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Sarah Hasan Siddiqui.
Aga Khan University

Nadeem Ahmed Memon
Aga Khan University

Ravi Shanker
Aga Khan University

CASE REPORT

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Sarah Hasan Siddiqui, Nadeem Ahmed Memon, Ravi Shanker

Section of Neurology, Department of Medicine, Aga Khan University, Karachi, Pakistan

Correspondence to
Dr Sarah Hasan Siddiqui, s_hasan_s@yahoo.com

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SUMMARY

A 60-year-old woman with major depressive disorder, developed high blood pressure, confusion and dyskinesias of face, neck and jaw, following an increase in her dose of duloxetine. Routine blood tests including toxic, infective and metabolic workup were unremarkable. Cerebrospinal fluid analysis and electroencephalogram were also normal. MRI brain showed bilaterally symmetrical diffusion-restricted areas in deep cerebral white matter. Duloxetine was held on suspicion of drug adverse effect. She had complete resolution of symptoms within 48 hours and resolution of MRI brain changes over 6 weeks. Serotonin norepinephrine reuptake inhibitors such as duloxetine may have the potential to cause drug-induced movement disorders, confusion and high blood pressure and should be used cautiously especially in elderly.

BACKGROUND

Serotonin norepinephrine reuptake inhibitors (SNRI) are a class of drugs which include duloxetine, venlafaxine, desvenlafaxine and levomilnacipran.[1] They have been approved for management of various psychiatric conditions such as major depressive disorder, generalised anxiety disorder. They are also used for certain painful conditions such as fibromyalgia, diabetic neuropathic pain, chronic musculoskeletal pain and urinary stress incontinence.[2–6] Adverse reactions related to use of SNRI include fatigue, nausea, somnolence, dry mouth, headaches, loss of appetite and hypertension. Life-threatening complications such as serotonin syndrome and neuroleptic malignant syndrome are also known to occur. Rarely, reports of extrapyramidal side effects related to SNRI have been published in the literature.[7–11]

CASE PRESENTATION

A 60-year-old female had complaints of low mood, decreased appetite, weight loss and inability to concentrate for the past 2 years. She was diagnosed with major depressive disorder by her primary care physician and was started on duloxetine 30 mg. After 3 weeks, dose was increased to 60 mg once daily. About 7 days after her dose was increased, she presented to our emergency department with 10–12 hours history of abnormal behaviour (putting all of the milk into the kettle, emptying whole bowl of sugar on her hand), difficulty speaking and abnormal movements of neck, face and jaw. There was no history of fever, seizure, motor weakness or head trauma. She was not taking any other prescribed or over the counter medications. She was not on any nutritional supplements and had no history of use of illegal drugs or substance abuse. On arrival her blood pressures were 190/90 mm Hg, heart rate of 85 beats per minute, regular rhythm and temperature of 37.2°C measured sublingually. On neurological examination, patient was awake but confused and disoriented to place and time. Speech was dysarthric. She was having oromandibular dyskinesias, jaw trismus, lip pouting and right laterocollis. Pupils were 3 mm and bilaterally equally reactive to light, with normal extraocular movements. Facial nerve examination was normal. Gag and tongue movements were difficult to assess because of jaw trismus. There was no pyramidal weakness and tone and reflexes in all limbs were normal along with bilaterally flexor plantar responses. No cerebellar abnormalities of ataxia, hypotonia or nystagmus were found. Other than high blood pressures, there were no symptoms or signs of autonomic instability such as flushing, diaphoresis, vomiting, diarrhoea, hyperthermia or tachycardia. There were no signs of meningeal irritation.

INVESTIGATIONS

Her haemoglobin, white cell count, renal function, electrolytes, liver function, thyroid function and blood glucose were normal.

MRI brain showed bilaterally symmetrical diffusion-restricted areas in deep cerebral white matter, without any postcontrast enhancement (figures 1 and 2).

Cerebrospinal fluid (CSF) analysis was done to rule out central nervous system (CNS) infection or inflammation and it was normal. Electroencephalogram (EEG) did not show any seizure activity and it was also normal.

DIFFERENTIAL DIAGNOSIS

Following differentials were considered.

- Duloxetine-related adverse effect of dyskinesias, confusion and high blood pressure.
- Metabolic or toxic encephalopathy.
- Serotonin syndrome.
- Hypertensive encephalopathy.
- Neuroleptic malignant syndrome.
- Posterior reversible encephalopathy syndrome (based on MRI).
- Seizures.
- Encephalitis.

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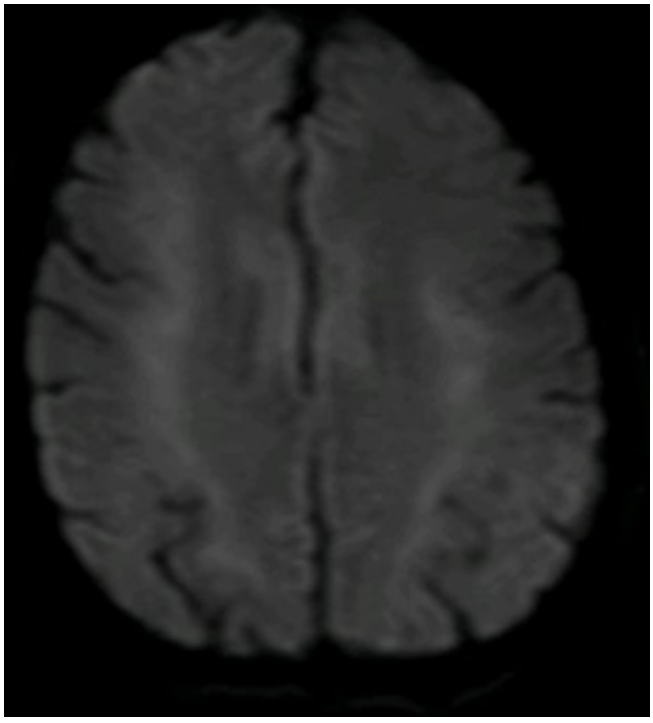

Figure 1 MRI brain, diffusion weighted imaging axial section showing hyperintense signals in bilateral deep white matter.

TREATMENT

As her toxic, metabolic panel, CSF and EEG were all normal and there was no evidence of fever, tachycardia, rigidity, hyperreflexia, clonus or signs of autonomic dysfunction, therefore, she was managed on the lines of drug-induced multiple adverse effects including acute dystonia, confusion and hypertensive urgency. She was managed with antihypertensive medications and her duloxetine was held.

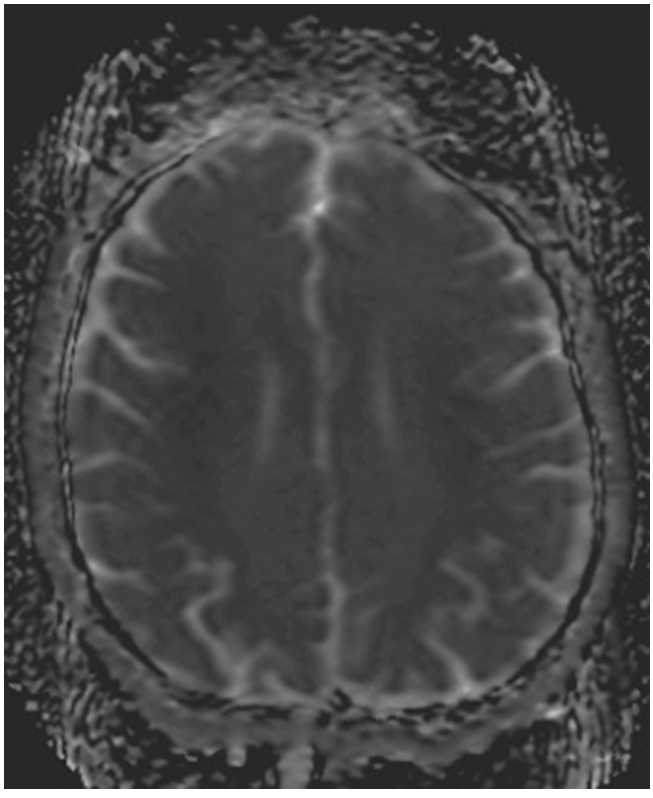

Figure 2 MRI brain, apparent diffusion coefficient sequence, axial section showing signal drop out in the regions corresponding to hyperintense signals on diffusion weighted imaging.

OUTCOME AND FOLLOW-UP

Over the next 48 hours, her abnormal movements of face, jaw and neck resolved completely and her confusion settled. Blood pressures were also normalised. She remained well and was discharged home. A follow-up MRI brain done after 6 weeks showed complete resolution of the prior changes. After a follow-up of 3 months, she was doing well and had no recurrence of symptoms.

DISCUSSION

Duloxetine belongs to the class of SNRI drugs. The mechanism of dual inhibition of both serotonin and norepinephrine reuptake is effective in patients with depressive disorders. It is also effective in the treatment of diabetic neuropathic pain, anxiety, musculoskeletal pain, fibromyalgia and urinary stress incontinence.[2–6] Various adverse effects have been associated with the use of SNRI. They include dry mouth, nausea, insomnia, somnolence, dizziness, headache, constipation, hypertension and life-threatening events such as serotonin syndrome and neuroleptic malignant syndrome.[7 10 11]

Drug-induced movement disorders (DIMD) are well-known adverse effects with dopamine receptor-blocking drugs. These include neuroleptics such as haloperidol, antiemetics such as prochlorperazine, metoclopramide and also atypical neuroleptic agents such as clozapine and olanzapine. They can also occur commonly as a side effect of dopaminergic drugs such as levodopa, pramipexole, ropinirole and cabergoline.[12] Antiepileptics, antiarrhythmics, antimicrobials, calcium antagonists, beta agonists, mood stabilisers, dopamine depleters, theophylline, corticosteroids, CNS stimulants, antihistamines, oral contraceptives, anxiolytics and antineoplastic drugs have also been implicated in DIMD.[13 14] They are also seen with different classes of antidepressants including nefazodone, trazodone, bupropion, tricyclic antidepressants, escitalopram, citalopram, fluoxetine and paroxetine.[15 16] Reports have been published regarding the association of DIMD with the use of SNRI class of drugs such as duloxetine and venlafexine.[17 18] Both acute onset (from dose initiation or escalation) and late onset (tardive) forms have been described. Duloxetine-related acute dystonia has been described to occur as early as 10 hours after dose initiation.[9] Likewise, duloxetine-associated tardive syndrome has been reported to occur from duloxetine use of as early as 4 months. Symptoms may include akathisia, dystonia, parkinsonism and dyskinesias. These effects may or may not be dose related.[8 9 17–20]

Mechanisms leading to dyskinesias related to levodopa include a complex interaction between N-methyl-D-aspartate (NMDA) receptors and dopamine. NMDA receptors potentiate the output gamma-aminobutyric acid-ergic neurons in striatum, under the influence of cortical glutamate activation. Depletion of nigrostriatal dopamine leads to glutaminergic over activity and is the postulated mechanism for levodopa-induced dyskinesias.[21] However, mechanisms leading to dyskinesias related to SNRI are unclear. It is postulated that increased serotonin transmission possibly inhibits the dopaminergic neurotransmission. Additionally, the disruption of normal dopamine-norepinephrine balance may contribute to the dystonias associated with SNRI use.[8 9 19]

Serotonin syndrome is a potentially life-threatening condition, requiring prompt recognition and treatment. It can occur following the use of serotonergic drugs. It is characterised by symptoms of mental state changes, signs of neuromuscular hyper excitability such as rigidity, hyperreflexia, clonus and features of autonomic dysfunction such as flushing, tachycardia or hyperthermia. This is caused by activation of serotonin 2A receptors in central nervous system as a result of increase in serotonin levels secondary to selective or non-selective serotonin reuptake inhibitors and monoamine oxidase inhibitors.[22] In our patient, the absence of fever, rigidity, hyperreflexia, clonus and signs of autonomic dysfunction such as flushing, diaphoresis or tachycardia (with the exception of high blood pressure) was not consistent with the Hunter Serotonin Toxicity criteria for serotonin syndrome.[23] High blood pressures may have been due to the effect of duloxetine.[24 25]

Our patient presented with oral dyskinesias, trismus and neck dystonia after increase in her dose of duloxetine. These symptoms gradually improved over 48 hours after discontinuation of duloxetine. This case is in a large part similar to the one reported by Görkem Karakas *et al* in which acute dystonia occurred just after a single dose of duloxetine and resolved completely after stopping the drug.[9] However, our case is different from the above reports in that our patient in addition to the drug-induced acute dystonia also presented with high blood pressures. SNRI especially duloxetine is known to cause hypertensive encephalopathy and urgency.[24 25]

Moreover, the MRI changes in our patient are representative of a toxic or metabolic insult. These white matter changes were non-specific and could have been a consequence of hypertension-induced reversible oedema,[26] an atypical form of posterior reversible encephalopathy syndrome (PRES),[27 28] or may be a direct toxic effect of duloxetine by unknown mechanism. As there were no cortical abnormalities, therefore, a diagnosis of PRES was not consistent with the overall clinical and radiological scenario. Her metabolic profile was normal, urine toxicology was negative for benzodiazepines, amphetamine, cocaine and opioid and EEG and CSF studies were also normal, thus helping to rule out other differential diagnosis.

Learning points

- Behavioural changes such as confusion, insomnia and agitation can occur with commonly prescribed antidepressants especially in elderly patients.
- Uncontrolled blood pressures if undetected for prolonged periods can be detrimental.
- Clinicians should be aware of the potential of serotonin norepinephrine reuptake inhibitors (SNRI) to cause drug-induced movement disorders as these can be painful, distressing and at times terrifying not only for the patients but also for their caregivers.
- Isolated extrapyramidal adverse drug reactions are rare and life-threatening drug reactions from SNRI's such as serotonin syndrome and neuroleptic malignant syndrome should always be kept in mind which can present with extrapyramidal symptoms such as rigidity.
- Patients should be made aware of these adverse effects as early recognition and discontinuation can lead to resolution of symptoms.
- Duloxetine may cause reversible white matter MRI brain changes, possibly consistent with a toxic insult. However, this finding needs further studies.

The temporal relation of MRI brain changes and resolution of these changes after discontinuation of duloxetine suggests that they may also be related to duloxetine.

Our patient suffered from multiple adverse effects (dyskinesias, confusion, high blood pressure, MRI brain abnormalities) related to duloxetine and all were reversed after discontinuation. To the best of our knowledge, this is the first report of diffusion-restricted white matter changes in MRI of brain after treatment with duloxetine.

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