



## CASE REPORT

# Quetiapine-induced peripheral edema: case series

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### ABSTRACT

Quetiapine is a commonly prescribed antipsychotic in the treatment of psychiatric disorders. Although it has a relatively moderate side-effect profile, peripheral edema might be much more common than reported in clinical trials. All other second-generation antipsychotics may also induce peripheral edema, which could be important for treatment compliance. Therefore, clinicians must be aware of the possibility of edema development. This case series aims to discuss the related variables and underlying pathophysiology of SGA-related edema.

**Keywords:** Edema, peripheral edema, quetiapine, second-generation antipsychotics

## INTRODUCTION

Quetiapine is a second-generation atypical antipsychotic (SGA) which is chemically similar to clozapine. In addition to its D2 receptor antagonism, quetiapine also effects serotonergic (5-HT<sub>2A</sub>, 5-HT<sub>2C</sub>, 5-HT<sub>6</sub>, 5-HT<sub>7</sub>), muscarinic (M<sub>1</sub>, M<sub>3</sub>), histaminergic (H<sub>1</sub>), adrenergic (alpha<sub>1</sub>, alpha<sub>2</sub>) receptor antagonism and 5HT<sub>1A</sub> partial agonism. Sedation, weight gain, orthostatic hypotension, and cardiometabolic problems are common side effects of quetiapine (1).

Edema is a tissue swelling resulting from excessive interstitial fluid volume. If an edema is localized on the hands, wrists, feet, and ankles, it is called peripheral edema. Peripheral edema is caused either by systemic diseases such as liver cirrhosis, kidney diseases, congestive heart failure, lymphedema, hypoproteinemia, or cancer, or by the use of substances like non-steroidal

anti-inflammatory drugs, anti-hypertensive drugs, immunosuppressive drugs, and steroids (2). Peripheral edema, although not life-threatening, is nevertheless an important side effect interfering with treatment compliance. Peripheral edema induced by quetiapine use has been reported previously (3).

In this report, we aimed to present 5 cases of peripheral edema induced by quetiapine use and resolved after treatment termination. We have obtained full written consent from these patients and their first-degree relatives. The Naranjo Adverse Drug Reaction Probability Scale (NADRPS) was used to assess whether peripheral edema in these cases was the result of a drug side effect. The NADRPS solicits answers to 10 questions, and based on the total score, the suspected adverse drug reactions are assigned a probability as follows: >9: highly probable, 5-8=probable, 1-4=possible, and 0=doubtful (4).

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## CASES

### Case 1

A 46-year-old female patient who had been followed with bipolar mood disorder for 10 years was taken to the psychiatric emergency service with complaints of “aggression, paranoid thoughts, insomnia, and excessive talking.” Her family reported that she had stopped her maintenance treatment of sodium valproate 3 months ago. The patient was admitted to the psychiatric inpatient clinic with a diagnosis of Bipolar I Disorder, manic episode with psychotic symptoms according to DSM-IV. Considering the patient’s psychotic symptoms like paranoid delusions, quetiapine 20mg/day was added in the first week of hospitalization and increased to 600mg/day in a two-week period. On admission, sodium valproate 500mg/day was prescribed and increased to 1500mg/day given that she had benefited from sodium valproate 1500mg/day as a mood stabilizer previously. Although her psychiatric symptoms started to decline, she presented with leg pain with 3+ pitting edema on the 17th day of treatment. In addition to consultations with a cardiologist and a cardiovascular surgeon, blood biochemistry panel, complete blood count (CBC), and thyroid function tests (TFT) were performed to assess the patient’s other medical conditions. Since all medical evaluations revealed normal results, this condition was considered to be a drug side effect. Because she had been on valproic acid previously without any problems, the peripheral edema was thought to be associated with quetiapine. Following the termination of quetiapine treatment, the pretibial edema decreased and disappeared within one week. The NADRPS score was calculated to be 6 (probable). The patient was discharged on haloperidol 5mg/day and no recurrence of peripheral edema was observed at follow-up.

### Case 2

A 52-year-old female patient who had been followed with Bipolar Disorder-Not Otherwise Specified according to DSM-IV for 5 years presented to the outpatient clinic with complaints of “insomnia and increased energy.” She was not receiving any psychiatric treatment and it was learned that she had responded well to quetiapine 600mg/day with no significant side effects in her previous mood episode 2 years ago. Therefore, she was again prescribed quetiapine 200mg/day, which was increased to 400mg/day for the current episode. She responded well to the treatment; however, she developed a 2+ pitting edema after 2 weeks. In order

to assess the patient’s other medical conditions; blood biochemistry panel, CBC, and TFT were performed following consultations with a cardiologist and a cardiovascular surgeon. As all other medical tests revealed normal results and the patient was not using any other medication, this condition was considered to be a side effect of quetiapine. After discontinuation of the quetiapine treatment, the pretibial edema regressed within ten days. The NADRPS score was calculated to be 6 (probable). The patient was discharged on paliperidone 6mg/day and later, due to non-compliance, she switched to once-monthly paliperidone palmitate 75mg injection. There was no recurrence of peripheral edema at follow-up.

### Case 3

A 43-year-old female patient who had been on sodium valproate treatment for the maintenance of Bipolar-I Disorder for the last 10 years presented to the psychiatric emergency service. As she had suffered from “insomnia, pressured speech, and paranoid thoughts” for the last 5 days, she was diagnosed with Bipolar-I Disorder according to DSM-IV, and quetiapine 300mg/day was added to the treatment and increased to 600mg/day in the first week of treatment. However, pretibial 2+ pitting edema was determined at the patient’s physical examination presenting with leg pain in the 2nd week. All evaluations, including blood biochemistry panel, CBC, and TFT, yielded normal results, as did the consultations with a cardiologist and a cardiovascular surgeon. The peripheral edema was thus considered to be a side effect of quetiapine, since the patient had been using sodium valproate for a long time. Following the reduction of the quetiapine dose to 300mg/day, on the 10th day the edema also reduced but did not disappear completely. Only after the cessation of quetiapine treatment, the peripheral edema resolved completely within 3 days. The NADRPS score was calculated to be 7 (probable). The patient was discharged on olanzapine 10mg/day and the peripheral edema was not observed again.

### Case 4

A 50-year-old female patient with a diagnosis of Bipolar-I Disorder according to DSM IV who had been using sodium valproate for 7 years was hospitalized because of a manic episode with psychotic features. Quetiapine 300mg/day was added to the ongoing sodium valproate treatment and increased to 800mg/day. Although she responded well to the treatment, a 2+ pitting edema developed on the 5th day of treatment.

For differential diagnosis, blood biochemistry panel, CBC, and TFT were performed following consultations with a cardiologist and a cardiovascular surgeon. Since all results were within normal limits, the condition was considered to be a side effect of quetiapine. After reduction of the quetiapine dose by half, the edema began to recede but did not disappear. Only after 7 days following the complete discontinuation of quetiapine, the peripheral edema resolved completely. The NADRPS score was calculated to be 7 (probable). The patient was discharged with risperidone 4mg/day being added to the sodium valproate treatment, with no re-occurrence of the edema. Further investigation in this patient uncovered a past history of peripheral edema with olanzapine 10mg/day 4 years earlier.

### Case 5

A 22-year-old female patient at 34 weeks of gestation was treated on the obstetrics ward of a university hospital. She had been followed with Bipolar-I Disorder according to DSM IV for 5 years. The maintenance treatment of lithium was gradually decreased 1.5 years ago since she decided to have a baby. In the 26<sup>th</sup> week of gestation, she was prescribed quetiapine 300mg/day plus olanzapine 5mg/day for complaints of “excessive talking, increased energy, paranoid thoughts, and insomnia” in another mental health clinic. A few weeks later, the quetiapine dose was increased to 600mg/day. With the increased dosage of quetiapine, a mild peripheral edema began to develop. In the last 2 weeks, due to a dramatic increase in the severity of the edema she was hospitalized with a possible diagnosis of preeclampsia with 3+ pitting edema. Detailed investigation of liver function tests, kidney function tests, and 24-hour urine protein test revealed normal results, and the blood pressure monitoring was within normal limits. After ruling out the diagnosis of preeclampsia, peripheral edema was considered as a potential drug side effect. Following the termination of quetiapine treatment, the edema resolved within one week. In order to stabilize the symptoms, the olanzapine dose was increased from 5mg/day to 10mg/day. No recurrence of peripheral edema was observed at follow-up. The NADRPS score was calculated to be 7 (probable).

## DISCUSSION

Edema has been reported in individuals using atypical antipsychotics (3,5). Although it has been suggested that peripheral edema arising from the use of SGA is

caused by dopaminergic antagonism, the mechanism is not yet clear (6). Peripheral edema associated with other dopamine receptor antagonists such as olanzapine (5,7) and risperidone (8,9) as well as quetiapine has also been reported (10-15). In a review conducted by Chen et al. (16), SGAs with the highest peripheral edema risk were found to be risperidone and olanzapine with 33.3%, followed by quetiapine with 27.8%. In the cases presented above, the absence of any other comorbid medical condition, timing of edema development, and resolution after cessation of quetiapine support a strong association between peripheral edema and quetiapine use.

The presence of additional medical diseases, or the deterioration of thyroid, cardiac, liver, and kidney function might also have contributed to the development of peripheral edema among elder patients (5). In fact, senility is an important predictor of a higher quetiapine concentration due to a reduction of hepatic activity of CYP3A4, the principal metabolizing isoenzyme of quetiapine (1). However, the age range of the cases we present in this case series lies between 22 and 54 years, and the patients had no additional diseases and totally normal thyroid, liver and kidney functions.

The mean time of developing antipsychotic-related edema can vary from one day to several months after the start of treatment. In Umar and Abdullahi's study, the mean onset of edema was 22.9 days and regression of edema was observed in a mean of 10.3 days (less than 4 weeks) (17). In the majority of reported cases, edema developed in both legs and less frequently in the hands, arms, face, eyelids, and periorbital region. All the five cases we present here had bilateral pretibial edema.

Having any history of peripheral edema associated with any one SGA may increase the risk for peripheral edema with another SGA. Koleva et al. (3) reported a similar adverse event following the use of other atypical antipsychotics in 2 of 3 quetiapine-associated peripheral edemas in their case series (3). In the 4<sup>th</sup> case we present, the patient had a history of edema associated with olanzapine use.

In some case reports, peripheral edema was reported to resolve after reduction of SGA dosage (12,18). The rate of antipsychotic dosage increase (gradual vs. rapid increase) may also play a role in the development of antipsychotic-induced edema. However, in our 3<sup>rd</sup> and 4<sup>th</sup> cases, the edema began to recede but did not completely disappear following a decrease in quetiapine dosage.

The mechanism of edema formation is not yet clear. It is thought that they may occur for several different

reasons such as dopamine antagonism, 5-HT<sub>2</sub>, alpha<sub>1</sub>, muscarinic (M<sub>1</sub>), histamine-1 receptor blockade, or IgE-mediated allergic reaction (11). Peripheral dopaminergic blockade through a variety of receptor subtypes may affect natriuresis; epithelial fluid resorption, vascular smooth muscle relaxation, and the renin-angiotensin system play a role in the formation of edema by altering renal fluid-electrolyte regulation (11). Kuchel et al. (19) reported that low urinary dopamine levels may contribute to edema formation through the renin-aldosterone system. Moreover, the contribution of the inactive components of antipsychotic drugs to the development of edema is still unknown.

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Category 1	Concept/Design	A.P., R.G.
	Literature review	H.T., N.G.
	Data analysis/Interpretation	A.P.
	Case follow-up (if applicable)	N/A
Category 2	Drafting manuscript	A.P., N.G.
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Category 3	Final approval and accountability	A.P., R.G., H.T.
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