

# Angioedema Caused by Oral Paliperidone Augmentation in the Major Depressive Disorder Treatment: A Case Report

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## ABSTRACT:

Angioedema caused by oral paliperidone augmentation in the major depressive disorder treatment: a case report

Angioedema is a rare but life-threatening condition characterized by swelling in subcutaneous tissues and mucosa. Paliperidone is an effective treatment option for treatment-resistant patients with depression. While the most common adverse effect caused by medication is headaches, it is also less likely to observe edema or anaphylactic reaction. In this case report, an adolescent diagnosed with major depression and suffered from angioedema following oral paliperidone augmentation during the treatment was presented. Edema regressed spontaneously about 24-30 hours following the last drug intake. No significant laboratory finding that could explain this condition was found. The patient no longer suffered from a similar problem following discontinuation of paliperidone. This case suggests that the clinician should be alerted against possible allergic reactions by reason of oral usage of paliperidone in adolescents and further studies are needed to explore the underlying mechanisms of allergic responses for these patients.

**Keywords:** paliperidone, risperidone, angioedema, adolescent

**Journal of Mood Disorders (JMood) 2017;7(2):128-30**



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**Date of received:**  
February 16, 2017

**Date of acceptance:**  
April 4, 2017

## Declaration of interest:

C.B.: The author reported no conflicts of interest related to this article.

## INTRODUCTION

Paliperidone, which is also known as 9-hydroxy-risperidone, is an active extended-release risperidone metabolite and in addition to its antipsychotic activity, it is also reported to display anti-depressive characteristics (1). The most common adverse effect of oral paliperidone usage is headaches as well as rare edema and anaphylactic reaction (2). Angioedema is a type of edema, which covers subcutaneous tissues and mucosa due to an increase in the vascular dilatation and permeability. Drug-induced angioedema is reported related to bradykinin increase (3). However, the effect of mast cell degranulation on opiate-induced angioedema must be noted (4).

There are various hypotheses in the literature regarding the peripheral edema and allergic reactions caused by anti-

psychotic drugs but the etiology of reactions related to paliperidone remains relatively unexplored. This case report presents an adolescent who was diagnosed with secondary major depressive disorder along with obsessive compulsive disorder and suffered from angioedema following oral paliperidone augmentation to discuss the mechanisms underlying this condition.

## CASE PRESENTATION

A 17-year-old patient was admitted to our clinic due to her obsession with cleanliness. The patient has been avoiding to meet her friends because of her obsession for about a year. She did not carry any currency with herself, changed her school because not want to use public transportation and she sometimes thought about committing suicide.

There were no psychiatric or allergic disease in her or family's history. Her body mass index (BMI) was 31.6 kg/m<sup>2</sup> at initial admission. The patient was diagnosed with obsessive compulsive disorder (OCD) and comorbid depressive disorder. In addition to cognitive behavioral approaches, sertraline, fluoxetine, aripiprazole and clomipramine treatments have been tried but drug doses could not be increased to the effective level due to their side effects. Finally she was recommended to take venlafaxine 37.5 mg/day. It was gradually increased to 75 mg/day but three weeks later there was no decline in depressive symptoms and paliperidone 3 mg/day was added to the treatment.

After paliperidone augmentation, it was observed that the patient's tongue was swollen and she had difficulty in breathing during sleep. However, she continued taking her pills. She reported that she suddenly woke up on the 5th day of the treatment and she was admitted to emergency by reason of apparent swelling on her face, particularly around her eyes and tongue. The patient was kept under observation in the emergency unit, and her medical problem spontaneously regressed 24–30 hours following her last drug intake. The analysis demonstrated that complete blood count, electrolyte levels, liver, kidney and thyroid function tests, anti-ds DNA, anti-nuclear antibody, anti-TPO levels, C1 esterase inhibitor, C3, C4, and Ig E levels were at a normal level. After paliperidone was discontinued, the patient did not complain about the same problem. The patient was not recommended to take paliperidone again because of fatality risk and ethical concerns. The patient and her family were asked for an informed consent.

## DISCUSSION

Major depressive disorder is the most common comorbidity for adult OCD cases but its prevalence is low for adolescents. However, it is reported that secondary depressive symptoms of OCD increases with age, and one fifth of all cases display depressive symptoms at a clinically significant level (5). In this patient with OCD, depressive symptoms became apparent and did not improve despite the OCD treatment. Finally venlafaxine, a serotonin and noradrenaline re-uptake inhibitor was recommended and oral paliperidone was added to the treatment. Paliperidone is an effective treatment option for treatment-resistant patients with depression. The antagonistic effect of

paliperidone on hydroxytryptamine 2A (5-HT<sub>2A</sub>), 5-HT<sub>7</sub> and  $\alpha$ -2 adrenergic receptors is known to augment serotonin or noradrenaline re-uptake inhibitor effect (6). Besides, unlike risperidone, it does not undergo any changes in its metabolism when used along with venlafaxine (7). On the other hand, weight gain and sedative characteristics of paliperidone are lower than that of risperidone albeit they activate similar receptors (8). In the light of the above, paliperidone was preferred in this patient's treatment.

It is reported that the antagonistic effects of atypical antipsychotic on dopamine, serotonin (5-HT<sub>2</sub>) and  $\alpha$ -adrenergic receptors lead to direct or indirect vascular dilation, deterioration of renin-angiotensin system, natriuresis, blood pressure rise and leakage of intracellular fluid into paracellular space, thus contributing to the edema mechanism. In addition, Type I or Type IV allergic reactions may play a role in drug-induced edema (9). The edema that this patient suffered from was considered as angioedema as it was limited to the facial area, caused swelling subcutaneous tissues and mucosa and led to difficulty in breathing. The analysis did not yield any laboratory findings that could account for the patient's condition. It was considered as a drug-induced reaction because the patient had no allergic personal or family history, never complained about a similar problem before or when she used venlafaxine, was not prescribed any medications other than paliperidone or did not consume any different type of food and this condition became apparent only after she started using paliperidone and ceased following discontinuation of the drug. However, challenge test was not carried out due to ethical concerns. According to the Naranjo Adverse Drug Reaction (ADR) Probability Scale (10), the relationship between oral paliperidone and angioedema in this case is considered probable (6 points).

Drug-induced angioedema can be related to the deterioration in the kinin metabolism. Bradykinin mediated angioedema is divided into two groups based on the deficiency of complementary 1 inhibitor (C1INH). For drug-induced cases, it is reported that C1INH is at a normal level and that the disappearance of swelling may last 72 hours and even a few weeks following the discontinuation of the drug (4,11). The patient's C1INH level was at a normal range. However, swelling which became apparent on the facial area, mouth, and upper respiratory tract on the fifth

day, spontaneously regressed 24–30 hours following the discontinuation of the drug. It is reported that swellings disappear typically within 48 hours in case of angioedema caused by mast cell degranulation. C1INH levels of the cases in this group are also normal. Additionally, cases are divided into two groups based on whether they are IgE-mediated or not (11). This patient's IgE level was normal, and without any additional drug intake, her swellings regressed with discontinuation of the drug, suggesting that the patient's condition, similar to opiates, is a mast-cell mediated angioedema. Another adolescent was reported to have angioedema following dose increase of oral paliperidone with normal complement and IgE levels.

However, this patient's condition became apparent in 1-2 hour following the drug intake and his condition improved in a week following the discontinuation of the drug (12).

A limited number of prospective studies on the use of paliperidone in adolescents have shown that paliperidone is generally well-tolerated (13,14). However, these case reports indicate that despite the clinical differences, it is necessary to be alerted against allergic reactions in adolescents prescribed with oral paliperidone. It is suggested that further studies may clarify the clinical features and possible risk factors of this condition and so the side effects can be predicted and the patients can be treated more effectively.

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