Published in final edited form as:

J Psychopharmacol. 2020 October ; 34(10): 1112–1118. doi:10.1177/0269881120944154.

Hypertension and Orthostatic Hypotension with Venlafaxine Treatment in Depressed Older Adults

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Abstract

BACKGROUND: Venlafaxine, a serotonin-norepinephrine reuptake inhibitor, is often used as first or second line therapy for depression in older adults. It can be associated with adverse blood pressure effects.

METHODS: Adults aged 60 and older in a current major depressive episode were treated in a protocolized manner with venlafaxine-XR; 429 participants were treated for 8 to 16 weeks with daily dose up to 300 mg to achieve remission from depression. Cardiac measures included sitting and standing blood pressures and heart rate.

RESULTS: 6.5% of participants who were normotensive at baseline were found to have elevated blood pressure during the study (1.9% < 225 mg/day; 9.8% ≥ 225mg/day). There was no significant change in mean blood pressure in the overall sample, or in the subgroup treated with doses ≥ 225mg/day. Additionally, 20.1% of the participants who did not have orthostatic hypotension at baseline were found to have orthostatic hypotension (16.8% < 225 mg/day, and 22.4% ≥ 225mg/day). Participants with new-onset orthostatic hypotension were significantly more likely to fall than the other participants.

CONCLUSION: A large proportion of older adults treated with venlafaxine experience orthostatic hypotension putting them at risk for falls. A smaller proportion experience elevated blood pressure. Older patients prescribed venlafaxine, particularly at high dose, should be advised and counselled about these adverse effects.

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Author Contributions

DMB and BHM conceived and designed the study. LT, KWG, and RW provided input on the study design. DMB, KWG, LT, MS, RW developed the statistical analysis plan. MS completed the data analysis. All authors contributed to the interpretation of data. DMB, LT, BHM, KWG, RW drafted the manuscript. All authors contributed to critical revisions of the manuscript. DMB had final responsibility for submission of the manuscript.

Keywords

depression; geriatric; hypertension; orthostatic hypotension; venlafaxine; serotonin; norepinephrine; reuptake inhibitor

INTRODUCTION

Venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), is a common first-line treatment for depression in older adults. It is also frequently used as a second-line treatment in those who fail to respond to selective serotonin reuptake inhibitors (Alexopoulos et al., 2001; Wellington and Perry, 2001). Depression in older adults is challenging to treat due to comorbid physical illness and adverse effects, in particular cardiovascular adverse effects (Johnson et al., 2006; Oslin et al., 2003; Rojas-Fernandez et al., 2010). Depression is linked with increased suicidal behaviors, and emotional turmoil in bereaved significant others who are suicide survivors may increase their own suicide risk (Pompili et al., 2013). Specific biological factors, including prolactin and thyroid hormone, may be dysregulated in patients with depression who are more likely to attempt suicide (Pompili et al., 2012).

There have been inconsistent reports of cardiovascular effects of venlafaxine in older adults with depression (Mbaya et al., 2007). While some studies report no change in systolic or diastolic blood pressure (BP) (Allard et al., 2004; Devanand et al., 2004; Ibor et al., 2008; Johnson et al., 2006), others report either a decrease (Cervera-Enguix et al., 2004) or an increase (Oslin et al., 2003; Shatzberg et al., 2006). While the venlafaxine product monograph approved by the US Food and Drug Administration warns about the risks of hypertension, new onset orthostatic hypotension has been identified in up to 29% of older adults prescribed venlafaxine (Johnson et al., 2006; Prescribers' Digital Reference, n.d.). Hence, there is a need to clarify the acute cardiovascular effects of venlafaxine in late-life depression (LLD). Orthostatic hypotension is a risk factor for falls in older adults. Similarly, other cardiovascular effects, including elevation in BP, may limit the use of venlafaxine as a long-term treatment option for certain patients.

The main aim of treatment with venlafaxine in this study was to prospectively define treatment resistance, and we used this data to characterize the effect of venlafaxine on blood pressure and heart rate when used for LLD. Also, since venlafaxine appears to have dose-dependent effects, including significant inhibition of serotonin reuptake at lower doses (75–150mg/day), and increased noradrenergic effect at higher doses (≥ 225 mg/day) (Debonnel et al., 2007; Harvey et al., 2000), we compared the cardiac effects of venlafaxine at lower (< 225 mg/day) and higher (≥ 225 mg/day) dosages. We hypothesized that higher doses would be associated with more adverse effects on blood pressure and heart rate.

METHODS

Data for this analysis were drawn from the open-treatment phase of a multi-centre trial assessing aripiprazole augmentation in patients treated with venlafaxine ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00892047) Identifier: [NCT00892047](https://clinicaltrials.gov/ct2/show/study/NCT00892047)). The methods of this trial have been reported in detail and are briefly summarized here (Lenze et al., 2015).

Participants

Participants were recruited at three academic institutions (Centre for Addiction and Mental Health, Toronto, Canada, University of Pittsburgh, Pennsylvania, USA, and Washington University, St. Louis, Missouri, USA).

Participants were 60 years of age or older with a DSM-IV diagnosis of unipolar, nonpsychotic, major depressive disorder (MDD) and a Montgomery-Asberg Depression Rating Scale (MADRS) of at least 15. Patients with a diagnosis of dementia, bipolar disorder, or a psychotic disorder were excluded from the study, as were those with substance misuse (including alcohol) over the previous 3 months, a Mini-Mental Status Examination (MMSE) less than or equal to 21, suicide risk precluding safe participation in a clinical trial, unstable medical problems (e.g., poorly controlled diabetes mellitus or hypertension), or a contraindication to venlafaxine or aripiprazole. The study was approved by the institutional review boards of all three academic centers and all participants provided written informed consent.

Venlafaxine Treatment Protocol

The first phase of the study was up to 16 weeks of open-label treatment with venlafaxine XR. While attempts were made to lower the dose or discontinue these medications, participants taking lorazepam (up to 2mg/day), trazodone, and other sedative hypnotics could continue those medications. All other psychotropic medications were discontinued. Venlafaxine XR was initiated at a dose of 37.5 mg/day, then increased by 37.5 mg/day (with a minimum interval of 3 days, depending on side effects). By week 4, venlafaxine XR was titrated up to 150 mg/day. After week 6, venlafaxine XR was increased up to 300 mg/day in participants who did not achieve remission (defined as a MADRS ≤ 10). The titration could be slowed or stopped based on lack of tolerability. Upon reaching the highest dose tolerated, participants were assessed for a minimum of 4 weeks at weekly intervals for the first two weeks and biweekly thereafter. Plasma samples were collected at weeks 4, 6, 10, and 12 for assessment of venlafaxine levels.

Assessment

The MADRS was used to characterize depressive symptoms throughout the trial. Sitting and standing heart rate and BP were recorded and analyzed at baseline, week 6, and the final visit. Orthostatic vitals and BP were measured according to standard practice. The time between sitting and standing BP measurements was 60 seconds. Participants were classified as having elevated BP if, their BP was above the BP thresholds used for diagnosing hypertension according to the criteria of the International Classification of Disease 9 (ICD 9): systolic BP ≥ 140 mmHg or diastolic ≥ 90 mmHg. Orthostatic hypotension was defined as a drop in systolic blood pressure of ≥ 20 mmHg, a drop in diastolic blood pressure of ≥ 10 mmHg, or an increase in heart rate of ≥ 20 beats per minute upon standing from a sitting position. Current antihypertensive and cardiac medication use was assessed at baseline and initiation of new hypertensive or cardiac medications was recorded over the course of the study. Participants were asked at each visit to report adverse events, including falls.

Statistical Analysis

Statistical analysis was conducted using SAS version 9.4. Mean (standard deviation) or n (%) were used to characterize participants at baseline and subsequent visits. Participants were classified as having developed elevated BP or orthostatic hypotension if they met normotensive criteria at baseline and met the criteria listed above at week 6 or at the final visit. Differences in continuous variables, measured at baseline and the final visit, were calculated and analyzed using paired t-tests or signed rank tests. Analysis was performed on the overall sample and stratified by final venlafaxine dose (< 225 mg/day and ≥ 225 mg/day). Maximum achieved dose of venlafaxine was assessed at the final visit. We used Fisher's exact test to compare proportions of participants who developed elevated BP and orthostatic hypotension, in relation to final venlafaxine dose. Fisher's exact test was also used to assess the association between reported adverse events (i.e., at least one report of fall, gait abnormality, or any subjective complaint related to balance and equilibrium) and the development of orthostatic hypotension. All analyses included only participants for whom values were available at both baseline and final visit. All statistical analyses used $\alpha = 0.05$ with a two-tailed significance.

RESULTS

Participant Characteristics

A total of 468 participants entered the study and 429 were included in analysis: 39 were excluded because they were either already on venlafaxine prior to baseline (n=33), or had undetectable venlafaxine plasma level at any time during the study (n=6). Table 1 presents the characteristics of the 429 participants included in the analysis. They received venlafaxine for a mean (SD) duration of 12.4 (4.2) weeks; the mean (SD) final dose of venlafaxine was 221.4 (81.7) mg/day (median 225.0, range 37.5–300.0). The BP and heart rate values at the final visit are summarized in Supplementary Table S1.

Blood Pressure

At baseline, 216 of 429 participants (50.4%) had a clinical diagnosis of hypertension and 221 of 429 (51.5%) were taking an antihypertensive medication. Four hundred and twenty-three participants had baseline BP measures recorded, of which 37 (8.8%) had elevated blood pressure. Ten of 429 (2.3%) participants started a new antihypertensive during the study.

BP and heart rate were available at all 3 time points (baseline, week 6, and final visit) for 331 and 329 subjects, respectively (Figure 1). There was no significant change in mean BP or heart rate in the overall sample at any time point. There was no significant difference in mean BP change during the study between lower and higher final venlafaxine dosage groups. The proportions of participants with elevated BP at the final visit did not differ between venlafaxine responders and non-responders (with response defined as a 50% decrease in MADRS score).

Three hundred and eighty-six participants were normotensive at baseline and had BP measures recorded at week 6 and/or at final visit. Twenty-five of 386 participants (6.5%)

who were initially normotensive had elevated BP subsequently. The proportion of patients that had an elevated BP at the final visit differed between those with a lower final venlafaxine dosage (3 of 161 [1.9%]) and those with higher final dosage (22 of 225 [9.8%]) (Fisher's exact test $p=0.001$). Figure 2 shows participant level changes in systolic and diastolic BP amongst those who developed elevated BP. Final BP was available for 24 of the 37 participants who had elevated BP at baseline; they experienced a significant decrease in both mean (SD) systolic BP (-16.4 mmHg (13.5) $t = 5.93$, $df = 23$, $p < 0.0001$) and mean (SD) diastolic BP (-11.3 mmHg (8.7) $t = -6.4$, $df = 23$, $p < 0.001$) (Supplementary Table S2). Fifteen of these 24 participants (62.5%) were co-prescribed antihypertensive medication during the study.

Orthostatic Hypotension

Two hundred and ninety-two participants had orthostatic vitals recorded at baseline, of which 34 (11.6%) had orthostatic hypotension. Only half of the sample was assessed at baseline and final visit because of confusion amongst the three sites around when to complete protocolized orthostatic vitals assessments leading to differential operating procedures on this measure. Sitting and standing BP and heart rates were available for 228 participants at baseline and the final visit. This group (or the lower and higher venlafaxine dosage groups) did not experience significant changes in mean orthostatic BP or heart rate. Furthermore, the proportion of participants with orthostatic hypotension at the final visit did not differ between venlafaxine responders and non-responders.

Two hundred and twenty-nine participants did not have orthostatic hypotension at baseline, and had orthostatic vitals recorded at week 6 and/or at final visit. Forty-six of 229 participants (20.1%) who did not have orthostatic hypotension at baseline, had orthostatic hypotension over the course of the study. Thirty-one of these 46 participants (67.0%) were co-prescribed cardiac medications associated with orthostatic hypotension (i.e. antihypertensives, antianginals, or antiarrhythmics). Twenty of these 46 participants (43.5%) were co-prescribed benzodiazepines. The proportion of patients that had orthostatic hypotension at the final visit did not differ between those with a lower final venlafaxine dosage (16 of 95 participants [16.8%]) and those with higher final dosage (30 of 134 [22.4%]) (Fisher's exact test $p=0.194$). Figure 3 shows participant level changes in sitting and standing BP amongst those who developed orthostatic hypotension. In the 27 participants who had orthostatic hypotension at baseline and available final BP, there was a significant improvement in mean (SD) systolic drop, of 7.3 (14.1) mmHg ($t = 103.5$, $df = 26$, $p=0.013$), from baseline to the final visit (Supplementary Table S2).

Participants who developed orthostatic hypotension were more likely to report gait abnormality or to experience at least one fall than those who did not develop orthostatic hypotension (Table 2). Similarly, the number of subjective complaints related to balance and equilibrium was higher in those who developed orthostatic hypotension but it did not differ significantly from the number in those who did not (Table 2). Five of 19 participants (26.3%) who developed orthostatic hypotension and experienced a fall also reported subjective complaints such as dizziness. One hundred of 110 participants (91.0%) who experienced a fall were co-prescribed a fall promoting medication (i.e. antihypertensives,

diuretics, beta-blockers, GABA positive allosteric modulators, narcotics, or non-steroidal anti-inflammatory medications). Seventeen of 19 participants (89.5%) who developed orthostatic hypotension and experienced a fall were co-prescribed a fall promoting medication. Thirteen of 27 participants (48.1%) who had orthostatic hypotension (at baseline or during the study) and experienced a fall were co-prescribed GABA positive allosteric modulators and/or narcotics. Nineteen of 196 falls (9.7%) experienced in those who developed orthostatic hypotension required participants to seek medical attention, and 3 of 196 falls (1.5%) required participants to be hospitalized.

DISCUSSION

The present study evaluated the effects of venlafaxine XR on BP and heart rate in 429 older adults with major depression. Elevated BP or orthostatic hypotension developed in a small but clinically meaningful proportion of participants treated with venlafaxine (5.8% and 17.8%, respectively). These changes were more pronounced with higher dosage (i.e., 225mg/day). There was no significant change in mean BP or heart rate during the study. Amongst participants who developed orthostatic hypotension, 67% were co-prescribed cardiac medications and 44% were co-prescribed benzodiazepines. Participants who developed orthostatic hypotension were more likely to report gait abnormalities and experience falls. Ten percent of falls in those who developed orthostatic hypotension required participants to seek medical attention.

Previous studies have found inconsistent results with regard to BP and venlafaxine treatment (Allard et al., 2004; Cevera-Enguix et al., 2004; Devanand et al., 2004; Ibor et al., 2008; Johnson et al., 2006; Oslin et al., 2003; Schatzberg et al., 2006). Hypertension is a common diagnosis in older adults and an important risk factor for serious cardiovascular events (Turgut et al., 2013). In this sample, 50.4% had a clinical diagnosis of hypertension. Venlafaxine may contribute to elevated BP via the potentiation of norepinephrine in the cardiovascular system, and subsequent sympathetic vasoconstriction (Howell et al., 2007). The product monograph for venlafaxine does mention a risk of dose-dependent increases in BP and rare incidents of acute severe hypertension (Prescribers' Digital Reference, n.d.). We did not observe an increase in mean BP, even in the subgroup treated with dosage above 225 mg/day. However, this subgroup had a statistically higher proportion of participants who developed elevated BP, suggesting the presence of unidentified patient or treatment-related factors which make a small but significant number develop this complication. A potential hypothesis is that venlafaxine XR starts to block norepinephrine uptake at doses of 225mg and above, which may cause a noradrenergic mediated hypertensive effect in some patients (Debonnel et al., 2007; Harvey et al., 2000). As a group, participants with elevated BP at baseline actually experienced a significant decrease in both systolic and diastolic BP and only a small number of participants were started on a new antihypertensive. Previous studies have found that successful treatment of depression leads to improvement in other medical conditions, including hypertension (Bogner and de Vries, 2008; Fu et al., 2015). While we confirmed that venlafaxine XR is associated with elevated BP in older depressed patients who are normotensive prior to starting this medication, the incidence is low and clinically insignificant. Participants with hypertension prior to starting venlafaxine XR experienced significant decreases in both systolic and diastolic blood pressure, although a majority were

co-prescribed antihypertensive medications. These observations suggest that incident hypertension should be considered but is not a relative contraindication to the use of venlafaxine XR in LLD.

Orthostatic hypotension occurs more frequently than incident hypertension, and it is associated with an increased risk of falls and associated injury (Pepersack et al., 2013). Previous studies have suggested that depression is correlated with orthostatic hypotension, beyond the effects of antidepressant and antihypertensive medications (Briggs et al., 2018; Richardson et al., 2009). However, several reports have linked venlafaxine with postural hypotension in older adults (de Vasconceles Cunha et al., 2007; Johnson et al., 2006). While on a group level, we did not observe significant changes in mean orthostatic BP or heart rate, about one in six participants developed orthostatic hypotension. The risk of orthostatic hypotension was higher in participants receiving higher doses of venlafaxine XR, congruent with previous reports of prominent orthostatic hypotension in older depressed adults treated with dosages above 225 mg/day (Johnson et al., 2006).

Approximately two-thirds of participants who developed orthostatic hypotension were co-prescribed antihypertensive or cardiac medication, demonstrating the compounding effects of polypharmacy in this population. Almost half the participants who developed orthostatic hypotension were co-prescribed a benzodiazepine and almost half the participants with orthostatic hypotension who experienced a fall were co-prescribed GABA positive allosteric modulators and/or narcotics. These are medications that psychiatrists should be mindful of in older adults and particularly with medications that are associated with orthostatic hypotension such as venlafaxine. Another study which included younger adults assessed the efficacy of venlafaxine at doses >225mg with only 16% of participants using lorazepam and found that 7% of total participants reported dizziness, which suggests that refraining from benzodiazepines and other sedatives may reduce the risk of orthostatic hypotension with venlafaxine (Vermeiden et al., 2013). It is imperative to make efforts to optimize tolerability and safety when prescribing venlafaxine as this may be the only effective antidepressant for severely depressed older adults who are unable to tolerate tricyclic antidepressants (Staab and Evans, 2000).

The development of orthostatic hypotension was associated with reports of gait abnormality and a significant increase in the risk of falls. Given the high mortality associated with falls in older adults, patients prescribed venlafaxine XR should be advised about the risks of orthostatic hypotension and counselled on how to minimize the risk of falls (e.g., by sitting first when rising from a prone position and by waiting for a few seconds before starting to walk when standing). Occurrence of symptoms associated with orthostasis, such as light headedness, dizziness, feeling faint, and syncope, merits a thorough evaluation and management.

The strengths of this study include prospective monitoring of BP and heart rate in a relatively large sample of older outpatients with major depression. As we obtained venlafaxine plasma levels, we were able to exclude several participants with absolute non-compliance. There were several limitations to this study: slightly over one-third of total study participants did not complete orthostatic measures at baseline, indications for

antihypertensive medication changes during the study were not available, the absence of a control group precludes the identification of causal relationships, and there was no standardized timeframe for measuring orthostatic vitals (which could lead to variability in measurements). Furthermore, we cannot characterize the course of elevated BP and orthostatic hypotension, i.e., we do not know how quickly they occurred and whether they would persist or resolve over a longer period of time. Older adults experience significant visit-to-visit variability in BP, which could result in participants moving between elevated and normal BP groups during the time intervals of this study (Wu et al., 2017).

With the aging of the population globally, it is imperative to better characterize the safety profile of medications commonly used in older adults. Venlafaxine is a common and clinically effective option to treat late-life depression (Staab and Evans, 2000). Our findings suggest that a minority of these older patients may experience elevated BP or orthostatic hypotension particularly when doses are increased to 225mg or higher. They also support the need for ongoing evaluation of postural vital signs in older patients treated with venlafaxine, particularly at higher doses. Incident hypertension should not be considered a relative contraindication to the use of venlafaxine XR in older adults. Older adults prescribed venlafaxine should be monitored for orthostatic hypotension, counselled about increased risk of falls, and de-prescribed medication including GABA positive allosteric modulators.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGEMENTS

Conflict of Interest

RW receives research support from the Clinician Scientist Program through the Department of Psychiatry at the University of Toronto.

BHM currently receives research support from Brain Canada, the Canadian Institutes of Health Research, the CAMH Foundation, the Patient-Centered Outcomes Research Institute (PCORI), the US National Institute of Health (NIH), Capital Solution Design LLC (software used in a study founded by CAMH Foundation), and HAPPYneuron (software used in a study founded by Brain Canada). He directly own stocks of General Electric (less than \$5,000). Within the past three years, he has also received research support from Eli Lilly (medications for a NIH-funded clinical trial) and Pfizer (medications for a NIH-funded clinical trial).

LT reports no biomedical interests

KWG reports no biomedical interests

EJL – receives research support from the US National Institute of Health (NIH), the Patient-Centered Outcomes Research Institute (PCORI), McKnight Brain Research Foundation, Takeda, Lundbeck, and consulting fees (past) from Janssen and Jazz Pharmaceuticals

JFK receipt of medication supplies for investigator initiated studies from Pfizer and Indivior. Service on scientific advisory board of Aifred Health

MS - reports no biomedical interests

CFR - has received research support from the NIH, PCORI, the Center for Medicare and Medicaid Services, the American Foundation for Suicide Prevention, the Brain and Behavior Research Foundation, and the Commonwealth of Pennsylvania. Bristol Meyers Squib and Pfizer have provided pharmaceutical supplies for his NIH sponsored research.

DMB receives research support from the Canadian Institutes of Health Research (CIHR), National Institutes of Health – US (NIH), Weston Brain Institute, Brain Canada and the Temerty Family through the CAMH Foundation and the Campbell Research Institute. He received research support and in-kind equipment support for an investigator-initiated study from Brainsway Ltd. and he is the site principal investigator for three sponsor-initiated studies for Brainsway Ltd. He receives in-kind equipment support from Magventure for two investigator-initiated studies. He received medication supplies for an investigator-initiated trial from Indivior. He has participated in an advisory board for Janssen.

REFERENCES

- Alexopoulos GS, Katz IR, Reynolds CF, et al. (2001) The expert consensus guideline series. Pharmacotherapy of depressive disorders in older patients. Postgraduate Medicine Spec No Pharmacotherapy: 1–86.
- Allard P, Gram L, Timdahl K, et al. (2004) Efficacy and tolerability of venlafaxine in geriatric outpatients with major depression: a double-blind, randomised 6-month comparative trial with citalopram. *International Journal of Geriatric Psychiatry* 19(12): 1123–1130. [PubMed: 15526307]
- Bogner HR and de Vries HF (2008) Integration of depression and hypertension treatment: a pilot, randomized controlled trial. *Annals of Family Medicine* 6(4): 295–301. [PubMed: 18626028]
- Briggs R, Carey D, Kennelly SP, et al. (2018) Longitudinal association between orthostatic hypotension at 30 seconds post-standing and late-life depression. *Hypertension* 71(5): 946–954. [PubMed: 29632103]
- de Vasconcelos Cunha UG, Lopes Rocha F, Avila de Melo R, et al. (2007) A placebo-controlled double-blind randomized study of venlafaxine in the treatment of depression in dementia. *Dementia and Geriatric Cognitive Disorders* 24(1): 36–41. [PubMed: 17495474]
- Debonnel G, Saint-André E, Hébert C, et al. (2007) Differential physiological effects of a low dose and high doses of venlafaxine in major depression. *The International Journal of Neuropsychopharmacology* 10(1): 51–61. [PubMed: 16690006]
- Devanand DP, Juszcak N, Nobler MS, et al. (2004) An open treatment trial of venlafaxine for elderly patients with dysthymic disorder. *Journal of Geriatric Psychiatry and Neurology* 17(4): 219–224. [PubMed: 15533993]
- Fu W, Ma L, Zhao X, et al. (2015) Antidepressant medication can improve hypertension in elderly patients with depression. *Journal of Clinical Neuroscience: Official Journal of the Neurosurgical Society of Australasia* 22(12): 1911–1915. [PubMed: 26256065]
- Harvey AT, Rudolph RL and Preskorn SH (2000) Evidence of the dual mechanisms of action of venlafaxine. *Archives of General Psychiatry* 57(5): 503–509. [PubMed: 10807491]
- Howell C, Wilson AD and Waring WS (2007) Cardiovascular toxicity due to venlafaxine poisoning in adults: a review of 235 consecutive cases. *British Journal of Clinical Pharmacology* 64(2): 192–197. [PubMed: 17298480]
- Ibor JLL, Carrasco JL, Prieto R, et al. (2008a) Effectiveness and safety of venlafaxine extended release in elderly depressed patients. *Archives of Gerontology and Geriatrics* 46(3): 317–326. [PubMed: 17617478]
- Johnson EM, Whyte E, Mulsant BH, et al. (2006) Cardiovascular changes associated with venlafaxine in the treatment of late-life depression. *The American Journal of Geriatric Psychiatry* (9): 796–802. [PubMed: 16943176]
- Lenze EJ, Mulsant BH, Blumberger DM, et al. (2015) Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomised, double-blind, placebo-controlled trial. *Lancet (London, England)* 386(10011): 2404–2412.
- Mbaya P, Alam F, Ashim S, et al. (2007) Cardiovascular effects of high dose venlafaxine XL in patients with major depressive disorder. *Human Psychopharmacology* 22(3): 129–133. [PubMed: 17397100]
- Oslin DW, Ten Have TR, Streim JE, et al. (2003) Probing the safety of medications in the frail elderly: evidence from a randomized clinical trial of sertraline and venlafaxine in depressed nursing home residents. *The Journal of Clinical Psychiatry* 64(8): 875–882. [PubMed: 12927001]
- Pepersack T, Gilles C, Petrovic M, et al. (2013) Prevalence of orthostatic hypotension and relationship with drug use amongst older patients. *Acta Clinica Belgica* 68(2): 107–112. [PubMed: 23967718]

- Pompili M, Gibiino S, Innamorati M, et al. (2012) Prolactin and thyroid hormone levels are associated with suicide attempts in psychiatric patients. *Psychiatry Research* 200(2–3): 389–394. [PubMed: 22748186]
- Pompili M, Shrivastava A, Serafini G, et al. (2013) Bereavement after the suicide of a significant other. *Indian Journal of Psychiatry* 55(3): 256–263. [PubMed: 24082246]
- Prescribers' Digital Reference (n.d.) Venlafaxine Hydrochloride Extended Release Tablets (venlafaxine hydrochloride) Drug Information. Available at: <https://pdr.net/drug-summary/Venlafaxine-Hydrochloride-Extended-Release-Tablets-venlafaxine-hydrochloride-3520> (accessed 1 October 2019).
- Richardson J, Kerr SRJ, Shaw F, et al. (2009) A study of orthostatic hypotension in late-life depression. *The American Journal of Geriatric Psychiatry* 17(11): 996–999. [PubMed: 20104056]
- Rojas-Fernandez CH, Miller LJ and Sadowski CA (2010) Considerations in the treatment of geriatric depression: Overview of pharmacotherapeutic and psychotherapeutic treatment interventions. *Research in Gerontological Nursing* 3(3): 176–186. [PubMed: 20635802]
- Schatzberg A and Roose S (2006) A double-blind, placebo-controlled study of venlafaxine and fluoxetine in geriatric outpatients with major depression. *The American Journal of Geriatric Psychiatry* 14(4): 361–370. [PubMed: 16582045]
- Staab JP and Evans DL (2000) Efficacy of venlafaxine in geriatric depression. *Depression and Anxiety* 12 Suppl 1: 63–68.
- Turgut F, Yesil Y, Balogun RA, et al. (2013) Hypertension in the elderly: unique challenges and management. *Clinics in Geriatric Medicine* 29(3): 593–609. [PubMed: 23849010]
- Vermeiden M, Mulder PG, van den Broek WW, et al. (2013) A double-blind randomized study comparing plasma level-targeted dose imipramine and high-dose venlafaxine in depressed inpatients. *Journal of Psychiatric Research* 47(10): 1337–1342. [PubMed: 23800419]
- Wellington K and Perry CM (2001) Venlafaxine extended-release: a review of its use in the management of major depression. *CNS Drugs* 15(8): 643–669. [PubMed: 11524036]
- Wu C, Shlipak MG, Stawski RS, et al. (2017) Visit-to-visit blood pressure variability and mortality and cardiovascular outcomes among older adults: The health, aging, and body composition study. *American Journal of Hypertension* 30(2): 151–158. [PubMed: 27600581]

Figure 1: Boxplots of Sitting HR, Sitting Systolic BP, and Sitting Diastolic BP at baseline, week 6, and final visit.

Abbreviations: HR= heart rate, BP= blood pressure, BPM= beats per minute, SD=standard deviation. The following descriptive statistics report HR in units of BPM, and BP in units of mmHg. Sitting HR at BL: mean (SD)=73.0 (13.9), median=72, range=101. Sitting HR at week 6: mean (SD)=75.7 (12.7), median=74, range=78. Sitting HR at final visit: mean (SD)=75.8 (11.5), median=76, range=58. Sitting systolic BP at BL; mean (SD)=132.2 (19.1), median=130, range=109. Sitting systolic BP at week 6: mean (SD)=130.2 (19.1), median=130, range=146. Sitting systolic BP at final visit: mean (SD)=128.9 (17.1), median=129, range=110. Sitting diastolic BP at BL: mean (SD)=76.4 (11.4), median=76, range=68. Sitting diastolic BP at week 6: mean (SD)=76.2 (11.6), median=76, range= 69. Sitting diastolic BP at final visit: mean (SD)= 74.7 (10.0), median=74, range=58.

Figure 2: Scatter plots of blood pressure changes in participants who developed elevated blood pressure in relation to lower and higher final venlafaxine dose.

Scatter plots showing changes in systolic and diastolic blood pressure in participants who developed elevated blood pressure, in relation to final venlafaxine dose <225mg (top) and 225 mg (bottom). Abbreviations: BL=baseline, Wk 6= week 6, End=phase end.

Figure 3: Scatter plots of blood pressure changes in participants who developed orthostatic hypotension in relation to lower and higher final venlafaxine dose.

Scatter plots showing changes in sitting and standing blood pressure in participants who developed orthostatic hypotension, in relation to final venlafaxine dose <225mg (top) and 225 mg (bottom). Abbreviations: BL=baseline, Wk 6=week 6, End=phase end.

Table 1.

Baseline Characteristics

Characteristic	N=429
Age, years (mean, SD, range, median)	69.1 (7.2) Median=67.3 Range: 60.0–91.1
Gender (%, n)	F: 64.3% (n=276) M: 35.7% (n=153)
Final venlafaxine XR daily dosage, mg (mean, SD, range, median)	221.4 (81.7) Median=225 Range: 37.5–300.0
Length of time in study, weeks (mean, SD, range, median)	12.4 (4.2) Median=12.3 Range: 0.3–30.0
Current duration of depressive episode, weeks (mean, SD, range, median)	288.3 (603.2) Median=72.0 Range: 2.0–3744.0 n=427
Baseline MADRS score (mean, SD, range, median)	26.6 (5.8) Median=26.0 Range: 15.0 – 47.0
Clinical diagnosis of hypertension at baseline (%, n)	50.4 (n=216)
On an hypertensive drug at baseline (%, n)	51.5 (n=221)
Elevated blood pressure at baseline (systolic 140 mm Hg or diastolic 90 mmHg) (%, n)	8.7 (n=37/423)
Orthostatic hypotension at baseline (Standing systolic BP – Sitting systolic BP –20 mmHg or Standing diastolic BP – Sitting diastolic BP –10 mmHg or Standing pulse rate – Sitting pulse rate 20 BPM) (%, n)	11.6 (n=34/292)
Tachycardia at baseline (Heart rate>100bpm) (%, n)	2.1 (n=9/428)

Abbreviations: MADRS= Montgomery-Asperg Depression Rating Scale, BP= blood pressure, BPM= beats per minute

Table 2.

Events Associated with Development of Orthostatic Hypotension

		Developed Orthostatic Hypotension ^I						p-value Fisher's Test
		No		Yes		Total		
		Count	%	Count	%	Count	%	
Fall	No	157	74.8%	27	58.7%	184	71.9%	0.045
	Yes	53	25.2%	19	41.3%	72	28.1%	
Gait Abnormality	No	141	67.1%	23	50.0%	164	64.1%	0.041
	Yes	69	32.9%	23	50.0%	92	35.9%	
Subjective Complaint	No	178	84.8%	34	73.9%	212	82.8%	0.086
	Yes	32	15.2%	12	26.1%	44	17.2%	

^I. Participant did not have orthostatic hypotension at baseline, but had it at week 6 or at final visit