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Whole-body edema with olanzapine: A case report and literature review

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Abstract

Olanzapine is a second-generation antipsychotic (SGA) that has been shown to promote disease remission in persons with treatment-resistant depression when used in combination with fluoxetine. However, tolerability of treatment augmentation with SGAs may be limited because of common adverse effects, such as weight gain, hypertriglyceridemia, and elevated glucose. Data exist pertaining to rare localized edematous reactions or angioedema with use of SGAs, but diffuse whole-body edema has yet to be documented. A 47-year-old white female with treatment-resistant depression presented with a 5-day history of weight gain and swelling of her torso and extremities. Five days prior, she had initiated olanzapine/fluoxetine 6/50 mg daily following failure of fluoxetine 40 mg daily monotherapy. The patient was noted to have gained 3.6 kg since her last appointment and exhibited profuse pitting edema on her forearms, lower limbs, hands, and chest. Olanzapine/fluoxetine was discontinued and the patient was prescribed a 3-day course of a loop diuretic for symptomatic management. A follow-up visit 5 days later noted complete resolution of symptoms. Because of the temporal relationship of symptoms with initiation of olanzapine, we recommend monitoring for edema with initiation and/or titration of therapy.

Keywords: olanzapine, second-generation antipsychotic, atypical antipsychotic, edema

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Background

Antidepressants, such as selective serotonin reuptake inhibitors (SSRIs), are first-line agents for the treatment of major depressive disorder, as substantiated by robust efficacy and safety data from clinical trials.[1,2] However, it is estimated that 25% to 65% of individuals who fail to respond to initial therapy with an SSRI will respond to a second, different course of treatment.[3] The commonly accepted definition of treatment-resistant depression (TRD) is the failure to achieve a clinically meaningful response after a trial of 2 or more antidepressant agents, prescribed in adequate doses, for an adequate treatment duration and affirmation of treatment adherence.[1,4] In persons with TRD who exhibit an insufficient response to monotherapy with an antidepressant, a variety of augmentation strategies are available, including the adjunctive use of second-generation antipsychotics (SGAs).[1-3]

The SGA and SSRI combination product, olanzapine/fluoxetine, was approved by the US Food and Drug

Administration in 2003 for the management of TRD, as well as acute depressive episodes associated with bipolar 1 disorder.[5] A Cochrane systematic review and meta-analysis[6] analyzed the efficacy and safety of augmentation therapy with the SGAs aripiprazole, olanzapine, quetiapine, or risperidone, compared to placebo in individuals with major depressive disorder or dysthymia. Augmentation of antidepressant therapy with olanzapine compared with placebo resulted in a reduction in depressive symptoms and improvement in disease remission, but a large number of individuals discontinued therapy because of unacceptable side effects, such as weight gain, sedation, and prolactin elevation.[6]

Sedation, metabolic, and anticholinergic side effects are common with use of olanzapine. Although far less common, edema with olanzapine was noted to have occurred at a rate of approximately 15% in clinical trials.[5,7] However, no reports exist to date that detail whole-body edema with the use of olanzapine. This case report describes a patient who exhibited diffuse edema and rapid weight gain, attributed to fluid retention, following initiation of olanzapine for the management of treatment-resistant depression.

Case Report

A 47-year-old white female presented to a primary care clinic with the chief complaints of weight gain and edema, which had progressed in severity during a 5-day period. The patient's past medical history was significant for generalized anxiety disorder, attention deficit hyperactivity disorder, insomnia, major depressive disorder, and nicotine dependence. She had no previous diagnoses affiliated with cardiac, hepatic, or renal dysfunction. Documented medication allergies included pruritus with exposure to penicillin and meloxicam. Her home medication regimen was composed of clonazepam, lisdexamfetamine, olanzapine/fluoxetine, and zolpidem, and she appeared to be adherent to all medication based on refill data. Medications that had previously failed to result in remission of her depressive symptoms included amitriptyline, bupropion extended release, citalopram, fluoxetine, and venlafaxine extended release, all of which were titrated to adequate doses, trialed for adequate durations, and appeared to have been taken in an adherent manner by the patient. Her only recent medication change was discontinuation of fluoxetine 40 mg by mouth daily and the initiation of the combination product, olanzapine/fluoxetine 6 mg/50 mg by mouth once daily, for TRD. Olanzapine/fluoxetine had been dispensed to the patient by the clinic pharmacy the same day of her appointment but was self-initiated by the patient 2 days after she had discontinued her fluoxetine monotherapy.

The patient presented to clinic for evaluation a total of 5 days after initiating olanzapine/fluoxetine. The patient stated that in the 3 days following initiation of olanzapine/fluoxetine, and 2 days prior to her presenting to clinic, she began to experience paresthesias in her oral cavity and lips. She denied symptoms indicative of angioedema, such as swelling of the tongue, throat, and other mucosal membranes. Additionally, she noticed that the sleeves of her shirts and jackets, as well as the legs of her pants, had become tight and uncomfortable due to swelling. These symptoms progressed in severity during the next 2 days, with the patient becoming unable to dress herself in long-sleeved shirts or pants without extreme discomfort, resulting in her scheduling an urgent appointment in clinic.

Vital signs were within normal limits, with the exception of the patient's weight, which increased by 3.6 kg (85.45-89.05 kg), and systolic blood pressure, which increased from 122/102 mm Hg to 140/80 mm Hg, from her last clinic appointment 1 week prior. A comprehensive physical exam noted no evidence of erythema, rash, or scaling on the patient's skin. However, the patient exhibited bilateral grade 3 pitting edema (noticeably swollen extremities, skin indentation of 13 mm with digital pressure, and indentation returning to normal in approximately 1 minute) on her forearms, lower limbs, feet, hands, and feet, as well as grade 2 pitting edema (no marked visual changes to skin, indentation of 6 mm with digital pressure, and indentation returning to normal within 15 seconds) on her chest.[8] The patient's fingers and toes were visibly swollen, with blanching on the distal, middle, and proximal interphalangeal joints of the hands and feet. Dorsalis pedis, posterior tibial, and radial pulses were evident bilaterally, and there were no apparent changes in skin temperature.

Based on physical findings and onset of symptoms, in conjunction with initiation of olanzapine, the provider deemed this to be a drug-induced reaction until further laboratory evidence was obtained. Olanzapine/fluoxetine was discontinued in clinic, and a 3-day course of furosemide 20 mg by mouth daily was initiated for symptomatic relief. A hepatic function panel, complete metabolic panel, thyroid panel, and complete blood count were obtained prior to the patient leaving the clinic. All laboratory values returned within normal limits, with the exception of her white blood cells, which were marginally elevated at 12.2 U/L (institutional reference range, 4.0-11.0 U/L). On subsequent follow-up, 5 days after the urgent encounter, assessment of edema using the digital pressure method on arms, legs, and chest was unremarkable, and the patient reported complete resolution of oral paresthesias. Additionally, the patient's weight was reduced to 85.6 kg at this follow-up visit. Therapy with furosemide was discontinued, and olanzapine was noted

as a medication intolerance on the patient's electronic medical record.

Literature Search

A literature search was conducted on PubMed through March 2020 using the following key words: *antipsychotic edema*, *olanzapine edema*, and *olanzapine/fluoxetine edema*. Results published in English were included. The initial search of *antipsychotic edema* yielded 458 articles. Of the initial 458 articles, a subsequent search of *olanzapine edema* yielded 33 articles, of which 14 detailed edema induced by olanzapine. Zero case reports concerning edema related to the search terms *olanzapine/fluoxetine edema* were found.

Discussion

Olanzapine is an SGA that antagonizes serotonin $5HT_{2A/2C}$, $5HT_6$, dopamine D_{1-4}, histamine H_1, and adrenergic α_1 receptors. The addition of olanzapine to fluoxetine is hypothesized to enhance antidepressant effects by interacting with serotonergic, dopaminergic, and noradrenergic monoamine pathways.[9] The multiple receptor subtypes targeted by olanzapine offer a variety of hypotheses as to why whole-body edema may have developed in our patient when it was added to fluoxetine. One prominent mechanism speculated to induce olanzapine-related edema pertains to α_1 adrenergic receptor blockade. Antagonism of these adrenergic-receptor subtypes may result in vasodilation, decreased vascular resistance, and subsequent movement of fluid into the intravascular space.[10-12] Furthermore, blockade of H1 and 5HT-2 receptors has been shown to downregulate inositol triphosphate-sensitive calcium channels to promote smooth muscle relaxation in the vasculature, resulting in subsequent edema. Such effects may also be triggered through an alternative pathway mediated by 5-HT2 receptor blockade, which can potentially increase cyclic adenosine monophosphate, inhibiting phosphorylation of myosin light chain kinase, resulting in vascular relaxation.[13] It may also be postulated that dopaminergic antagonism played a role in this adverse event, because hypodopaminergic states may disrupt fluid and electrolyte balance, resulting in idiopathic edema.[14,15]

This case described a patient who exhibited diffuse edema following initiation of olanzapine to augment existing fluoxetine therapy. The Naranjo Adverse Drug Reaction Probability Score for this case was 7, deeming it *probable* that the event was attributed to the addition of olanzapine.[16] The acuity of symptom onset following the initiation of olanzapine, the patient's previous tolerance of fluoxetine monotherapy, and resolution of symptoms after stopping olanzapine are strong indicators that this reaction is affiliated with olanzapine. It is unlikely that metabolic side effects, such as accumulation of adipose tissue, could have resulted in the rapid weight gain exhibited by the patient during the course of 5 days.[7] Additionally, the likelihood of the patient's medications, used prior to the introduction of olanzapine, inciting edema was determined to be negligible, because she had been stabilized on them for quite some time. Furthermore, clinical trial data for clonazapam, lisdexamfetamine, and zolpidem cite that edematous reactions are only noted to occur at a less than 1% rate, reducing the likelihood of these being confounding variables.[17-19] Detailed clinical and laboratory assessments failed to detect any other causal condition for the whole-body edema pertaining to allergic, dermatologic, cardiac, renal, hepatic, or thyroid disorders. Additionally, significant pharmacodynamic and/or pharmacokinetic drug interactions that may have incited fluid retention were not evident between olanzapine and the patient's other home medications. Peripheral or localized edematous reactions have been reported more frequently in olanzapine and olanzapine/fluoxetine groups, compared with placebo (15% vs 2%), in clinical trials.[5]

The available literature[11,12,14,20-25] suggests this reaction may occur at any dose of olanzapine, and it may not necessarily be dose dependent in nature, as noted by the cases describing persons who experienced edema with initiation of the drug (Table). Furthermore, timing of edema onset and resolution appears to be variable, ranging from 2 days to 2 months.[11,12,14,20-30] In most cases, symptom resolution occurred after withdrawal, or dose reduction, of olanzapine.[11,12,14,20-30] Based on these findings, it may be reasonable to rechallenge patients with a lower dose of olanzapine that was previously tolerated. It may also be reasonable to trial augmentation of antidepressants with an alternate SGA if olanzapine at any dose was not tolerated.

Several case reports detailed the use of loop diuretics to facilitate more rapid relief of edematous reactions.[11,25] Most cases of olanzapine-induced edema did not have evidence of an immune-mediated reaction, but in the 2 cases[20,22] presenting with olanzapine-induced angioedema, immune modulation medications, such as systemic corticosteroids or antihistamines, appeared helpful in resolving symptoms. There does not appear to be a set of patient-specific characteristics, or risk factors, among these cases that would compound the likelihood of experiencing olanzapine-associated edema. The degree of variability among case presentation and symptomatic management suggests that additional research on olanzapine-associated edema is warranted to determine when intervention beyond discontinuation of the drug alone is warranted.[11,12,14,20-30]

TABLE: Case reports of olanzapine-induced edema[11,12,14,20-30]

Source[a]	Starting Dose, mg/d	Dose Inciting Symptoms, mg/d	Characteristics/ Location	Onset	Duration	Treatment
Williams[20] (2019)	10	10	Angioedema	2 d	7 d	OW, antihistamine, H2 antagonist, systemic corticosteroids
Arslan et al[26] (2019)	10	15	Pericardium, hands, legs, ankles	2 d	14 d	OW
Kuppili et al[27] (2018)	5	12.5	Lower eyelids	2 mo	NR	Dose reduction of olanzapine to 5 mg
Umar and Abdullahai[11] (2016)	10	20	Hands, lower limbs	1 mo	3 wk	OW, loop diuretic
	20	20	Lower limbs	2 wk	1 wk	Dose reduction of olanzapine to 10 mg
Menon et al[28] (2015)	10	12.5	Lower limbs	7 d	NR	OW
Malhotra and Shrivastava[21] (2013)	NR	20	Periorbital region	7 mo	3 d	OW
	15	15	Face, periorbital region	1 mo	7 d	OW
Akın et al[14] (2013)	5	5	Face, hands, feet	20 d	NR	OW
Honma et al[22] (2012)	10	10	Angioedema, lower limbs	2 wk	1 mo	OW, antihistamine, Th2 cytokine inhibitor, glycyrrhizic acid
Nayak et al[23] (2009)	7.5	7.5	Feet	45 d	20 d	OW
Yaluğ et al[12] (2007)	10	10	NR	1 mo	1 mo	OW
	10	10	NR	1 mo	1 wk	Dose reduction of olanzapine to 5 mg
Zink et al[24] (2007)	5	5	Eyelids	1 d	1 wk	OW
Deshauer et al[25] (2006)	2.5	2.5	Hands, ankles	2 d	NR	Loop diuretic
Christensen and Honsig[29] (2003)	10	20	Ankles, feet	10 d	7 d	OW
Yovtcheva et al[30] (2000)	2.5	10	Feet	2 mo	2 wk	OW

NR = not reported; OW = olanzapine withdrawal.

[a]Studies organized in reverse chronological order, with reports listed most recently at the top.

Conclusion

This case describes a patient who exhibited whole-body edema and rapid weight gain following the addition of olanzapine to fluoxetine. At present, limited data exist regarding the mechanism behind such reactions to SGAs. Because of the temporal relationship of symptoms with initiation of olanzapine, we recommend monitoring for edema with initiation and/or titration of therapy.

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