Age- and dose-independent adverse effect of venlafaxine-extended release on blood pressure: a case series of 13 normotensive psychiatric outpatients

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Dear Editor,

the first antidepressant medication of the serotonin-norepinephrine reuptake inhibitor class is venlafaxine (effexor), which is taken orally with a half-life of 5 hours; however, its effective and chief metabolite (*i.e.*, O-desmethylvenlafaxine) owns a half-life of 11 hours.[1] The United States Food and Drug Administration has approved venlafaxine for social anxiety disorder, cataplexy, and major depressive disorder. It is also prescribed "off-label" for attention-deficit/hyperactivity disorder in children/adolescents and adults, migraine prevention, diabetic neuropathy, obsessive-compulsive disorder, hot flashes, premenstrual dysphoric disorder, bipolar depression, and post-traumatic stress disorder.[2] The typical venlafaxine starting dose is 37.5 mg, which can be gradually elevated up to 375 mg once per day when it is tolerated. It seems that venlafaxine possesses dose-dependent effects, such as an augmented noradrenergic impact at higher doses (≥225 mg/day) and considerable prevention of serotonin reuptake at lower doses (75-150 mg/day).[1] Despite the safety profile and the overall side effects of venlafaxine are comparable to other newer antidepressants, venlafaxine can lead to both sustained and transient increases in blood pressure (particularly diastolic blood pressure), through an elevated vascular and myocardial sensitivity to sympathetic stimulation, increasing cardiac output and, in turn, causing a rise in blood pressure.[1] For instance, Wathra *et al.*[3] studied the adverse impact of venlafaxine-extended release (XR) on blood pressure among 429 adults aged ≥60 with depression, indicating that 6.5% of the participants normotensive at baseline (n=386) experienced elevated blood pressure over 8-16 weeks follow-up (1.9% <225 mg/day; 9.8% ≥225 mg/day). Furthermore, for a 23-year-old patient, Kıvrak *et al.*[4] observed elevated blood pressure 10 months after taking venlafaxine of 150 mg per day. Nevertheless, based on our consecutive case series study, 13 patients (female=6, male=7) with psychiatric disorders (including attention-deficit/hyperactivity disorder, major depressive disorder, obsessive-compulsive disorder, generalized anxiety disorder, and post-traumatic stress disorder) and a varied age range [19-65 years old, mean±standard deviation (M±SD)= 40.07±14.02 years old] experienced sustained elevations of both systolic (M±SD=2.21±0.76 mmHg) and diastolic (M±SD=1.81±0.48 mmHg) blood pressure after 37.5-300 mg/day venlafaxine-XR intake (M±SD=135.57±77.36 mg/day) over 4-14 weeks (M±SD=8.00±3.16 weeks) (Table 1). As observed for all patients, blood pressure normalized after venlafaxine-XR was discontinued. As a critical hypothesis, these findings suggest that the harmful impact of venlafaxine-XR may be exerted irrespective of age and drug dose. Here is one interesting question to be raised: if the prescribed venlafaxine-XR causes arterial hypertension over a wide range of age and drug dosage, what is its mechanism of action?

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Table 1. Demographic and clinical characteristics of patients treated with venlafaxine-extended release.

	Age	Gender	DVU	DDV	SBP*	SBP**	DBP*	DBP**	CSBP	CDBP
Case 1	19	Male	4	37.5	11.50	14.40	7.50	9.20	2.90	1.70
Case 2	28	Female	6	150	12.80	14.50	8.00	9.20	1.70	1.20
Case 3	42	Male	6	75	13.50	15.20	8.40	9.50	1.70	1.10
Case 4	38	Male	8	75	12.95	15.00	7.30	9.30	2.05	2.00
Case 5	49	Male	10	75	13.80	14.80	8.20	9.90	1.00	1.70
Case 6	25	Female	6	150	11.70	14.30	6.50	9.40	2.60	2.90
Case 7	65	Female	12	150	13.40	15.20	8.00	9.80	1.80	1.80
Case 8	33	Female	8	225	12.00	14.80	7.80	10.10	2.80	2.30
Case 9	58	Female	14	75	13.50	15.10	8.60	10.00	1.60	1.40
Case 10	44	Male	12	225	12.20	14.80	8.10	9.80	2.60	1.70
Case 11	23	Male	8	300	10.20	14.20	6.90	9.20	4.00	2.30
Case 12	51	Male	6	75	12.00	14.20	7.60	9.50	2.20	1.90
Case 13	46	Female	4	150	13.00	14.90	8.50	10.10	1.90	1.60

CDBP, changes in diastolic blood pressure in mmHg; CSBP, changes in systolic blood pressure in mmHg; DBP, diastolic blood pressure; DDV, daily dosage of venlafaxine-XR in milligrams; DVU, duration of venlafaxine-XR usage in weeks; SBP, systolic blood pressure. *Before taking venlafaxine-XR; **after taking venlafaxine-XR.

The literature has provided confusing pharmacodynamic elucidation of venlafaxine-induced arterial hypertension, which has remained poorly understood. For instance, it was suggested by Humbert *et al.*[5] that serotonin transporter (SERT) inhibition can raise serotonin levels resulting in vasoconstrictor effects. They also stated that nitric oxide synthesis can be inhibited by serotonin reuptake inhibitors, thereby decreasing nitric oxide-mediated vasodilation. As proposed by O'Donnell *et al.*,[2] the venlafaxine hypertensive effect is not likely to be related to norepinephrine transporter (NET) inhibition since this effect is not observed with duloxetine. Further, Montastruc *et al.*[1] suggested that the risk of arterial hypertension after prescribing serotonin-norepinephrine reuptake inhibitor antidepressants was associated with NET/SERT pKi ratio, not values of NET or SERT pKi alone, *i.e.*, higher values of the pKi ratio led to a higher risk of arterial hypertension with serotonin-norepinephrine reuptake inhibitor antidepressants. Nonetheless, further investigations are required to identify the venlafaxine-XR mechanism of action in arterial hypertension development.

In conclusion, our data can play an important role in selecting hypertensive risk-free antidepressants not only among at-risk or hypertensive patients but also in normotensive subjects. Therefore, venlafaxine-XR-based treatment needs careful monitoring even among normotensive patients due to the probability of increased blood pressure and facilitated occurrence of hypertensive crisis. When prescribing venlafaxine-XR, the clinician is required to cautiously assess its risk/benefit ratio given that normal blood pressure does not necessarily alleviate the risk of arterial hypertension induced by venlafaxine-XR.

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