

# Duloxetine-Induced Hypertension: A Case Report



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## SUMMARY

Duloxetine, a serotonin-norepinephrine reuptake inhibitor, is used for diabetic neuropathic pain and fibromyalgia as well as major depressive disorder. Serotonin-norepinephrine reuptake inhibitors may lead to increased blood pressure via their noradrenergic effects in addition to their cardiovascular side effects. In this paper, we report a case with increased blood pressure after the initiation of duloxetine that recovered by discontinuation of the medication.

**Key words:** Duloxetine, hypertension, side effect

## INTRODUCTION

Selective serotonin-norepinephrine reuptake inhibitors (SNRIs) are a second generation drug used in the treatment of depression. Since venlafaxine was introduced onto the market in 1993 all SNRIs became a common and reliable option in the treatment of major depression for psychiatrists. Since the tolerability and reliability profiles are positive as compared to TCAs it is also preferred in terms of patient compliance and overdose. Due to these features, they are the second most common anti-depression drug group prescribed (13.6%) in Europe following the common selective serotonin reuptake inhibitors (Bauer et al. 2008).

Duloxetine is SNRI used for the treatment of diabetic neuropathic pain and fibromyalgia as well as major depressive disorder. The most common side effects observed are nausea, xerostomia, dizziness, diminished appetite, constipation and insomnia (Preskorn et al., 2007, Perahia et al. 2006).

Although cardiovascular side effects are not commonly observed among SNRIs, they may increase blood pressure since they affect the noradrenergic system. Several studies have proven that venlafaxine (one of the SNRI group drugs) over 200 mg doses causes clinically significant (diastolic blood pressure  $\geq$  105 mmHg or 15 mmHg increase compared to

pre-treatment) and continuous increase in the blood pressure in 5.5% of the patients, while this effect is less in doses smaller than 200 mg.

It has been determined that the effect of duloxetine on blood pressure is not as significant as venlafaxine and it increases heart rate and systolic pressure slightly, albeit to a significant level (1-2 mmHg) (Thase et al. 2005).

There are several cases related to hypertension cases regarding the use of venlafaxine and milnacipran in the literature (Pardal et al. 2001, De Toledo and Guerra 2007). However, there have not been cases encountered in the literature in which duloxetine causes hypertension, although it is known that it increases blood pressure 1-2 mmHg. In this paper, we describe a case of hypertension in a patient who was placed on duloxetine with the diagnosis of depressive disorder.

## CASE

A 45 year old, married, female patient consulted our polyclinic with the complaints of distress, loss of interest and insomnia. It was understood from the history that the patient was having complaints for three months and had not consulted a psychiatry clinic before. The patient, of whom

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the routine laboratory parameters were normal, was given 30 mg/day duloxetine and 0.5 mg/day alprazolam with the diagnosis of depressive disorder. Three days after the patient was exposed to duloxetine the patient had severe headaches and the laboratory parameters performed in the emergency serviced she consulted were evaluated as normal. The patient's blood pressure was 170/110 mmHg and was prescribed 30 mg/day nifedipine and it was recommended that she follow-up for her blood pressure. The patient, whose blood pressure decreased to 140/90 mmHg after she began taking 30 mg/day nifedipine consulted the emergency service due to headache and her blood pressure increased to 160/100 mmHg. The nifedipine was increased to 60 mg/day and the blood pressure decreased to 120/80 mmHg. The patient's blood pressure increased to 140/90 mmHg sometimes consulted to out polyclinic for the control the following week. Although there were no psycho-social stress factors, the increase in the blood pressure of the patient who did not have any history of hypertension or cardiovascular disease or the use of additional drugs led us to believe the hypertension was due to duloxetine. The administration of duloxetine was stopped and 10 mg/day of escitalopram was started and we recommended the patient have a blood pressure follow-up. After the patient discontinued the duloxetine and began taking escitalopram, her hypertension ceased. Nifedipine was stopped gradually by tapering her dose over a period of 10 days and no increase in the blood pressure was observed during this process.

## DISCUSSION

We believe that the severe headaches in this patient and increase in blood pressure to 170/110 mmHg without any history of cardiovascular disease points to duloxetine as the causative agent. This hypothesis is further supported by cessation of the headaches and hypertension upon discontinuation of the drug.

Cardiovascular side effects are not common with SNRI use. An analysis of the literature revealed a lack of information stating that duloxetine causes hypertension. The only statements include that there are cases of hypertension dependent on the use of venlafaxine and milnacipran, which are SNRI group drugs (Pardal et al. 2001, De Toledo and Guerra 2007).

It has been shown that venlafaxine (one of SNRI group drugs) given at doses over 200 mg causes clinically significant (diastolic blood pressure  $\geq 105$  mmHg or 15 mmHg increase compared to pre-treatment) and continuous increases in blood pressure in 5.5% of patients, while this increase is less in dosage forms smaller than 200 mg relatively (Montgomery 2008). In a study in which a meta-analysis of 3744 patients was performed, it was determined that the effect of venlafaxine is dependent on the dosage and diastolic blood pressure reaches statistical significance in doses over 300 mg/

day (Thase 1998). In another study stated that there is an increase in blood pressure only in 3% of the patients using a normal dose (75-150 mg) of venlafaxine of the long oscillation formulation (Thase 1998). Another study stated that the probability of the increase in the blood pressure for the patients using venlafaxine less than 100 mg/day is 2% and it is 5% for patients using 100-200 mg/day (Rudolph and Derivan 1996). It is thought that the probable mechanism of hypertension dependent on the use of venlafaxine is an increase in norepinephrine and later on strengthening noradrenergic neurotransmission. The use of venlafaxine is not recommended for patients with hypertension, cardiac dysfunction, coroner artery disease and EKG anomalies (Thase 1998).

Hypertension is rarer in the use of milnacipran compared to venlafaxine. There is no changes determined in the blood pressure with clinical significance in 100-200 mg/day milnacipran (average increase  $<1$  mmHg), however it causes tachycardia dependent to dosage (3% in 100 mg, 6% in 200 mg, heart rate  $>100$ /min.) (Montgomery 2008).

SNRI group drugs block serotonin and norepinephrine reuptake by different selectivity. While milnacipran blocks serotonin and norepinephrine reuptake equally,  $K_i$  values on the serotonin and norepinephrine blockage of duloxetine is 7.5 and 0.8 nM, respectively, with a proportion of 9. For venlafaxine these values are 2480 and 82 nM, respectively, with a proportion of 30. These proportions show that the efficiency of duloxetine on norepinephrine reuptake is higher than the efficiency of venlafaxine. Moreover its effect on both serotonin and NE reuptake is higher than venlafaxine (Bymaster et al. 2001). It has been determined that duloxetine increases heart rate and systolic pressure slightly but to a significant level (1-2 mmHg) (Thase et al 2005). Although duloxetine is a stronger norepinephrine reuptake inhibitor than venlafaxine, its effects on blood pressure are less than venlafaxine. The risk of continuous high blood pressure is more than the risk observed in the patients treated with placebo during duloxetine treatment with a rate of 1%. Weirdly, the risk of increased blood pressure does not seem to be dependent on the dosage, unlike venlafaxine. The occurrence of hypertension while on 30 mg/day of duloxetine use in our case supports this finding. These interesting findings remind us that the reason for an increased frequency of high blood pressure observed during venlafaxine treatment than duloxetine treatment may not only be the function of double reuptake inhibition (Sadock and Sadock 2000).

As a result, it is important to keep in mind that the blood pressure of patients treated with duloxetine for depression may increase even in small dosages and to carry out blood pressure follow-ups accordingly. In order to understand the effect of duloxetine on blood pressure, improved systematic studies and case reports are required.

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