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LETTER TO THE EDITOR

Duloxetine-associated recurrent angioedema: A dechallenge–rechallenge case

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Dear Editor,

Duloxetine is a selective serotonin–norepinephrine reuptake inhibitor (SNRI) widely used in the treatment of major depressive disorder, anxiety disorders, neuropathic pain syndromes, and fibromyalgia (1). Its safety profile has been well documented, with commonly reported adverse effects including nausea, diarrhea, dizziness, hypertension, and palpitations (2). However, rare hypersensitivity reactions, including angioedema and other severe cutaneous reactions, have been described in association with duloxetine use (3). Here, we report a case of angioedema temporally associated with duloxetine exposure in which dechallenge and rechallenge findings suggest a probable drug-related reaction.

The patient was a 56-year-old woman whose psychiatric symptoms began during her university years and included insomnia, anhedonia, reduced motivation, and prominent somatic complaints. Regular psychiatric follow-up was initiated in 2021 because of progressively worsening anxiety and depressive symptoms. Amitriptyline was maintained for approximately four years with good tolerability; however, because of weight gain and hypersomnia, it was gradually tapered and discontinued before initiation of duloxetine. Duloxetine was started in September 2024 at 30 mg/day and increased to 60 mg/day after partial clinical improvement, with Beck Depression Inventory (BDI) scores decreasing from 31 at baseline to 23 before the onset of angioedema.

Approximately seven months after treatment initiation, the patient developed unilateral swelling of the right lip and cheek accompanied by mild swallowing discomfort without respiratory compromise. She presented to the emergency department, where intravenous corticosteroids and antihistamines provided transient partial relief. Physical examination revealed localized non-pitting facial edema without urticaria, mucosal or upper airway involvement, wheezing, or dermographism. Over the following three months, recurrent episodes occurred, with progressive extension of edema and diminishing response to treatment.

Dermatologic evaluation established a diagnosis of angioedema. The patient had no history of autoimmune or lymphoproliferative disease, thyroid dysfunction, or prior hypersensitivity conditions, and no family history suggestive of hereditary angioedema. Laboratory investigations—including C1q, C1 esterase inhibitor levels, complement C4, total immunoglobulin E, and peripheral eosinophil count—were within normal limits. These findings were considered sufficient to exclude hereditary or bradykinin-mediated angioedema. No exposure to medications or conditions commonly associated with drug-induced angioedema, including angiotensin-converting enzyme inhibitors, aspirin, opioids, recent infection, food allergens, or herbal supplements, was identified.

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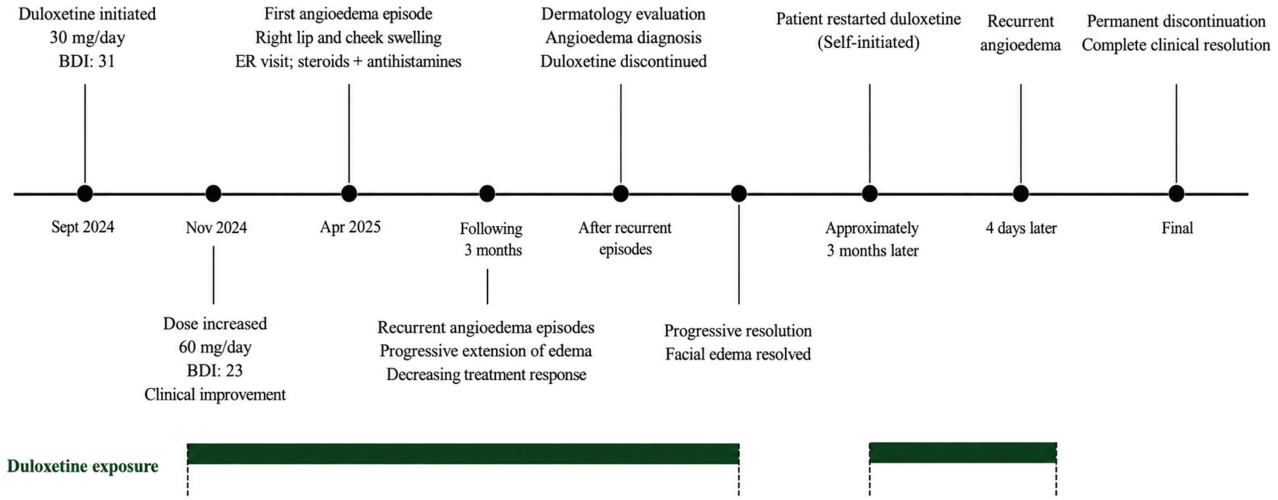

Figure 1. Clinical timeline of duloxetine exposure, angioedema episodes, dechallenge, rechallenge, and symptom resolution. Green bars indicate periods of duloxetine exposure.

BDI: Beck Depression Inventory; ER: Emergency room.

Duloxetine was discontinued under psychiatric supervision, resulting in progressive resolution of facial edema. Approximately three months later, the patient independently restarted duloxetine because of persistent depressive symptoms. Facial swelling recurred within four days in the absence of any identifiable trigger. Repeat dermatologic evaluation confirmed duloxetine-associated angioedema, and permanent discontinuation of duloxetine led to complete clinical resolution. The clinical course of duloxetine exposure and angioedema episodes is summarized in Figure 1.

Angioedema is characterized by localized, transient swelling of subcutaneous or submucosal tissues caused by increased vascular permeability (4). It most commonly affects the face, lips, oropharynx, and extremities. Various drugs, foods, insect stings, and chemical agents have been reported as triggers (5, 6). Angioedema may arise through several pathophysiological mechanisms, most commonly histamine-mediated mast cell activation or bradykinin-mediated pathways. Histamine-mediated forms result from mast cell degranulation and release of vasoactive mediators, whereas bradykinin-mediated angioedema is related to dysregulation of the kallikrein–kinin system and accumulation of bradykinin, a potent vasoactive peptide that promotes vasodilation and tissue edema. In drug-induced cases, additional idiosyncratic immune or neurovascular mechanisms have also been proposed (7).

Although angioedema is not commonly listed among the adverse effects of SNRI medications, isolated cases associated with duloxetine and venlafaxine have been reported (8, 9). Similar reactions have also been described with other serotonergic antidepressants, and increased peripheral serotonin concentrations, as well as immune-mediated mechanisms, have been proposed as potential contributors to antidepressant-associated urticaria and angioedema (10).

Although the precise mechanism underlying duloxetine-associated angioedema remains unclear, the absence of urticaria together with only partial response to antihistamines in our patient may suggest a non-histaminergic pathway. Symptom resolution following duloxetine discontinuation, recurrence after re-initiation, and exclusion of alternative etiologies support a drug-related association between duloxetine and angioedema. The Naranjo Adverse Drug Reaction Probability Scale yielded a score of 8, indicating a "probable" adverse drug reaction, while the rapid recurrence after rechallenge may be compatible with a sensitization-related hypersensitivity mechanism.

This case highlights a rare but clinically relevant adverse reaction and emphasizes the importance of considering medication-related causes in patients presenting with late-onset angioedema during otherwise stable antidepressant therapy.

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