Peripheral edema in an individual with treatment resistant major depressive disorder treated with olanzapine/fluoxetine combination

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Abstract

Olanzapine/fluoxetine combination therapy is a widely prescribed antipsychotic-antidepressant regimen for treatment resistant depression and is reported to have a side effect of peripheral edema. The theoretical underpinnings of peripheral edema in association with olanzapine/fluoxetine combination therapy are still unclear. Although peripheral edema associated with olanzapine/fluoxetine combination is rarely reported, the mechanism of drug interaction and effect on cytochrome P450 enzymes may induce it. We review the case of a middle-aged patient, who presented with peripheral edema after the administration of olanzapine/fluoxetine combination therapy.

Introduction

Treatment resistant depression (TRD) is a debilitating condition that can be perpetuated by a failure of efficacy in antidepressant monotherapy of adequate dose and duration. Remission response rates to antidepressants tend to decrease as the number of failed treatment courses increase.[1] Patients who fail two or more initial trials of adequate antidepressant monotherapy are often started on alternative treatments to control their depression symptoms. One common approach is to use a combination therapy of an antidepressant with an atypical antipsychotic as an augmentation agent. A widely prescribed antipsychotic-antidepressant drug for the treatment of TRD is olanzapine/fluoxetine combination (OFC) therapy.[2] Many studies have advocated for its increased efficacy, as it demonstrates higher remission rates and improvement in depressive symptoms when compared to monotherapy. Although OFC therapy is considered a superior treatment for TRD, it has demonstrated a variety of aversive side effects. The most common side effects of OFC therapy are increased appetite, weight gain, dry mouth, somnolence, fatigue, headache, and metabolic changes.[1,3,4] Peripheral edema can also present secondary to a medical condition, medication side effect, or idiopathic cause. In this article, we aim to present the case of a patient with TRD, who developed drug-induced peripheral edema after the administration of OFC therapy, to highlight the relationship between the two.

Furthermore, a literature search was conducted using key terms, such as "Treatment Resistant Depression", "Olanzapine Fluoxetine combination therapy", "Edema", and/or other combinations, to assess whether similar cases were described within the current literature on peripheral edema. No cases were found that assessed the development of peripheral edema in individuals with TRD on OFC therapy.

Case presentation

A 36-year-old, university-educated male twin with TRD exhibited symptoms of low mood, anhedonia, difficulty in managing activities of daily living (ADLs)/instrumental activities of daily living (IADLs), disturbed sleep, social isolation, apathy, amotivation, reduced energy, diminished concentration, reduced appetite, and passive suicidality. He had had a diagnosis of major depressive disorder for 16 years. Initially, he was exhibiting mild to moderate depressive symptoms, which progressed to severe depression with a recurrent episode that had worsened within the past year. He was referred to Ontario Shores Centre for Mental Health Sciences to receive electroconvulsive therapy (ECT) and to stabilize his symptoms. Previously failed drug class trials included antidepressants (almost all selective serotonin reuptake inhibitors, SSRIs, and serotonin and norepinephrine reuptake inhibitors, SNRIs), mood stabilizers, anxiolytics, hypnotic medications, intranasal ketamine, and ECT without continuing benefits.

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Medication on admission to Ontario Shores was brexpiprazole (1.5 mg), fluoxetine (40 mg), and gabapentin (1200 mg). A trial OFC therapy was recommended. The patient had a previous trial of olanzapine (12.5 mg) monotherapy, and combination therapy of olanzapine (7.5 mg) and divalproex (1000 mg). Fluoxetine dose was increased to 60 mg, and an olanzapine-brexpiprazole cross taper was initiated. On day one, olanzapine was started at 5 mg and brexpiprazole was reduced to 1 mg. After 6 days, olanzapine reached 15 mg dosage and brexpiprazole was discontinued. The patient indicated improvements to his mood and appetite after medication changes were made.

Within a month after the commencement of OFC therapy, the patient had an onset of pedal edema. He was ambulatory and experienced no pain associated with edema. Blood pressure was stable, and peripheral pulses were palpable 2+ and symmetrical. He had good perfusion, however his feet were warm upon examination. There was 1+ to 2+ pitting edema to the mid-tibia bilaterally. There was mild symmetrical, non-tender swelling on the calves and ankles, and Homan's sign was negative. There were no signs of erythema, ulceration, or colour change on the edematous area. He had no significant past medical history or other chronic medical co-morbidities of congestive heart failure, cirrhosis, renal failure, nephrotic syndrome, or any other systemic disease. No abnormalities were found in complete blood count, renal function, hepatic panel, thyroid function test, or basic metabolic panel.

The patient had been on gabapentin (1200 mg) since 2018 and did not experience any side effects during his continuous use. Gabapentin was tapered by 300 mg every 3 days until discontinuation 9 days later to account for its possible confounding effect on the patient's peripheral edema. Following gabapentin discontinuation, the patient presented with the same findings. The swelling was more prominent with leg-dependent activities, such as standing or sitting. The patient used various techniques to reduce the peripheral edema, including elevating or changing leg positions to alleviate the swelling, not wearing constricting socks, and wearing sandals if the swelling notably worsened.

The patient reported a substantial reduction of his depressive symptoms on OFC therapy. He also reported associated symptoms of fatigue and weight gain of approximately 9 kg. The doses of fluoxetine and olanzapine at the time of discharge were 80 mg per day and 20 mg per day, respectively. No reductions to OFC therapy were made since the patient noticed improved changes in his mood. The patient was advised to weigh the benefits of continuing OFC treatment with the side effects.

Discussion

Patients with TRD are at a higher risk of increased morbidities, which include a greater risk of suicide, substance abuse, and social impairment, than patients with depression treated to full remission.[1] As patients accumulate more unsuccessful treatment trials, there is an increase in demoralization and hesitancy to adhere to alternative pharmacotherapy as well as an increase in reduced remission rates.[5] The Sequenced Treatment Alternatives to Relieve Depression (STAR*D) treatment trials have displayed that the use of OFC therapy can result in remission rates of 25.5% for those with TRD.[3] Other studies have also revealed that participants on OFC treatments experience a rapid onset of action and a sustained improvement of depressive symptoms. Such outcomes are displayed through higher remission rates and lower relapse rates than participants on olanzapine and fluoxetine monotherapies.[1] OFC-treated patients also demonstrate significant improvement in Montgomery-Asberg Depression Rating Scale (MADRS) scores.[3]

Reports in the current literature demonstrate mixed findings on aversive side effects related to OFC therapy when compared to olanzapine and fluoxetine monotherapies. Peripheral edema is reported in ≥ 5% of patients as a result of OFC therapy; additionally, peripheral edema presents at a rate significantly higher than fluoxetine and olanzapine monotherapies.[6] Luan et al. reported that even though OFC therapy did not demonstrate higher adverse events in their study, when compared to monotherapies, it had a higher discontinuation rate due to undesirable outcomes.[6] There is no evidence of clinically significant risk of extrapyramidal symptoms while using OFC therapy in comparison to olanzapine or fluoxetine monotherapy.[3,4] Long-term use of OFC therapy, however, resulted in weight gain and metabolic changes, including increased glucose, increased total cholesterol, increased triglycerides, and decreased high-density lipoprotein cholesterol.[1,3]

This patient's genetic assay revealed extensive metabolizing across the cytochrome P450 system. There is a possible pharmacokinetic interaction when both olanzapine and fluoxetine are combined due to the inhibition of CYP2D6 and other cytochrome P450 enzymes by fluoxetine.[7] Olanzapine undergoes extensive Phase I and Phase II metabolism, achieving maximum plasma concentration after 6 hours and forming inactive metabolites in the liver. Fluoxetine is metabolized by CYP2C9 and CYP2D6, and it does not follow a linear pharmacokinetic profile like olanzapine. With dose increments, the plasma concentration of fluoxetine does not increase in a dose-proportional pattern.

Fluoxetine appears to increase serum olanzapine levels. Healthy non-smoking adults were given fluoxetine (60 mg per day) in addition to olanzapine (5 mg) and were found to have an olanzapine plasma concentration 18% higher in comparison to the same dose given in the same subjects without the combined fluoxetine.[7] In addition, OFC-treated rats showed an increase in extracellular serotonin (338%), dopamine (332%), and norepinephrine (260%) in the prefrontal cortex after 4 hours of administration of OFC therapy.[8] These findings may suggest that olanzapine could enhance the psychotropic activity of fluoxetine through additive or synergistic effects by increasing the inhibitory effect on the presynaptic serotonergic reuptake transporter.

Conclusion

This case looks at the use of OFC therapy in TRD resulting in the side effect of peripheral edema. Interestingly, the patient was previously trialed on olanzapine monotherapy in 2012 as well as a combination therapy of olanzapine and divalproex in 2015, and peripheral edema did not ensue with either trial. Furthermore, fluoxetine with brexpiprazole combination therapy was trialed in 2019 and peripheral edema was not evident. Current literature shows olanzapine monotherapy can cause peripheral edema.[9,10]

Since the initial use of olanzapine did not prompt the onset of edema in our case, we can suggest the presentation of peripheral edema was due to the combination of olanzapine and fluoxetine therapies. Gabapentin is another medication known to cause peripheral edema, however the patient had been taking it for one year prior and peripheral edema was only noted after OFC therapy initiation. After gabapentin was discontinued, symptoms of peripheral edema persisted. Lastly, this patient was found to be an extensive metabolizer across the cytochrome P450 system, which plays a significant role in the metabolism of both fluoxetine and olanzapine. The lack of remission in TRD is associated with an increase in morbidity and greater chance of impairment. Given this alternative, some may choose to make lifestyle modifications to cope with associated side effects in order to alleviate the symptoms associated with psychiatric illness.

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