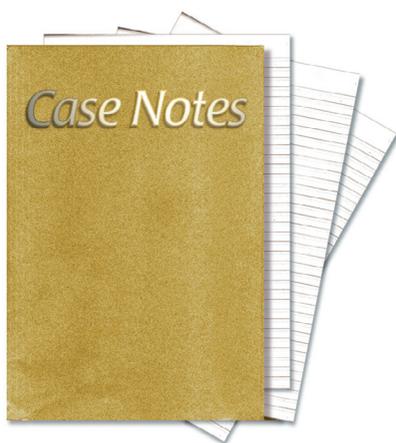


Case notes

Pedal oedema associated with atypical antipsychotics



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There are only a few case reports of pedal oedema attributed to atypical antipsychotic medications. Here, the authors describe three cases of pedal oedema occurring in patients taking atypical antipsychotics and discuss the possible mechanisms that may be involved.

Although atypical antipsychotics have less propensity to cause extrapyramidal symptoms than typical antipsychotics, unfortunately they can be associated with other side-effects including weight gain and elevated blood glucose concentration. Another possible side-effect is pedal oedema, which may not be as uncommon as previously thought. There are several pathophysiological mechanisms for the development of pedal oedema.¹ It has been suggested that atypical antipsychotics may cause oedema by increasing capillary permeability and increasing retention of sodium by the kidneys via their action on many different receptor types, including dopamine, serotonin and alpha-adrenergic receptors.

In this article, we describe three cases of pedal oedema that appeared to be associated with the use of atypical antipsychotics and discuss the possible mechanisms that may underlie the oedema.

Case presentations

Case 1

A 41-year-old, mixed race, divorced man first made contact with mental health services with symptoms of persistent depressed mood and anxiety associated with second-person auditory hallucinations. He was diagnosed with severe depression with psychotic symptoms as

per the ICD-10 diagnostic criteria. He was treated with citalopram 20mg daily and olanzapine 2.5mg daily. His symptoms improved, but he disengaged with the primary care liaison team after six months of treatment.

Two years later, he had a relapse with a three-month history of anxiety and depression associated with second-person auditory hallucinations, which were derogatory in nature. At the time of presentation, although he was taking citalopram 40mg daily, he had discontinued olanzapine. Olanzapine was restarted at 5mg daily and gradually increased to 10mg daily. He developed pedal oedema on day 3 of starting olanzapine. Pedal oedema became more obvious after one week when the dose was increased. The evaluation by his physician did not reveal any physical cause for the pedal oedema. However, his full blood count showed mild microcytic hypochromic anaemia. All other investigations including urea and electrolytes, liver function tests, thyroid function tests and lipid profile were normal. He underwent further investigations to find the cause of the anaemia.

The patient refused to continue olanzapine as he felt it had caused the pedal oedema and he had also gained weight. The treating team decided to discontinue the olanza-

pine and he was started on quetiapine. The oedema subsided completely within a week of stopping olanzapine.

Case 2

A 48-year-old African Caribbean woman with a 13-year history of schizophrenia as per ICD-10 diagnostic criteria had persecutory delusions of a bizarre nature and third-person auditory hallucinations. She had had a deep vein thrombosis five years previously.

Her medication compliance was poor and she developed extrapyramidal symptoms with thioridazine at a dosage of 50mg daily. Her medication was switched to olanzapine 5mg daily. She never took medications as prescribed and always had residual psychotic symptoms. A year following the switch, olanzapine 5mg daily was reduced to 2.5mg daily due to complaints of severe sedation.

She was referred to the home treatment team four years later following worsening of her psychotic symptoms. She was restarted on olanzapine 5mg daily, which was gradually increased to 10mg daily. Subsequent to her increase in olanzapine, it was noticed that she developed severe bilateral pedal oedema, tenderness in her breasts as well as galactorrhoea. There were no signs or symptoms sug-

gestive of recurrence of deep vein thrombosis.

She was reviewed by a physician and no physical cause for the oedema was found. Her haematological and biochemical profile, including full blood count, serum albumin, lipid profile, liver function tests, thyroid function tests, urea and electrolytes, were normal. Due to worsening of the physical symptoms, olanzapine was discontinued, which resulted in complete resolution of the pedal oedema, galactorrhoea and breast tenderness.

Case 3

A 41-year-old Caucasian man with an ICD-10 diagnosis of delusional disorder presented with a four-month history of well-systematised persecutory delusions. He believed an organised crime gang was trying to steal his art work. According to him, people were trying to gain access to his flat. He believed gunmen were watching with snipers through the window and so he was crawling in the house to avoid being sighted by them. He was started on risperidone 1mg twice daily, which was gradually increased to 5mg daily.

Pedal oedema was noticed after his first dose of risperidone, which gradually increased and he had pitting oedema up to his shin. Physical examination and relevant medical investigations were unremarkable. He refused to continue risperidone due to the increasing pedal oedema. The oedema began to subside as soon as risperidone was stopped. On day three of discontinuing risperidone, the pedal oedema completely disappeared. He was then switched to aripiprazole, which was well tolerated by the patient.

Discussion

In Case 1, there was temporal correlation between initiating olanzapine

and onset of oedema that resolved following discontinuation of the drug. Microcytic hypochromic anaemia is an unlikely cause of this patient's oedema as he continued to have anaemia even when the oedema has subsided. In Case 2, it is unlikely that deep vein thrombosis was a cause of pedal oedema, as the oedema was bilateral and there was no clinical or investigative evidence of thrombosis. Galactorrhoea associated with olanzapine is indicative of an increase in prolactin levels. Prolactin has been reported to cause sodium retention, which could lead to oedema.²

We found only one other case report of risperidone alone associated with pedal oedema.³ This makes us believe that our patient described in Case 3 represents the second reported case of pedal oedema associated with risperidone alone. In two other cases reported, pedal oedema developed in conjunction with sodium valproate.^{4,5} As sodium valproate itself can cause pedal oedema, it is difficult to ascertain the contribution of risperidone to the pedal oedema. None of the patients in our three cases were on any additional medication that is associated with oedema.

Atypical antipsychotics⁶ have complex effects on variety of receptors, most commonly serotonin and dopamine receptors with additional effects on adrenergic, histaminergic (H₁) and muscarinic receptors. Due to their multiple and complex actions on various receptors, atypical antipsychotics are associated with several adverse effects, including pedal oedema. No precise mechanism has been identified for atypical antipsychotic associated oedema; however, several possibilities have been suggested. They may produce oedema by increasing vascular permeability, which is similar to the pathophysiology involved in oedema due to inflammation and

cell injury.¹ They may also induce oedema by increasing sodium retention by the kidney by activating the renin-angiotensin system.² They may duplicate the elevated levels of renin found in idiopathic oedema following blockade of dopamine receptors⁷ or by causing vasodilatation through smooth muscle relaxation following alpha-receptor blockade.

Atypical antipsychotics can also potentially increase cyclic AMP levels and hence relax vascular smooth muscle following blockade of 5HT₂ receptors. High plasma concentrations of cyclic AMP have been found in patients with idiopathic oedema.⁸ It is also possible that their action on muscarinic (M₁), histamine (H₁) and serotonin (5HT₂) receptors eventually causes down-regulation of the ATP-dependent calcium pump. This can cause a secondary reduction in smooth muscle contractility, resulting in vasodilatation and oedema.⁹

Olanzapine has more affinity for dopamine D₁ and D₄ receptors. Pedal oedema is associated more with olanzapine than other atypical antipsychotics. Pre-marketing trials of olanzapine demonstrated a prevalence of pedal oedema of around 3 per cent. In contrast, Ng et al.⁹ reported pedal oedema in 57 per cent of patients taking olanzapine. However, the validity of these results is questionable as the patients in this study suffered other non-psychiatric medical disorders including thyroid hormone abnormalities, hypertension and cardiovascular problems. Several other case reports describe pedal oedema in association with olanzapine.¹⁰⁻¹³ Most of the patients in the case reports were also taking additional medications such as lithium and sodium valproate, which itself has a propensity to cause oedema, or patients were suffering from severe physical illnesses.

Case notes

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In a placebo-controlled trial of 704 patients treated with sertindole,¹⁴ 23 (3 per cent) patients developed pedal oedema, which is similar to the incidence reported with olanzapine. We found one case report each on amisulpride,¹⁵ ziprasidone,¹⁶ and quetiapine¹⁷ associated oedema. However, ziprasidone-related oedema was associated with an increase in immunoglobulin E (IgE) levels, which might suggest oedema due to an allergic reaction. To the best of our knowledge, there are no reports of oedema caused by aripiprazole. However, facial oedema and lingual oedema as part of a hypersensitivity reaction have been reported.¹⁸ In 12 acutely manic patients treated with zotepine, one developed pedal oedema.¹⁹

Dopamine D₄ receptor activation has natriuretic and diuretic effects on the renal system. Pedal oedema associated with clozapine may be linked to its antagonistic action on D₄ receptors, an effect that has been demonstrated in experimental animals.²⁰ In a case report by Durst *et al*,²¹ though there was a temporal correlation of clozapine treatment and pedal oedema, blood tests showed an increase in eosinophil count. This could suggest that pedal oedema may be part of an allergic response. However, eosinophilia is also one of the adverse effects of clozapine. Similarly, oedema due to an allergic reaction has been

reported with both risperidone²² and ziprasidone.¹⁶

It is surprising that, although the incidence of pedal oedema with atypical antipsychotics is believed to be not uncommon, it is not often picked up in clinical practice or reported by patients. This is probably because it is usually self-limiting and transient. However, we suggest it is prudent and good practice to look out for this side-effect, especially during the first few days after initiating an atypical antipsychotic drug. In our experience, pedal oedema associated with atypical antipsychotic medications does not require any additional treatment; either reduction of the dosage or switching to a different medication is usually sufficient.

Acknowledgments

The authors would like to acknowledge Dr Sudhir Kumar CT MD, MRCPsych, Institute of Psychiatry, London

Conflicts of interest

None.

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