E-mail: cocukpsikiyatrist@gmail.com **ORCID:** orcid.org/0000-0003-0888-2370

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Introduction

Priapism is a urological emergency characterized by a persistent penile erection lasting more than 3-4 hours and typically occurring in the absence of sexual stimulation.¹ Clinically, it is classified into three subtypes: ischemic, non-ischemic, and recurrent (stuttering) priapism. Among these, ischemic priapism is the most common form and requires urgent medical intervention; if left untreated, it can result in permanent erectile dysfunction.²

Hematological disorders, spinal cord injuries, substance use, and various medications are causes of priapism. Psychotropic drugs, particularly antipsychotics, antidepressants, and anticonvulsants, have been reported to increase the risk of priapism.³ Individuals using multiple psychotropic medications are at increased risk for developing priapism; however, detailed case reports focusing on this patient group remain limited in the literature.

In this case report, we aimed to discuss the late development of ischemic priapism in a male patient who received long-term multiple psychotropic drug. We particularly emphasized that adverse effects related to polypharmacy should not be ignored in psychiatric treatment processes.

Written consent was obtained from the patient and his parents for publication of this case report.

Case Report

An 11-year-old male patient, who had been followed up in our clinic for approximately five years with autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and anxiety disorder, applied at the age of four with inadequate social interaction, speech delay, limited eye contact and marked motor hyperactivity. It was observed that he was conscious, but spontaneous eye contact and joint attention skills were not developed.

It was learned that the patient was born at term, with a birth weight of 3500 grams, via caesarean section; he was treated in intensive care for 20 days due to postnatal infection. It was stated that he started to sit without support at six months, walk at 12 months and say single words at 18 months; he was breastfed for approximately 36 months.

Methylphenidate treatment was terminated and replaced with a combination of atomoxetine 24 mg/day and risperidone 0.5 mg/day because of insufficient treatment response. During the follow-up period, a decrease in stereotypic behaviors, an increase in social communication, and strengthening of emotional expression were observed. Due to the existing attention problems, the atomoxetine dose was gradually increased to 44 mg/day according to the patient's body weight. During the clinical follow-up, fluoxetine 10 mg/day was added to the treatment because of separation anxiety, emotional fluctuations, introversion, and unexplained fear complaints. The patient was followed up with a combination of atomoxetine 44 mg/day, risperidone 0.75 mg/day, and fluoxetine 10 mg/

day for approximately one year. It was observed that the family regularly complied with the treatment process.

The patient was consulted to our outpatient clinic by the pediatric surgery clinic on 21.02.2025 with a preliminary diagnosis of priapism for etiological research and treatment arrangement. In the history, it was reported by the patient's father that temporary penile erection was observed twice in the last year pre-urination; these episodes ended spontaneously after urinating and there was a long time interval between them.

Two days before the last episode, the patient's teacher contacted the family because of complaints of abdominal pain. The patient was evaluated by the family physician on the same day, and medical treatment was given, considering complaints related to the gastrointestinal system as the primary concern. The same evening, when his complaints continued at home, it was learned that the patient told his father "it hurts", that an erection was observed in the penis, but that it was similar to previous experiences, and that no intervention was made; the patient was directed to the toilet, after he slept without pain.

The next morning, the erection was observed to continue and the patient was examined again by the family physician. In the first stage, a urine test was performed with a preliminary diagnosis of lower urinary tract infection; then, he was referred to the hospital with the suspicion of priapism and admitted to the pediatric surgery clinic. No pathology was found in the physical examination and laboratory evaluations (complete blood count, coagulation parameters, general metabolic panel). No significant history or findings were detected in terms of infection, hematological disease, malignancy or genital trauma.

In the psychiatric consultation conducted by the pediatric surgery clinic to evaluate the potential effects of psychotropic drugs, it was decided to discontinue all psychotropic drugs (atomoxetine, risperidone, fluoxetine). It was observed that penile erection completely regressed and the priapism ended within 24 hours after the drugs were discontinued. After all psychotropic medications were discontinued and the priapism resolved, methylphenidate was reintroduced at a low dose to manage the patient's psychiatric symptoms, and no priapism side effect was observed during the three-month follow-up. Timeline is presented in Table 1.

Discussion

Priapism is most commonly seen in childhood because of sickle cell anemia, but it can also occur less frequently due to leukemia, trauma, or idiopathic causes.^{4,5} The absence of signs and symptoms of known organic factors in this case suggests that the most likely cause of priapism may be related to psychotropic medication use, particularly the presence of polypharmacy.

Although it is thought that antipsychotics may cause priapism, the pathophysiological mechanisms are not yet fully known. Current findings suggest that this effect may develop due to blockade of α -1 adrenergic receptors in the corpora cavernosa of the penis.⁶ Risperidone, as a strong α -adrenergic receptor antagonist, reduces sympathetic vasoconstrictor tone and

Table 1. This timeline summarizes the chronological clinical course, diagnostic evaluations, and treatment adjustments in the presented case

Date/time	Event/clinical course
	The patient was first admitted to the child and adolescent psychiatry clinic at age 4 due to impaired social interaction, speech delay, limited eye contact, and hyperactivity. Diagnosed with autism spectrum disorder.
	Continued psychiatric follow-up; diagnosis expanded to include attention deficit and hyperactivity disorder and anxiety disorder. Initiation of methylphenidate treatment.
	Approximately 1 year later, due to insufficient response, methylphenidate was replaced with atomoxetine (24 mg/day) and risperidone (0.5 mg/day). Marked clinical improvement observed.
	Atomoxetine increased to 44 mg/day according to body weight; fluoxetine (10 mg/day) added due to anxiety and emotional lability. Stable polypharmacy (atomoxetine + risperidone + fluoxetine) continued for ~1 year.
February 19, 2025	The patient complained of abdominal pain at school; evaluated by family physician for possible gastrointestinal problem.
February 21, 2025	Continuous erection evaluated by pediatric surgery clinic, referred to child psychiatry for etiologic assessment.
February 21-22, 2025	All psychotropic drugs discontinued; erection resolved completely within 24 hours.
Follow-up	No recurrence of priapism observed.

relatively increases parasympathetic activity; this mechanism may lead to involuntary and prolonged erection (ischemic priapism).

In a significant portion of drug-induced priapism cases, the causative agent is antipsychotics with pronounced α -blockade, such as risperidone, clozapine or olanzapine.⁷ The strong α_1 -receptor antagonism of risperidone used in our case has been evaluated as a pharmacological risk factor that may have been effective in the development of priapism.

Atomoxetine is a norepinephrine reuptake inhibitor and may cause both pharmacodynamic and pharmacokinetic interactions when used with risperidone. Although norepinephrine, which increases under the effect of atomoxetine, normally facilitates detumescence, this effect does not occur under α -blockade of risperidone and contributes to the prolongation of erection. In addition, since both atomoxetine and risperidone are metabolized by CYP2D6, atomoxetine may slow down the metabolism of risperidone and increase its plasma level.⁸ A pediatric case of priapism has been reported after atomoxetine was added to risperidone treatment.

Selective serotonin reuptake inhibitor antidepressants such as fluoxetine can rarely cause priapism.⁹ Fluoxetine is a strong CYP2D6 inhibitor and at high doses it has a weak norepinephrine reuptake blockade. Therefore, fluoxetine may increase the plasma levels of risperidone by inhibiting its metabolism and may increase the risk of priapism by having an additive effect on vascular tone in combined use.

In this case, the simultaneous use of three psychotropic drugs seems to have predisposed to priapism by interacting through different pharmacodynamic and pharmacokinetic mechanisms. While the strong α_1 adrenergic receptor antagonism of risperidone may lead to prolonged erection by preventing sympathetic detumescence, the increased norepinephrine levels

by atomoxetine may have contributed to the maintenance of erection. In addition, fluoxetine potentiated this effect by increasing the plasma levels of both risperidone and atomoxetine via CYP2D6 inhibition. It is noteworthy that priapism occurred approximately one year later despite this combination treatment without dose change. This delayed onset can be explained by hormonal and biochemical changes related to the peripubertal period of the case.¹⁰ Spontaneous erections and increased neurohormonal sensitivity frequently seen during adolescence may have increased the sensitivity of the organism to these pharmacological interactions. This provides important clues as to why some children receiving stable doses of therapy may develop late-onset priapism.

Priapism is a rare but serious urological emergency that can lead to permanent erectile dysfunction if not recognized and treated in a timely manner. Although cases of priapism due to psychotropic drugs such as risperidone, atomoxetine, and fluoxetine have been reported very rarely, this potential side effect should be taken into consideration during both monotherapy and combined treatments. Polypharmacy is common, especially in children and adolescents with comorbid diagnoses such as ASD and ADHD, and this situation may increase the risk of rare adverse effects. In addition, biochemical and hormonal changes experienced in the peripubertal period may make patients more sensitive to side effects. In clinical follow-up, it is of great importance to inform both physicians and relatives of the patients in order to detect possible side effects early. In addition, considering the difficulties experienced by individuals with ASD in verbal communication, careful monitoring of atypical symptoms that may occur in these patients and education of caregivers are of critical importance. Although rare, such adverse effects, which may lead to potentially serious consequences, should be evaluated in clinical decisions, taking into account the risk-benefit balance.

Ethics

Informed Consent: Written consent was obtained from the patient and his parents for publication of this case report.

Footnotes

Authorship Contributions

Surgical and Medical Practices: V.Ş., F.N.K., E.H., B.T., Concept: V.Ş., F.N.K., E.H., B.T., Design: V.Ş., F.N.K., E.H., B.T., Data Collection or Processing: V.Ş., F.N.K., E.H., B.T., Analysis or Interpretation: V.Ş., F.N.K., E.H., B.T., Literature Search: V.Ş., F.N.K., Writing: V.Ş., F.N.K., E.H., B.T.

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