

## Self-limiting Atypical Antipsychotics-induced Edema: Clinical Cases and Systematic Review

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### ABSTRACT

A number of atypical antipsychotics have been associated with peripheral edema. The exact cause is not known. We report two cases of olanzapine-induced edema and a brief review of atypical antipsychotic-induced edema, possible risk factors, etiology, and clinical features. The recommendation is given on different methods of managing this side effect.

**Key words:** *Atypical antipsychotics, edema, side-effect*

### INTRODUCTION

Olanzapine is an atypical antipsychotic that antagonizes dopamine D<sub>1</sub>, D<sub>2</sub>, and D<sub>4</sub> receptors.<sup>[1]</sup> It has antagonistic effect on histamine H<sub>1</sub>, muscarinic M<sub>4</sub>, serotonin 5HT<sub>2c</sub>, 5HT<sub>6</sub>, and 5HT<sub>7</sub> and  $\alpha_1$ -nordrenargic receptors. It is used for the treatment of schizophrenia and a manic episode of bipolar affective disorder,<sup>[2,3]</sup> and has shown benefit in the management of bipolar depression and relapsed prevention in bipolar disorder.<sup>[4]</sup> Weight gain, sedation, and postural hypotension are common side-effects of olanzapine,<sup>[1]</sup> however, recent studies have reported cases of peripheral edema.<sup>[5-7]</sup> Among atypical antipsychotics, edema has been reported in individuals using risperidone,<sup>[8]</sup> quetiapine,<sup>[9]</sup> ziprasidone,<sup>[10]</sup> amisulpride,<sup>[11]</sup> clozapine,<sup>[12]</sup> and paliperidone.<sup>[13]</sup>

We present two cases of peripheral edema associated with olanzapine treatment and a literature review of atypical antipsychotic-induced edema. Ethical review and clearance

were obtained from the Aminu Kano Teaching Hospital Ethical Committee. Thereafter, an informed consent was sought from the two patients and their guardians.

### CASE 1

A 35-year-old male who was being managed for bipolar affective disorder, currently with a manic episode. He was diagnosed 5 years ago and was on maintenance treatment with sodium valproate but had poor compliance to medication. During this index presentation, he was placed on olanzapine 10 mg daily and sodium valproate 400 mg twice a day. One week into admission the dose of olanzapine was increased to 20 mg daily because of increasing restlessness and grandiose delusion. About 1 month into admission, he was in remission but was noticed to have swelling of both legs and hands. The patient was not a known hypertensive

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**How to cite this article:** Umar MU, Abdullahi AT. Self-limiting atypical antipsychotics-induced edema: Clinical cases and systematic review. *Indian J Psychol Med* 2016;38:182-8.

Access this article online	
<b>Website:</b> www.ijpm.info	<b>Quick Response Code</b> 
<b>DOI:</b> 10.4103/0253-7176.183089	

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or diabetic. There was no history of use of alcohol but used cigarette and cannabis before presentation. The patient did not report any change in his dietary and fluid intake. He was not on any drug known to cause edema such as nonsteroidal anti-inflammatory drugs, steroids, antihypertensive, or immunosuppressive agents.

On examination, he had a nonpitting pedal severe edema while that of the hands were mild based on the classification of severity of edema.<sup>[14]</sup> Blood pressure, cardiac, and abdominal examinations were normal. The urea, creatinine, electrolytes, thyroid function test, liver function tests, and serum proteins were normal. Urine test, chest X-ray, electrocardiogram and abdominopelvic ultrasound were also normal.

When the above investigation turned out to be normal olanzapine was stopped, based on emerging evidence of rare association of olanzapine with peripheral edema.<sup>[7,14]</sup> One week after discontinuation of olanzapine, edema was moderately severe and therefore, frusemide 5 mg was introduced and within 2 weeks swelling completely resolved. He was then placed on risperidone 4 mg daily and sodium valproate. This patient had used sodium valproate without a report of edema in the past. The adverse effect was scored using the Naranjo's algorithm for adverse drug reaction probability scale,<sup>[15]</sup> and a score of 7 was obtained which indicate strong association of edema with olanzapine.

## CASE 2

A 41-year-old man presented with 7 months history of persecutory delusion, delusion of reference, auditory hallucination, and vagrant-like behavior. A diagnosis of schizophrenia was made. He was commenced on haloperidol 5 mg bid and later increased to 10 mg bid. Four weeks later the medication was changed to olanzapine at a dose of 20 mg daily after delusion persisted and had an extrapyramidal side-effect. The patient developed swelling of both legs, moderate edema up to the knee, 2 weeks after introduction of olanzapine. Physical examination of other system was normal. The urea and electrolyte, creatinine, urinalysis, liver function test, fasting blood glucose, and lipid profile were normal. Abdominal scan and chest X-ray were also normal. The thyroid function test was normal. There was no diurnal variation of edema or skin changes or itching. The olanzapine was reduced to 10 mg. Within 1 week of reducing olanzapine, the edema resolved. Due to the presence of psychopathology, the olanzapine was again increased to 20 mg but edema reappeared by the 5<sup>th</sup> day. This time around the edema was severe compared to the earlier presentation. Olanzapine was reduced to 10 mg, and the swelling of the lower limbs resolved after 1 week. Naranjo's score was 8.

## Causality

In both cases, the presence of peripheral edema could be attributed to use of olanzapine since edema disappeared in the first case when olanzapine was stopped and in the second case when it was reduced.

In the first case, the patient had been on sodium valproate before the introduction of olanzapine without peripheral edema, and edema did reduce with olanzapine stoppage while still taking sodium valproate. In some cases, it had been noted that valproate may increase the plasma concentration of antipsychotic.<sup>[16]</sup> Chen *et al.*<sup>[9]</sup> and Yalug *et al.*<sup>[17]</sup> reported edema in patients in which valproate was used as co-medication with quetiapine and olanzapine respectively. By decreasing the hepatic activity of CYP3A4, a metabolizing isoenzyme, it may contribute to higher level of plasma concentration of antipsychotic.<sup>[18]</sup> Valproate on its own has been associated with isolated peripheral edema.<sup>[19]</sup>

On the other hand, drug-induced edema may be due to dose-dependent mechanism,<sup>[20-22]</sup> and not related to co-medication with valproate.<sup>[17]</sup> This is consistent with our second case in which reduction of olanzapine resulted in the disappearance of edema.

In the two cases presented, edema can be attributed to olanzapine as other causes of edema such as renal, cardiac, and other drug-induced causes were ruled out. There was a temporal relationship between the start of olanzapine and the development of edema using the Naranjo's adverse reaction scale as causal assessment is regarded as having a score of at least 7.<sup>[15]</sup>

## SYSTEMATIC REVIEW OF ATYPICAL ANTIPSYCHOTIC-INDUCED EDEMA

A search was performed through August, 2015 on PubMed, EMBASE, and Google Scholar with keywords including "atypical antipsychotics," "edema," "peripheral edema," "olanzapine," "risperidone," "quetiapine," "aripiprazole," "ziprasidone," "amisulpride," "clozapine" and "paliperidone." The references of relevant articles were reviewed for additional citations. To assess causality for atypical antipsychotic-induced edema review reports with Naranjo's probability scale score of at least 5–8, showing a probable association with the medication, were included. Furthermore, articles on angioneurotic edema were excluded. In this review, we only included studies published in English.

A total of 108 articles were retrieved by web-based searching in the first instance. Forty-eight case reports were retrieved with 30 with a total of 34 cases fulfilling

the inclusion criteria while 3 cross-sectional studies of olanzapine-induced edema were also included.

The mean age of the patients in the case reports is 44 years with females constituting 70.6% of the cases, those with schizophrenia at 47.1% and bipolar disorder at 20.6%. Only 6 (17.6%) had a Naranjo score of 9 and above indicating definite causal relationship.

### Prevalence

In a randomized, double-blind study that was aimed at comparing the effect of risperidone with placebo on psychosis and behavioral disturbances in patients with dementia, reported a prevalence of 15.8% of risperidone-induced edema.<sup>[23]</sup> This study should be interpreted with caution as the average age of the study population was 82 years. This high rate of peripheral edema might be associated with deteriorating physical health state of the patients in terms of reduced cardiac and renal functioning. On the other hand, the study by Ng *et al.*<sup>[14]</sup> among 49 outpatients on olanzapine reported prevalence of 57% with 10.2% having edema with a severe degree. However, this study included patients with co-morbid medical conditions including hypertension, cardiovascular problems, and thyroid hormone abnormalities. On the other hand, a longitudinal observational study among Indian psychiatric outpatients reported that 0.85% had pedal edema in a study of adverse drug reaction from antipsychotics.<sup>[24]</sup>

In this review of cases, risperidone, olanzapine, and quetiapine were reported at the same rate of 29.4%. In a review by Chen *et al.*,<sup>[13]</sup> risperidone and olanzapine were the drugs most likely to be associated with edema and followed by quetiapine.

### Clinical features

The time to onset of edema after ingestion of atypical antipsychotic varies widely, from a day to several months.<sup>[6,25]</sup> In this review, the mean time of onset from the start of antipsychotic was 22.9 days (standard deviation [SD] = 23.51) but in majority of the case reports the onset was within the first 4 weeks [Table 1]. A review by Hsu and Chang of edema related to antipsychotic reported a mean time of onset of 25.8 days.<sup>[13]</sup>

Antipsychotic-induced peripheral edema can develop bilaterally in the legs in most reported cases [Table 1] but can also affect other parts of the body either alone or in combination with pedal edema. These include the eyelids,<sup>[25]</sup> face,<sup>[5,38]</sup> hands,<sup>[8,28]</sup> periorbital region,<sup>[21,42]</sup> forearms,<sup>[44]</sup> lower trunk,<sup>[10]</sup> and a combination of face, eyelid, and lower extremity.<sup>[37]</sup>

The time of resolution of edema took <4 weeks in the cases reviewed with mean of 10.3 days (SD = 7.98).

Even though individuals with schizophrenia and bipolar were represented more in the case reports, the cross-sectional study of Ng *et al.*<sup>[14]</sup> of 49 subjects receiving olanzapine reported no significant differences regarding concomitant diagnosis.

## MECHANISM OF ANTIPSYCHOTIC-INDUCED EDEMA

A plausible mechanism of olanzapine-induced edema is still unknown. Various theories have been postulated.

### Supersensitivity and vasodilatation theory

This states that there is super-sensitivity of  $\alpha$ -receptors to antipsychotic which occurred during the drug-free period.<sup>[22,41]</sup> The  $\alpha$ -receptors of the peripheral vascular system cause vasodilatation and thereby raising the hydrostatic pressure by decreasing the vascular resistance in the blood capillaries. This hydrostatic pressure moves the fluid from the intravascular compartment to the interstitial space, which leads to edema.<sup>[9,17]</sup> The associated vasodilatation is seen in patients using antipsychotics as a plausible cause of edema.<sup>[45]</sup> This theory postulates that there is a “critical drug-free period” during which reinstatement of the agent, in this case, risperidone, may increase the rate of manifestation of side-effect due to super-sensitivity of the neurons.<sup>[41]</sup>

### Dose-response (dose-dependent) relationship

Yang and Cheng,<sup>[44]</sup> reported switching their patient from oral to depot risperidone without having re-occurrence of edema. It was explained that the use of long-acting injectable risperidone leads to smaller peak-to-trough fluctuations in the plasma risperidone concentration compared with oral risperidone. On the contrary, Pelizza<sup>[42]</sup> reported a case of periorbital edema in a patient on depot risperidone.

For both cases in this report, the patients were on relatively high dose of olanzapine. In the second case, when olanzapine was reduced edema disappeared. This dose-dependent theory is supported by Tamam *et al.*<sup>[22]</sup> where within 1 week of reduction of risperidone edema resolved. In a randomized, double-blind controlled study by Katz *et al.*,<sup>[23]</sup> peripheral edema developed in a dose-related pattern. Edema may be the result of antipsychotic antagonism on the renal dopamine receptors ( $D_4$ ) thereby altering the renal regulation of fluid and electrolyte.<sup>[46,47]</sup> However, edema has been reported in individuals taking low-dose antipsychotics.<sup>[13,28,40,43]</sup>

### Rate of dose escalation

Kores Plesnicar *et al.*<sup>[21]</sup> reported that their patient that developed edema had her risperidone titrated from 2 to 6 mg within 2 weeks. Rapid dose increase of olanzapine may also be a factor in inducing peripheral edema.<sup>[7]</sup>

**Table 1: Atypical antipsychotic-induced edema: Demographic characteristics and medication variables**

Author	Number of cases	Age (years)	Gender	Diagnosis	Agent, dose (mg)	Time to onset	Site	Time to resolution (days)	Naranjo score	Measures taken
Yovtcheva and Yazel <sup>[26]</sup>	1	58	Male	Bipolar disorder	Olanzapine 10	8 weeks	Bilateral pedal	14	7	Substitution with quetiapine
Christensen <sup>[27]</sup>	1	34	Female	Bipolar disorder	Olanzapine 10	10 days	Bilateral pedal	NA	9	NA
Yalug <i>et al.</i> <sup>[17]</sup>	1	34	Female	Bipolar disorder	Olanzapine 10	12 weeks	Bilateral pedal	30	6	Substitution with risperidone
Zink <i>et al.</i> <sup>[25]</sup>		41	Male	Schizoaffective disorder	Olanzapine 5	1 day	Eyelid edema	1	7	Substitution with amisulpride
Deshauer <i>et al.</i> <sup>[28]</sup>	1	50	Female	Bipolar disorder	Olanzapine 2.5	2 day	Bilateral pedal and hands	7	10	Diuretics
Nayak <i>et al.</i> <sup>[7]</sup>	2:1	37	Male	Alcohol Withdrawal	Olanzapine 7.5	6 weeks	Bilateral pedal	20	7	Substitution with risperidone
	2	30	Male	Schizophrenia	Olanzapine 15	8 weeks	Bilateral pedal	15	7	Substitution with risperidone
Dada <i>et al.</i> <sup>[29]</sup>	1	40	Female	Schizophrenia	Olanzapine 10	4 weeks	Facial bilateral pedal	NA	7	NA
Vohra <sup>[30]</sup>	1	40	Female	Bipolar disorder	Olanzapine 30	4 weeks	Bilateral pedal hand edema	21	7	Substitution with chlorpromazine
Mathan <i>et al.</i> <sup>[31]</sup>	1	45	Female	Schizophrenia	Olanzapine 12.5	2 weeks	Bilateral lower limb	NA	8	Stopped
Rozzini <i>et al.</i> <sup>[32]</sup>		72	Male	Dementia	Quetiapine 150	NA	Bilateral pedal	NA	-	-
McSkimming <i>et al.</i> <sup>[33]</sup>	1	45	Female	Severe depression	Quetiapine 200	12 h	Bilateral pedal	1		Substitution with olanzapine
Roy <i>et al.</i> <sup>[34]</sup>	1	43	Female	Severe depression with psychosis	Quetiapine 300	NA	Bilateral pedal extending to thigh	NA	7	Diuretics
Chen <i>et al.</i> <sup>[9]</sup>	1	73	Female	Bipolar disorder	Quetiapine 100	<1 week	Bilateral pedal	5	7	Substitution with olanzapine
O'Connor <i>et al.</i> <sup>[35]</sup>	1	28	Male	Schizophrenia	Quetiapine 100	7 days	Bilateral pedal	12		Diuretics
Koleva <i>et al.</i> <sup>[20]</sup>	3:1	59	Female	Bipolar disorder	Quetiapine 150	4 weeks	Bilateral pedal	7	9	Olanzapine ↓, diuretics
	2	44	Female	Severe	Quetiapine 50	4 days	Bilateral pedal	2	7	Stopped
	3	38	Female	Depression psychosis	Quetiapine 200	1 day	Bilateral pedal	7	8	Perphenazine, diuretics
Chen <i>et al.</i> <sup>[36]</sup>	1	55	Male	Schizoaffective disorder	Quetiapine 800	5 weeks	Bilateral pedal	21	8	Olanzapine ↓
Chan and Chen <sup>[37]</sup>	1	60	Female	Severe depression	Quetiapine 25	3 days	Bilateral pedal, eyelid, facial edema	1	10	Substituted with duloxetine
Cooney and Nagy <sup>[38]</sup>	1	30	Female	Schizophrenia	Risperidone 6	2 weeks	Facial, periorbital	14		Stopped
Sanders and Lehre <sup>[39]</sup>	1	40	Female	Schizoaffective disorder	Risperidone 10	8 weeks	Bilateral pedal and hand	NA	8	NA
Kores Plesnicar <i>et al.</i> <sup>[21]</sup>	1	63	Female	Schizophrenia	Risperidone 6	4 weeks	Periorbital	7		Nil
Ravasia <sup>[40]</sup>	1	41	Female	Schizophrenia	Risperidone 1	3 days	Bilateral pedal	2	7	NA
Tamam <i>et al.</i> <sup>[22]</sup>	1	27	Female	Schizophrenia	Risperidone 4	3 weeks	Bilateral pedal, periorbital, facial	7	6	Risperidone ↓
Feroz-Nainar <i>et al.</i> <sup>[41]</sup>	1	16	Male	Autism, learning disability, epilepsy	Risperidone 2	Few weeks	Bilateral pedal	14	7	Risperidone ↓
Pelizza <sup>[42]</sup>	1	39	Female	Schizophrenia	Risperidone depot, 50	14 days	Periorbital	30	7	Substitution with olanzapine
Akdag <i>et al.</i> <sup>[43]</sup>	1	8	Female	Adjustment disorder	Risperidone oral 0.5	3 days	Bilateral pedal	2	7	NA
Hosseini and Ahmadi <sup>[8]</sup>	1	80	Female	Severe depression	Risperidone 2	<20 days	Bilateral pedal and hands	7	9	Substitution with quetiapine
Yang and Cheng <sup>[44]</sup>	1	51	Female	Schizophrenia	Risperidone 2, oral solution	4 days	Bilateral pedal, forearms, hands	7	10	Substitution with aripiprazole, risperidone depot
Ku <i>et al.</i> <sup>[10]</sup>	1	51	Female	Schizophrenia	Ziprasidone 80	6 weeks	Bilateral pedal to lower trunk	14	6	Substitution with Sulpiride, diuretics
Chen and Chou <sup>[11]</sup>	1	51	Male	Schizophrenia	Amisulpiride 800	4 weeks	Bilateral pedal	7	7	Amisulpiride ↓, diuretics
Chen <i>et al.</i> <sup>[13]</sup>	1	50	Male	Schizophrenia	Paliperidone 9	2 weeks	Bilateral pedal	7	8	Haloperidol
Durst <i>et al.</i> <sup>[12]</sup>	1	24	Female	Schizophrenia	Clozapine 400	6 weeks	Bilateral pedal and periorbital	10	7	Clozapine ↓

↓ – Medication was reduced; NA – Not available

The rate of dose escalation of antipsychotics may be a factor in antipsychotic-induced edema. Various factors such as age, previous exposure to antipsychotic, history of side effects, the severity of illness, presence of physical health condition, and the need for a rapid response in treatment usually determine the rate of antipsychotic dose escalation.<sup>[48]</sup>

No consensus has been reached on what is rapid dose escalation, even though Langan *et al.* attempted to define it mathematically.<sup>[49]</sup> The cumulative antipsychotic dose for an individual is calculated for days 1–15 and days 16–30 and then a ratio of first 15 days to second 15 days is generated. They authors defined dose escalation as a ratio of 4 times of the cumulative dose at the second 15 days compared to the first 15 days.

### Allergic reaction

Immune reaction may be implicated in the mechanism of drug-induced edema.<sup>[10,11,21,38]</sup> Immune components that were reported in case reports include elevated immunoglobulin E in relation to ziprasidone and amisulpride,<sup>[10,11]</sup> low C<sub>4</sub> and C<sub>1</sub> esterase inhibitor in relation to risperidone (Conney and Nagy, 1995).<sup>[38]</sup> However, other studies that assessed immunological reactions as possible cause of drug-induced edema did not find any impairment.<sup>[9,20,40,42]</sup> Patients with abrupt onset edema could be from allergic mechanism.

### Other risk factors

Older age has been suggested as a risk factor, especially in those with severe edema,<sup>[14]</sup> but it has also been reported in children and adolescents,<sup>[6,43]</sup> and reported a mean age of 44.1 years.<sup>[13]</sup> The mean age in this review of case reports is 44 years.

The majority of cases reported are among females (70.6%), and this was also found in the review of quetiapine-induced peripheral edema.<sup>[37]</sup> However, the cross-sectional study by Ng *et al.* reported no association with gender.<sup>[14]</sup>

Antithyroid bodies were significantly associated with olanzapine-induced edema.<sup>[14]</sup> No other study has replicated this finding.

Antipsychotics that contain some inactive compounds such as titanium dioxide, propylene glycol, and ionic compounds that contain sodium have also been implicated.<sup>[50]</sup>

## MANAGEMENT OF ANTIPSYCHOTIC-INDUCED EDEMA

In our first case, diuretic (frusemide) was given when olanzapine was stopped. This was because of the

slow rate of resolution of edema. Other studies have reported using diuretics in the management of atypical antipsychotic-induced edema.<sup>[10,28,35]</sup>

While in the second case, reduction of olanzapine was effective in the resolution of the edema. This method was reported in other case reports.<sup>[17,22,36,41]</sup> In other studies, the offending agent was reduced with the addition of diuretics.<sup>[11,20]</sup> On the other hand, most case reports stopped the offending antipsychotics and substituted them with others without reoccurrence of edema.<sup>[5,7,26,30,33]</sup>

### Limitation

Most of the patients in the case reports reviewed were also taking other medications such as valproate, escitalopram, and lithium which are also known to be associated with edema.<sup>[19,51-53]</sup> There are few cross-sectional and longitudinal studies addressing antipsychotic-induced thus limiting conclusion on the relationship between atypical antipsychotics and peripheral edema.

## CONCLUSION

Antipsychotic-induced edema is not an uncommon side-effect of atypical antipsychotics. Edema is uncomfortable to patients and usually requires a number of examinations to accurately determine its causes. The clinician should be alert to the following factors that may be associated with antipsychotic-induced edema.

- Antipsychotic-induced edema can occur with any dose of atypical antipsychotic<sup>[14,28,40]</sup>
- Edema can occur in any peripheral area of the body including the face and eyelids
- Sudden increase of dose of medication may be a factor, and therefore, gradual increase is advised<sup>[38]</sup>
- Replacement with another antipsychotic is advocated, but in cases where the offending medication is necessary, it should be gradually reduced<sup>[11,17,20,22,41]</sup>
- Diuretics may be used in cases that have not resolved with the stoppage of the offending agents, although the long-term effect of using diuretic is not known<sup>[10,11,20,28]</sup>
- The use of co-medication should be done with caution<sup>[9,17,39]</sup>
- Even after drug-free period with the implicated drugs, edema could still re-occur after reinstatement,<sup>[22,41]</sup> and therefore, it is preferable not to rechallenge with the offending agent<sup>[8,37]</sup>
- During reinstatement of antipsychotic that was previously implicated as the cause of edema, it is advised that the dose should be small and gradually increased to therapeutic level<sup>[41]</sup>
- Antipsychotic-induced edema is not associated with any diagnosis<sup>[14]</sup>

- Comorbid physical factors may not be predisposing factor<sup>[13]</sup>
- Older age may be a risk factor.<sup>[9,14]</sup>

Edema is often not enquired by physicians unless the patient complains about it. From the review, it shows that atypical antipsychotic-induced edema may not be a less frequent complication. Even though antipsychotic-induced edema may be transient and self-limited, it symptoms still carries with it uncomfortable feeling and, therefore, it is important to understand the risk factors and method of managing these cases and to initiate close monitoring when antipsychotic are prescribed. In the future, it is recommended that prospective studies be carried out to determine the risk factors associated with and the long-term implication of antipsychotic-induced edema.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

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