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Changes in cardiovascular function after venlafaxine but not pregabalin in healthy volunteers: a double-blind, placebo-controlled study of orthostatic challenge, blood pressure and heart rate

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It is generally thought that venlafaxine raises blood pressure at higher doses; however, some studies have found no effect or a decrease in blood pressure. The aim of this study was to evaluate the cardiovascular (CV) effects of 3 weeks of dosing with venlafaxine, pregabalin and placebo on young healthy adults.

Fifty-four participants, of mean age 23.1 years (sd 4.68), 29 male, were randomised into three parallel groups. Each group received one of the three drugs, dosed incrementally over a 3-week period to reach daily doses of 150 mg/day venlafaxine and 200 mg/day pregabalin. Blood pressure sphygmomanometer measurements, heart rate measurements, and orthostatic challenges recorded continuously beat-to-beat were performed weekly over this period and 5 days after treatment cessation.

Results showed resting systolic blood pressure (SBP) and resting and standing diastolic blood pressure (DBP) and heart rate (HR) were significantly raised by venlafaxine compared with the pregabalin and placebo groups. SBP drop on standing was larger, the resulting overshoot was smaller, and recovery was slower on venlafaxine. HR recovery was significantly impaired by venlafaxine. CV changes were observed after only 1 week of dosing at 112.5 mg/day. These effects of venlafaxine are likely to be due to its action of noradrenergic reuptake inhibition.

KEY WORDS—venlafaxine; pregabalin; blood pressure; heart rate; orthostatic

INTRODUCTION

Patients with depression have been found to be at risk of cardiovascular (CV) problems (Taylor, 2010) and have a reduced heart rate variability (HRV; Kemp *et al*. 2010). Reduced HRV is a condition whereby the interval between heart beats is less varied, a phenomenon also found in hypertensive patients (Bajkó *et al*., 2012). There is some debate as to whether reduced HRV is a symptom of depression (as Kemp *et al*. (2012) noted in their study of unmedicated, physically healthy depressed patients) or solely as an effect of antidepressant medication (as asserted by Licht *et al*., 2008). Because of this, Brunoni *et al*. (2012) have stated 'it is mandatory to investigate whether antidepressants might decrease HRV and whether this contributes to such elevated cardiovascular risk' (p. e27), and studies examining the CV effects of antidepressants are therefore required.

Venlafaxine is a serotonin and noradrenaline reuptake inhibitor (SNRI), with reported dopaminergic effects at higher doses, commonly used for the treatment of depression and anxiety. A clinically effective dose is between 75 and 150 mg (Lecrubier *et al*., 1997), but Rudolph *et al*. (1998) has concluded efficacy is dose dependent, with 225 and 375 mg being more clinically effective than 75 mg. Like all medications, venlafaxine can lead to side effects, which according to the British National Formulary include constipation, nausea, anorexia, weight changes, vomiting, hypertension, palpitation, and vasodilatation. Studies show dizziness was reported by 13% of patients taking venlafaxine compared with 3% on placebo (Nemeroff and Thase, 2007). Sheehan *et al*. (2009) found light headedness was reported by 16% of patients taking venlafaxine for 6 weeks, compared with 6% taking fluoxetine and 3% taking placebo. A common concern expressed about the

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first line use of venlafaxine is a risk of increased blood pressure (BP), raised heart rate (HR), and hypertension (Danjou and Hackett, 1995; Feighner, 1995), possibly due to noradrenergic effects (Muth *et al*., 1991), and Taylor (2008) concluded that venlafaxine should not be used in depressed patients with hypertension. Recent guidelines advise regular measurement of BP for all patients taking venlafaxine and dose reduction or discontinuation if a sustained increase is found (MHRA, 2006). Studies have shown venlafaxine administration over 2–3 weeks reduces HRV measured by paced breathing (Davidson *et al*., 2005; Siepmann *et al*., 2007). Some authors have claimed that venlafaxine has cardiotoxic effects (e.g. prolonged QT/QTc interval in the electrocardiogram (ECG)) (e.g. Combes *et al*., 2001; Johnson *et al*., 2006; Howell *et al*., 2007), some have not (e.g. Mbaya *et al*., 2007; Isbister, 2009), but most have stated in their work that venlafaxine increases BP. A search of PubMed publications (terms: venlafaxine and blood pressure, cardiovascular, heart rate, variability, orthostatic, hypotension, and hypertension) reveals a less conclusive picture.

Some studies of venlafaxine have found an increase in diastolic blood pressure (DBP) and systolic blood pressure (SBP) with single doses as low as 75 mg/day (Abdelmawla *et al*., 1999), whereas other studies have found a decrease over 8 weeks using a mean dose of 172 mg/day (Plesnicar, 2010). Alexandrino-Silva *et al*. (2008), in a case report of hypotension with venlafaxine, suggest this may be due to overstimulation of alpha-2-adrenoreceptors, which would lead to a reduction in noradrenaline (NA) release and subsequent hypotension. Overstimulation may occur in individuals with poor drug metabolism due to genetic polymorphism of genotype CYP2D6. Some studies have showed no significant BP effects after a year of up to 150 mg/day (Dierick *et al*., 1996). It could be argued that the negative results of these studies may be due to a lack of noradrenergic effects at lower doses. Data from our group on peripheral noradrenergic uptake blockade using a positron emission tomography radiotracer suggest that venlafaxine begins to block the NA uptake site at doses above about 125 mg (Melichar *et al*., 2001). In line with this, Abdelmawla *et al*. (1999) found venlafaxine 150 mg/day but not 75 mg/day increased NA-induced vasoconstriction. However, negative results have also been found in studies of larger doses. Blier *et al*. (2007), using a tyramine pressor response (a fixed dose of tyramine raises BP by a predictable amount, and an NA reuptake blocker can attenuate this effect), found no evidence for NA reuptake inhibition in healthy volunteers using one dose of 300 mg/day. Gründer *et al*. (1996) found no significant differences in BP after 2 weeks of up to 375 mg/day. Alternatively, differences in findings may be due to the comparator with venlafaxine. Reeves (1995) suggest BP can attenuate as a study progresses, which means any increases in BP may be missed if underlying BP is decreasing, if the comparator is baseline. Therefore, placebo-controlled studies are important to negate this bias and account for all other factors. Table 1 summarises studies of BP effect of venlafaxine. Indeed, placebo-controlled studies tend to show an increase in BP and HR, and all studies showing a decrease in BP and HR compare venlafaxine with baseline. However, other similar studies comparing venlafaxine with baseline show increases or a lack of change.

Orthostatic (postural) hypotension is a less common side effect of venlafaxine but has been reported. For example, Johnson *et al*. (2006) studied 59 depressed patients older than 60 years on a mean dose of 195.5 mg/day for 12 weeks and found 29% developed orthostatic hypotension. In a study of 52 migraine patients, Bulut *et al*. (2004) found one patient developed orthostatic hypotension whilst taking venlafaxine 150 mg/day. It is defined as an SBP drop of at least 20 mmHg or a DBP drop of at least 10 mmHg within 3 min of standing up (or a head-up tilt of 60° or more; Freeman *et al*., 2011). A normal response to standing up is shown in Figure 1. When standing, a person's initial muscle contraction causes tachycardia (A), resulting in an initial increase in HR and BP (2). A cardiopulmonary reflex allows gravity to pool blood in the lower extremities, which lowers arterial pressure and decreases cardiac output (Sprangers *et al*., 1991). Compensatory tachycardia then results in a second peak in HR (B). If blood perfusion of the brain is temporarily insufficient, it can lead to the symptoms of dizziness, light headedness, distortions in hearing and vision, nausea, and headache. The baroreceptor reflex activates, causing vasoconstriction, which forces blood back up into the body, initially causing a BP overshoot (4), followed by a reflex bradycardia (C), and finally normalised BP and a cessation of symptoms.

The most accurate measurement of HR and BP during orthostatic challenge can be achieved using arterial cannulation, but this is invasive and painful for patients and study volunteers. Because of this, assessment usually relies on subjective reports of light headedness, dizziness, and falls, or on supine and standing BP readings using a sphygmomanometer. However, subjective effects are not always reported when a drop in BP occurs, or other symptoms may be reported instead (e.g. nausea). Also, the sphygmomanometer does not capture subtle changes. For example, in a meta-analysis, Thase (1998) reported orthostatic BP readings were only taken 1 and 3 min after standing. In a compromise

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Table 1. Studies investigating the effects of venlafaxine on cardiovascular measures

Author(s)	Type of publication	No. of participants	Type of patient	Age (years)	Duration of study	Dose of venlafaxine/XR	Venlafaxine compared with	Effects on BP	Effects on DBP	Effects on SBP	Effects on HR
Allard *et al.* (2004)	Research	148	Depression	>65	6 months	XR up to 150 mg/day	Baseline Citalopram	No change No change			No change Decrease
Clerc *et al.* (1994)[b]	Research	68	MDD and melancholia	Adult	4/6 weeks	Up to 150 mg/day	Placebo	No change			
Dierick *et al.* (1996)[b]	Research	77	Depression	>65	1 year	50–150 mg /day	Baseline	No change			
Schwartz *et al.* (2004)	Case studies	16	Medical/surgical inpatients	26–99	2–74 days	XR 37.5–175 mg /day	Baseline	No change			
Gründer *et al.* (1996)[b]	Research	16	MDD and melancholia	24–63	14/28 days	Up to 375 mg/day	Baseline	No change			No change
Harrison *et al.* (2004)	Research	70	Depression	22–78	6 months	375–600 or 75–300 mg /day	Low dose versus high dose	No difference			
Howell *et al.* (2007)	Case studies	235	Overdose in depression	27–43	One dose	919–2800 mg	Baseline	Increase			Tachycardia
Debonnel *et al.* (2007)	Research	42	MDD	31–43	28 days 7/28 days	75 mg/day 375 mg/day	Baseline	No change Increase			
Schweizer *et al.* (1991)[b]	Research	60	Depression	Adults	6 weeks	Up to 375 mg/day	Placebo	Increase			
Rudolph and Derivan (1996); Hackett and Salinas (1997); Schweizer *et al.* (1997)	Meta-analysis/ reviews	2897 (22 controlled trials[a])	Depression	18–95	Various	101–200 mg Over 300 mg	Baseline, placebo, and impramine		5% increase 13% increase		
Thase (1998)	Meta-analysis	3744	Depression	Adult	>6 weeks	Over 300 mg/day	Placebo and imipramine		Increase		
Brent *et al.* (2008)	Research	334	SSRI-resistant depression	12–18	12 weeks	150–225 mg /day	Baseline		Increase	No change	Increase
Samuelian and Hackett (1998)	Research	34	MDD	18–71	43 days	Up to 150 mg/day	Baseline			No change	Decrease
Nemeroff and Thase (2007)	Research	96	Depression	19–70	6 weeks	Up to 225 mg/day	Placebo Fluoxetine		Increase No change	Trend of increase Increase	Increase Increase
Sir *et al.* (2005)	Research	84	Depression	Mean 37	8 weeks	XR 75–225 mg /day	Baseline		Increase	Increase	Increase
Abdelmawla *et al.* (1999)	Research	15	Healthy volunteers	20–28	One dose	75 mg/day 150 mg/day	Placebo		 Increase	Increase Increase	
Pardal *et al.* (2001)	Case study	1	Depression	55	4 weeks	150 mg/day	Baseline		Increase	Increase	
Sheehan *et al.* (2009)	Research	66	MDD and melancholia	Mean 41.7	6 weeks	Up to 375 mg/day	Placebo Fluoxetine		Increase Increase	Increase Increase	No change Increase
Alexandrino-Silva *et al.* (2008)	Case study	1	MDD	43	3 days	225 mg/day	Baseline		Decrease	Decrease	
Duggal *et al.* (2001)	Case study	1	Bipolar	46	1 week	225 mg/day	Baseline		Decrease	Decrease	
Plesnicar (2010)	Research	148	MDD	Mean 49.7	8 weeks	XR 75–325 mg /day	Baseline		Decrease	Decrease	No change

MDD, major depressive disorder; XR, extended release; DBP, diastolic blood pressure; SBP, systolic blood pressure; HR, heart rate.
Increases or decreases are statistically significant unless $n = 1$.
[a]Data on file, Medical Affairs Department, Wyeth-Ayerst International Inc.
[b]Study also included in meta-analyses.

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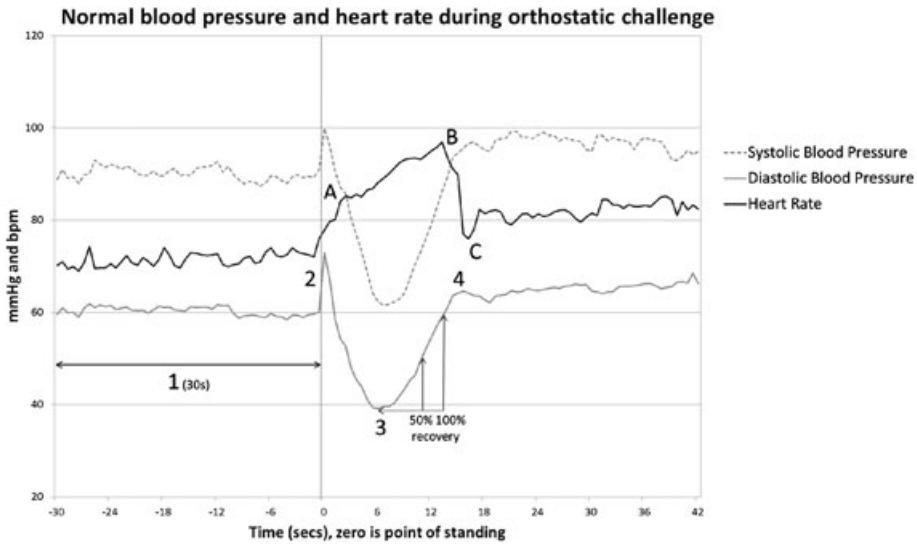

Figure 1. Example Finapres recording of normal response to standing, taken from one participant. The calculations of 50% and 100% recovery time shown on graph of diastolic blood pressure (DBP) are also applicable to the graph of systolic blood pressure (SBP). 1. Mean DBP over final 30 s before standing (control); 2. Pressor response to standing up; 3. Immediate blood pressure drop after standing; 4. Overshoot of BP on recovery; A. Initial tachycardia due to exercise reflex; B. Tachycardia reflex to BP fall; C. Bradycardia reflex to BP overshoot. Note that BP and heart rate levels stabilize above supine levels

between cannulation and sphygmomanometry, we used a non-invasive continuous beat-to-beat BP recording system (Finapres, Ohmeda, Englewood, Co, USA) and a standard automated sphygmomanometer (Dinamap, Critikon, Tampa, FL, USA) in healthy volunteers taking doses of venlafaxine up to 150 mg/day to measure CV function. The use of healthy volunteers aids the investigation of the effects of this drug without the confounds of a depressive illness, which may in itself have CV effects (Taylor, 2010). To provide context, venlafaxine was compared with parallel group dosing of placebo and a recognised treatment for generalised anxiety disorder that has no reported CV effects, pregabalin, in doses up to 200 mg/day. Pregabalin binds to the alpha-2-delta subunit of a voltage-gated calcium channel, and its anxiolytic effect is believed to result from a reduction in excitatory neurotransmission. Side effects include dizziness, drowsiness, dry mouth, irritability, vomiting, flatulence, oedema, and constipation, but there are no published reports of BP changes when taking this drug. The measurements were taken as part of a larger study investigating the anxiolytic effects of venlafaxine and pregabalin (Diaper *et al.*, 2013).

MATERIALS AND METHODS

Ethical considerations

The study protocol was approved by the Cambridgeshire 2 Research Ethics Committee and local National Health Service Trusts and performed in accordance with International Conference on Harmonisation Good Clinical Practice. All participants gave written informed consent after receiving a complete description of the study prior to their participation.

Participants

Details of the participants are described elsewhere (Diaper *et al.*, 2013), but briefly, 54 healthy participants completed the study, 29 male and 25 female, aged between 20 and 43 years (mean age 23.1, sd 4.68). Sixty volunteers were suitable for study inclusion and were randomised; however, six participants withdrew from the study because of adverse events (AEs): five from the venlafaxine group and one from the placebo group. All participants were recruited using an existing volunteer database and local advertisements. At screening, all participants passed strict inclusion and exclusion criteria and were given a physical examination by a study physician, including ECG, vital signs, and medical histories. Exclusion criteria included current or history of cardiovascular, respiratory or renal disease, hypertension, migraine, epilepsy, drug or alcohol abuse or dependence, and significant personal or family history of mental disorder. Normal BP was judged to be between the ranges of 100 and 140 mmHg systolic and 60 and 90 mmHg diastolic inclusive. Other screening checks included an alcohol breath test, and a urine sample was tested to screen for drugs of abuse, pregnancy in women, and for urinalysis. A blood sample was taken to screen for general health problems. No alcohol or illicit drugs were allowed for

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the duration of the whole study, and no medication was allowed for 2 weeks prior to and during the study (unless deemed by the investigator not to interfere with the study or to compromise safety). Caffeine and nicotine prior to measurements were not controlled. Participants' family doctors were informed of their participation, and participants were compensated £400 for their participation in the main study (Diaper *et al*., 2013).

Study design and procedure

This was a randomised, double-blind, placebo-controlled, parallel group study. Fifty-four participants were randomised to receive venlafaxine, pregabalin, or placebo over a 26-day period (18 in each treatment group). After randomisation, participants were asked to keep a diary of AEs and dose times and attended the research facility (the Psychopharmacology Unit clinical testing rooms at the Bristol Royal Infirmary) weekly for a brief health and compliance check (breath alcohol, urine drugs of abuse screen, temperature, and BP via sphygmomanometer). After 3 weeks of dose-increasing treatment, participants underwent transient anxiogenic challenges as part of the main study (CO_2 inhalation challenges; Diaper *et al*., 2013). For 5 days after the challenge day, dose levels were decreased, and participants attended a follow-up health check once withdrawn from the drug (Table 2).

Study drugs

The active treatments were venlafaxine and pregabalin, which were over-encapsulated to give the appearance of the red placebo capsule. Treatments were dose increased to avoid AEs over a 3-week period, to reach doses of 150 mg venlafaxine and 200 mg pregabalin by day 21 (Table 2). These doses were chosen to be within therapeutic range, but it was considered more important that the drugs should have minimal side effects in this healthy volunteer sample, rather than being fully equipotent.

The study drugs were provided in blister packs, and participants were instructed to take two capsules daily, one every morning and one every evening with food. Capsules were taken in the order set out on the blister pack (day 1 morning, day 1 evening, day 2 morning, day 2 evening, and so on). The drugs were labelled according to the point in the study when they were taken.

The first doses of study medication and the doses on the main study test day (day 21) were administered on site under direct supervision of two researchers. No other doses were witnessed, as participants were given the study medication to take home and self-administer, noting the times of doses and any side effects in a diary. Participants were required to bring their diaries and full or empty drug packaging with them at each visit for a compliance check that all medication had been taken, or note when participants had forgotten to take their medication. If participants forgot to take more than two capsules in 1 week, they would have been withdrawn from the study for non-compliance.

Cardiovascular measures

All BP measurements were taken in warm clinical rooms maintained at 22–24 °C . BP and HR were measured by a Dinamap sphygmomanometer at screening, baseline, weekly visits, and follow-up. Here, resting BP was measured after 5 min of reclined sitting (termed 'resting'). The participants then stood up, and standing BP was measured 2 min later (termed 'standing'). Continuous beat-to-beat measurements of BP and HR during this procedure were obtained at health checks at 1, 2, and 3 weeks after the start of dosing. This was recorded using the Finapres. For full details, see Coupland *et al*. (1995a), but briefly, the participants wore a finger cuff with a photosensitive cell connected via a servo-

Table 2. Doses of study drugs at each visit

Timeline	Placebo	Venlafaxine	Pregabalin
Day 0 – Randomisation			
Days 0–2	BID	75 mg (37.5 mg BID)	100 mg (50 mg BID)
Days 3–6	BID	112.5 mg (37.5 mg OD (AM), 75 mg OD (PM))	100 mg (50 mg BID)
Day 7 – Health check 1			
Days 7–13	BID	150 mg (75 mg BID)	200 mg (100 mg BID)
Day 14 – Health check 2			
Days 14–21	BID	150 mg (75 mg BID)	200 mg (100 mg BID)
Day 21 – Main study test day			
Days 22–24	BID	75 mg (37.5 mg BID)	100 mg (50 mg BID)
Days 25 and 26	BID	37.5 mg (37.5 mg OD)[a]	50 mg (50 mg OD)[a]
Day 26 – Follow-up visit			

[a]On days when active medication was given OD, active medication was given in the morning and placebo was given in the evening to maintain the study blind.

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controlled pump, which inflated the cuff to maintain a constant pressure on the finger. To avoid artefact, the participants were instructed to stay still when resting or standing. The hand where the Finapres was applied was maintained on the participant's chest approximately at the level of the fourth intercostal space over the sternum. The waveform of the recording was then checked as the participants reclined in a seated position on a clinical bed propped up by pillows. Recording commenced, and data were captured onto a DOS-based program. After 5 min rest, participants were instructed to stand up quickly but safely, over a time of approximately 1–3 s, and then to stand normally for another 5 min of recording. A researcher was present during this manoeuvre to record the moment of standing on the trace and to check the position of the Finapres.

Analyses

Analysis of CV data here includes Dinamap (sphygmomanometer)-measured BP and HR supine and standing and Finapres (continuous beat-to-beat)-measured BP and HR during orthostatic challenge, performed at weekly visits. Orthostatic challenges were only performed at health check 1 (day 7), health check 2 (day 14), and the main test day (day 21).

The variables analysed from the orthostatic challenges were SBP and DBP: drop, overshoot, time taken to achieve 50% recovery, and time taken to achieve 100% recovery; and HR: minimum, maximum, change from control to maximum, and the ratio of maximum to minimum (as a measure of HRV). These measures were chosen in accordance with analyses performed by Coupland *et al*. (1995a), shown in Figure 1. BP when standing consists of a small increase (pressor response, 2) followed by a large decrease (drop, 3). On return to recovery, BP usually rises beyond baseline (overshoot, 4). HR tends to show an initial peak on standing (A), followed by a further peak before recovery (B), and tends to take longer to recover than BP. The control comparator for HR and BP is defined as a mean over the last 30 s before standing (1). Drop is defined as the control minus the nadir value. Overshoot is defined as the peak of overshoot or, if not present, the highest BP within 30 s after standing, minus control. Recovery to 50% and 100% are the times from the nadir taken to reach 50% and 100% of the control value. Maximum HR is the second HR peak, and minimum HR is defined as the trough of the relative bradycardia or, if not present, the lowest HR within 30 s. Delta HR maximum is the maximum HR minus control, and HR ratio is defined as maximum HR divided by minimum HR. These measurements give an indication of HRV during standing, although this differs from conventional HRV measurements taken from ECG recordings (usually the R–R interval) during rest and paced breathing. Figure 2 (a)–(c) shows the average SBP, DBP, and HR during standing for each treatment group.

Analyses of Dinamap measurements were by two-way mixed model ANCOVA, with baseline (randomisation visit) measures as a covariate. In addition to BP analysis in each position (resting and standing), separate analyses of the differences at each visit between these two positions were also calculated. Finapres measurements were analysed by repeated measures ANOVA, both with Greenhouse–Geisser correction, using Bonferroni pairwise comparisons and Tukey's, respectively, for *post hoc* analysis unless otherwise stated. All data were analysed using SPSS Version 16.0 (IBM Corporation, Armonk, NY, USA) for Windows.

RESULTS

Participants

There were 54 completing participants in total, 29 male and 25 female, aged between 20 and 43 years (mean age 23.1, sd 4.68). Chi-square tests showed that there was no significant difference between numbers of men and women in each treatment group and no significant difference between numbers of each ethnic origin in each treatment group. One-way ANOVAs showed there was no significant difference between the treatment groups with respect to age, usual caffeine and alcohol intake, usual amounts of smoking, body mass index, and measures of personality and mood. Drug compliance between groups was not significantly different. For all details, please refer to Diaper *et al*. (2013).

One-way ANOVAs showed no significant difference between SBP and HR before randomisation between the three treatment groups. However, the difference between resting and standing DBP was significantly different between the treatment groups ($F(2,54) = 4.34$, $p < 0.05$). *Post hoc* analysis by Tukey's showed that there was a smaller increase in DBP on standing in the group that was about to receive pregabalin compared with the group about to receive placebo ($p < 0.05$). Because of this, and the fact that SBP in the group about to receive placebo appeared low on inspection, the resting and standing measures were analysed by including baseline values (taken at randomisation) as a covariate. This was not possible for orthostatic challenge measures as baseline values were not recorded. See Tables 3 and 4 for the data means and Figure 2(a)–(c) for SBP, DBP, and HR during orthostatic challenge as an average of participants in each group on day 21.

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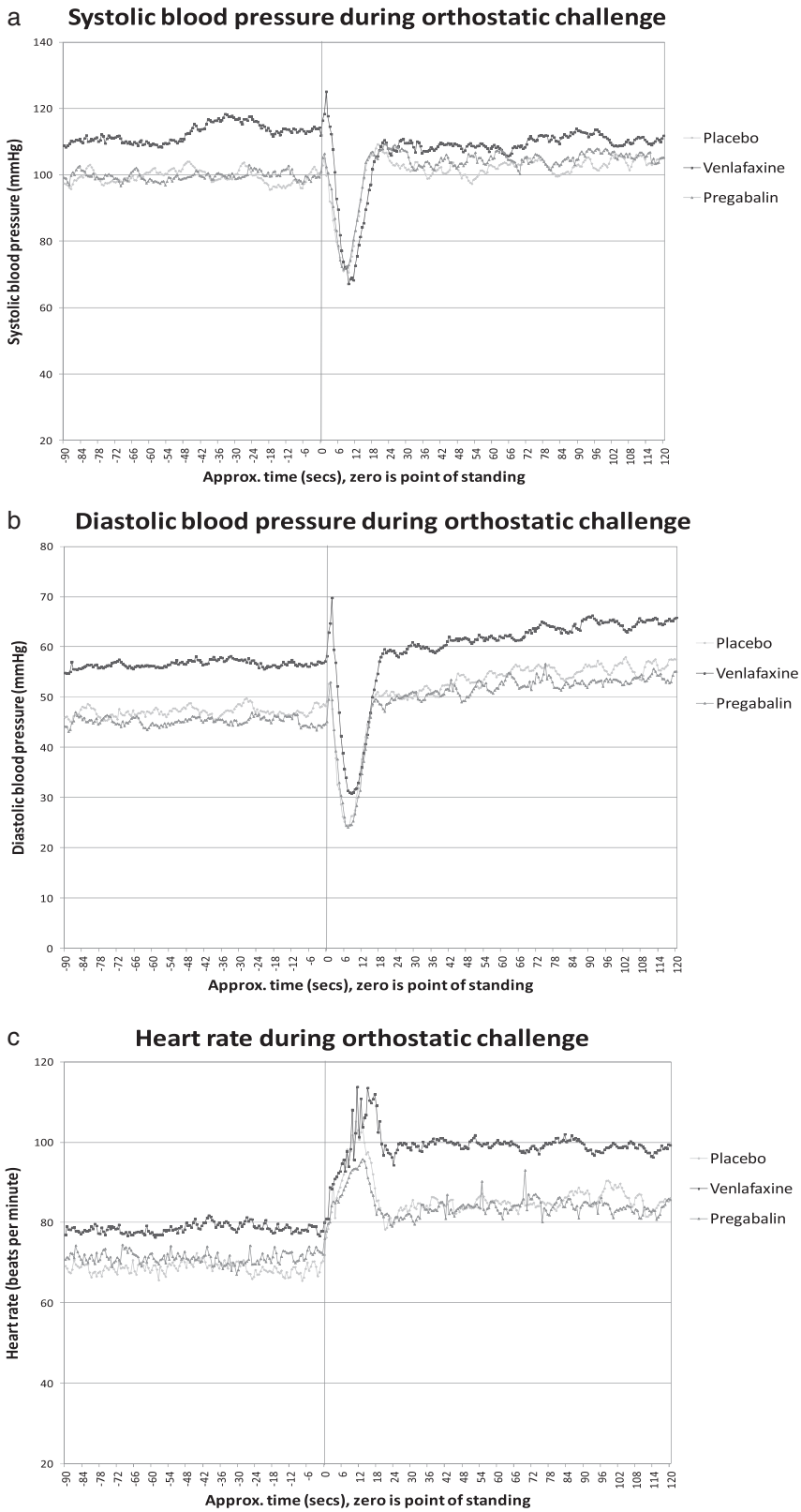

Figure 2. Graphs show the effect of standing from a resting position on Finapres measured (a) systolic blood pressure, (b) diastolic blood pressure, and (c) heart rate. Graphs show measurements during 1.5 min supine (rest period before standing was 5 min), at standing (time zero), and during 2 min of standing, averaged for participants in each drug group on day 21

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Table 3. Dinamap measured systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR)

		Screening	Randomisation	Day 7	Day 14	Day 21	Follow-up
SBP							
Placebo	Resting	114.8 (11.75)	112.4 (12.37)	114.3 (14.24)	113.7 (12.77)	114.3 (12.14)	113.0 (10.43)
	Standing	116.5 (13.44)	111.6 (13.08)	113.1 (17.70)	113.9 (12.88)	113.7 (18.98)	114.6 (12.93)
Venlafaxine	Resting	119.2 (13.03)	118.7 (11.61)	126.1[a] (14.16)	123.1 (14.51)	128.3[b,d] (11.04)	115.0 (13.20)
	Standing	119.6 (15.07)	119.7 (12.67)	121.6 (14.64)	121.5 (14.84)	120.5 (12.82)	116.2 (16.94)
Pregabalin	Resting	123.6 (14.89)	118.7 (13.54)	116.6 (12.42)	113.3 (14.05)	114.9 (13.73)	118.8 (15.22)
	Standing	124.6 (13.75)	120.8 (16.15)	117.7 (15.93)	113.1 (13.45)	115.6 (12.12)	118.5 (13.66)
DBP							
Placebo	Resting	68.8 (6.95)	64.7 (5.49)	64.0 (6.62)	64.6 (5.17)	65.0 (8.21)	63.2 (6.23)
	Standing	73.2 (8.18)	73.4 (6.60)	69.4 (6.28)	70.3 (6.52)	67.7 (9.76)	70.2 (9.31)
Venlafaxine	Resting	68.3 (9.59)	66.5 (9.04)	70.7[a] (9.40)	71.2[a,c] (8.48)	72.6[a] (8.89)	67.3 (10.98)
	Standing	71.5 (7.87)	73.4 (8.58)	76.6[a] (10.25)	75.4[a,c] (8.79)	75.2[a] (10.15)	73.2 (8.82)
Pregabalin	Resting	69.2 (8.66)	67.7 (5.72)	66.6 (6.96)	65.3 (7.70)	64.7 (5.22)	64.5 (8.49)
	Standing	73.8 (8.50)	70.4 (6.60)	70.5 (8.29)	68.1 (7.72)	69.0 (7.56)	71.7 (7.46)
HR							
Placebo	Resting	69.2 (12.04)	64.6 (9.36)	65.8 (6.37)	67.6 (9.13)	67.3 (10.54)	66.7 (9.68)
	Standing	75.9 (10.16)	77.3 (8.89)	80.3 (12.74)	79.7 (9.00)	83.9 (13.28)	81.9 (12.12)
Venlafaxine	Resting	70.2 (10.34)	74.3 (10.31)	71.7 (9.46)	77.8 (7.91)	79.6 (10.17)	77.4 (9.17)
	Standing	77.8 (11.00)	84.3 (12.61)	89.1[c] (13.26)	97.1[b,d] (12.55)	97.6[b,d] (13.27)	94.2[a,c] (9.96)
Pregabalin	Resting	70.3 (12.26)	67.8 (14.03)	67.8 (7.51)	69.1 (11.82)	71.2 (10.78)	70.8 (10.80)
	Standing	77.4 (8.23)	76.8 (11.01)	78.1 (9.69)	81 (10.73)	82.2 (11.21)	83.9 (14.02)

Mean rest and standing SBP, DBP, and HR over the study period are shown; $n = 18$ in each treatment arm, except for standing measurements in the venlafaxine group where $n = 17$. Standard deviations in parentheses.
[a]Venlafaxine significantly different to placebo, $p < 0.05$.
[b]Venlafaxine significantly different to placebo, $p < 0.01$.
[c]Venlafaxine significantly different to pregabalin, $p < 0.05$.
[d]Venlafaxine significantly different to pregabalin, $p < 0.01$.

Systolic blood pressure

Resting SBP (Dinamap). There was a significant effect of Drug ($F(2,54) = 3.34$, $p < 0.05$), where Bonferroni pairwise comparisons showed resting SBP was significantly higher on venlafaxine compared with pregabalin ($p < 0.05$). There was also a significant Drug*Visit interaction ($F(6,54) = 5.71$, $p < 0.001$). *Post hoc* analysis by one-way ANCOVAs showed a significant difference between drugs at day 7 ($F(2,54) = 3.68$, $p < 0.05$), day 14 ($F(2, 54) = 3.63$, p 0.05), and day 21 ($F(2,54) = 8.42$, $p < 0.01$). Bonferroni pairwise comparisons showed resting SBP was significantly higher on venlafaxine compared with pregabalin at days 7 ($p < 0.05$), 14 ($p < 0.05$), and 21 ($p < 0.01$). Resting SBP was also higher on venlafaxine compared with placebo on day 21 ($p < 0.05$). There was no significant difference between placebo and pregabalin. SBP on venlafaxine rose over the course of the study and dropped significantly on cessation back to baseline levels. There was no significant effect of Visit.

Standing SBP (Dinamap) and the difference between resting and standing SBP (Dinamap). There were no significant Drug effects, Visit effects, or Drug*Visit interaction.

Drop in SBP (Finapres). There was a significant effect of Drug ($F(2,54) = 6.11$, $p < 0.01$) but no significant effect of Visit or Drug*Visit interaction. *Post hoc* analysis showed that SBP drop was significantly larger on venlafaxine than placebo ($p < 0.05$) and pregabalin ($p < 0.01$). There was no significant difference between placebo and pregabalin.

Overshoot of SBP (Finapres). There was a significant effect of Drug ($F(2, 54) = 5.08$, $p < 0.05$) but no significant effect of Visit or Drug*Visit interaction. *Post hoc* analysis showed that SBP overshoot was significantly smaller on venlafaxine than placebo and pregabalin (both $p < 0.01$). There was no significant difference between placebo and pregabalin.

Time to 50% recovery of SBP (Finapres). There was a significant effect of Visit ($F(2,54) = 4.06$, $p < 0.05$) but no significant effect of Drug or Drug*Visit interaction. There was a trend towards a significant drug effect ($F(2,54) = 2.71$, $p = 0.076$), whereby Tukey's showed a non-significant trend towards 50% recovery being longer on venlafaxine than placebo ($p = 0.067$). Bonferroni pairwise comparisons showed that time to 50% SBP recovery was significantly longer at day 14 compared with day 7 ($p < 0.05$).

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Table 4. Finapres measured systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR)

	Drop[a,d]			Overshoot[b,d]			Time to 50% recovery			Time to 100% recovery[a,c]		
SBP	Day 7	Day 14	Day 21	Day 7	Day 14	Day 21	Day 7	Day 14	Day 21	Day 7	Day 14	Day 21
Placebo	45.2 (20.10)	37.0 (12.62)	32.7 (12.81)	16.8 (14.98)	14.0 (13.87)	19.5 (17.91)	3.1 (1.71)	4.9 (1.96)	3.8 (2.36)	6.6 (3.26)	9.3 (5.85)	8.1 (8.69)
Venlafaxine	47.4 (20.26)	53.9 (17.08)	52.0 (16.53)	8.7 (16.66)	6.5 (13.89)	5.5 (14.02)	4.2 (2.16)	5.7 (3.60)	5.7 (1.83)	10.4 (5.51)	11.8 (6.17)	12.9 (4.49)
Pregabalin	37.6 (15.27)	41.0 (15.47)	33.9 (19.48)	12.8 (9.19)	17.9 (11.60)	18.0 (14.61)	4.0 (1.69)	4.1 (2.17)	5.1 (4.27)	7.6 (2.18)	8.3 (5.46)	9.0 (6.34)
	Drop			Overshoot			Time to 50% recovery			Time to 100% recovery		
DBP	Day 7	Day 14	Day 21	Day 7	Day 14	Day 21	Day 7	Day 14	Day 21	Day 7	Day 14	Day 21
Placebo	26.6 (6.64)	26.9 (6.58)	26.7 (8.50)	11.1 (6.97)	9.4 (8.37)	10.6 (6.65)	4.4 (1.60)	5.0 (1.98)	5.3 (2.02)	6.9 (2.81)	8.6 (4.07)	8.8 (7.33)
Venlafaxine	29.9 (10.60)	31.7 (9.43)	28.6 (5.75)	9.2 (7.78)	7.5 (7.79)	8.2 (6.98)	4.9 (2.52)	5.9 (2.72)	5.4 (1.63)	9.0 (4.57)	10.2 (4.29)	9.3 (2.47)
Pregabalin	25.2 (6.78)	26.7 (5.80)	23.5 (10.23)	8.6 (6.55)	9.0 (4.18)	9.8 (6.87)	4.6 (1.72)	5.2 (1.91)	6.1 (4.56)	7.5 (1.58)	8.0 (3.89)	10.0 (8.17)
	HR_{max}			HR_{min}[b,d]			ΔHR_{max}			Ratio[b,d]		
HR	Day 7	Day 14	Day 21	Day 7	Day 14	Day 21	Day 7	Day 14	Day 21	Day 7	Day 14	Day 21
Placebo	108.3 (16.48)	115.6 (24.06)	111.6 (17.00)	71.6 (10.74)	71.4 (9.49)	71.4 (11.43)	38.3 (14.38)	45.4 (23.09)	43.5 (15.16)	1.5 (0.21)	1.6 (0.28)	1.6 (0.21)
Venlafaxine	110.5 (11.50)	113.4 (11.14)	116.4 (22.36)	80.9 (10.86)	89.1 (13.76)	87.6 (12.27)	37.6 (8.74)	35.1 (10.31)	38.0 (23.64)	1.4 (0.22)	1.3 (0.17)	1.4 (0.36)
Pregabalin	106.9 (11.08)	107.6 (15.05)	101.9 (11.50)	67.7 (8.01)	68.2 (11.40)	71.0 (11.71)	36.2 (14.53)	36.9 (14.87)	30.1 (11.64)	1.6 (0.24)	1.6 (0.31)	1.5 (0.24)

Mean SBP and DBP (mmHg): drop, overshoot, and time (in seconds) to 50% and 100% recovery; and HR (beats per minute): maximum (HR_{max}), minimum (HR_{min}), change from control to HR_{max} (ΔHR_{max}), and ratio of HR_{max}/HR_{min} (Ratio) are shown. $n = 18$ in each treatment arm. Standard deviations in parentheses.

[a]Venlafaxine significantly different to placebo, $p < 0.05$.

[b]Venlafaxine significantly different to placebo, $p < 0.01$.

[c]Venlafaxine significantly different to pregabalin, $p < 0.05$.

[d]Venlafaxine significantly different to pregabalin, $p < 0.01$.

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Time to 100% recovery of SBP (Finapres). There was a significant effect of Drug ($F(2,54) = 5.75$, $p < 0.01$) but no significant effect of Visit or Drug*Visit interaction. *Post hoc* analysis showed that time to 100% SBP recovery was significantly longer on venlafaxine than placebo and pregabalin (both $p < 0.05$). There was no significant difference between placebo and pregabalin.

Diastolic blood pressure

Resting DBP (Dinamap). There were no significant Visit effects or Drug*Visit interaction, but there was a significant effect of Drug ($F(2,54) = 6.34$, $p < 0.01$). Bonferroni pairwise comparisons showed resting DBP was significantly higher on venlafaxine compared with placebo ($p < 0.05$) and pregabalin ($p < 0.01$). There was no significant difference between placebo and pregabalin.

Standing DBP (Dinamap). There were no significant Visit effects or Drug*Visit interaction. There was a significant effect of Drug ($F(2,54) = 4.90$, $p < 0.05$), where Bonferroni pairwise comparisons showed standing DBP was significantly higher on venlafaxine compared with placebo ($p < 0.01$).

Difference between resting and standing DBP (Dinamap). There was no significant effect of Visit, Drug, or Drug*Visit interaction.

Drop in DBP (Finapres). There were no significant effects of Drug, Visit, or Drug*Visit interaction. There was a trend towards a drug effect ($F(2,54) = 3.01$, $p = 0.058$), whereby Tukey's showed a non-significant trend towards DBP drop being larger on venlafaxine than pregabalin ($p = 0.051$).

Overshoot of DBP (Finapres), time to 50% recovery, and time to 100% recovery of DBP (Finapres). There were no significant effects of Visit, Drug, or Drug*Visit interaction.

Heart rate

Resting HR (Dinamap). There were no significant Visit effects or Drug*Visit interaction. There was a significant effect of Drug ($F(2,54) = 4.29$, $p < 0.05$). Bonferroni pairwise comparisons showed resting HR on venlafaxine was significantly higher than on placebo ($p < 0.01$).

Standing HR (Dinamap). There were significant Drug effects ($F(2,54) = 8.21$, $p < 0.01$) but no Visit effects or Drug*Visit interaction. Bonferroni pairwise comparisons showed standing HR was significantly higher on venlafaxine compared with placebo ($p < 0.01$) and pregabalin ($p < 0.01$). There was no significant difference between placebo and pregabalin.

Difference between resting and standing HR (Dinamap). There was a significant effect of Drug ($F(2,54) = 3.45$, $p < 0.05$) but no effect of Visit or Drug*Visit interaction. Bonferroni pairwise comparisons showed the difference between standing and resting HR was significantly larger on venlafaxine compared with pregabalin ($p < 0.05$).

Maximum HR (Finapres). There were no significant effects of Visit, Drug, or Drug*Visit interaction.

Minimum HR (Finapres). There was a significant effect of Drug ($F(2,54) = 17.25$, $p < 0.001$) but no significant effect of Visit or Drug*Visit interaction. *Post hoc* analysis showed that minimum HR was significantly higher on venlafaxine than placebo and pregabalin (both $p < 0.001$). There was no significant difference between placebo and pregabalin.

Delta max HR (maximum HR minus control) (Finapres). There were no significant effects of Visit, Drug or Drug*Visit interaction.

HR ratio (Finapres). There was a significant effect of Drug ($F(2,54) = 9.24$, $p < 0.001$) but no significant effect of Visit or Drug*Visit interaction. *Post hoc* analysis showed that HR ratio was significantly lower on venlafaxine compared with placebo and pregabalin (both $p < 0.01$). This means there was a significantly smaller difference between minimum and maximum HRs during the orthostatic challenge when on venlafaxine compared with placebo and pregabalin. It is assumed this is due to the significantly higher minimum HR on venlafaxine. There was no significant difference between placebo and pregabalin.

Adverse events

Few clinical outcomes of the observed CV effects of venlafaxine were evident. Dizziness was experienced by 6 of the 18 participants on seven occasions in the venlafaxine group, by 6 of the 18 participants on 15 occasions in the pregabalin group, and by 3 of the 18 participants on four occasions in the placebo group. Postural dizziness was experienced by four participants on four occasions in the venlafaxine group, although CV measurements, such as BP drop, for these participants were not consistently significantly different to the other participants also taking venlafaxine. There were no reports of postural dizziness in the

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pregabalin group but reports by two participants on two occasions in the placebo group. Although doses between drugs may not have been directly comparable, the numbers of participants reporting dizziness was the same in both active drug groups. One participant taking venlafaxine reported increased HR on one occasion, whereas this was not reported in the pregabalin or placebo groups. All AEs were followed up, no adverse sequelae were reported, and there were no serious AEs.

DISCUSSION

This is the first study to compare the effects of venlafaxine, pregabalin, and placebo during orthostatic challenge. The purpose of this analysis was to investigate the effects of these drugs, focusing on venlafaxine, on BP and HR over 4 weeks of dosing in healthy volunteers.

In general, the results of this study support the assertion that venlafaxine increases BP and HR. SBP, DBP, and HR increased significantly after 1 week of treatment in the venlafaxine group compared with those in the pregabalin and placebo groups, and this effect of venlafaxine returned back to baseline levels at the end of the study after the drug was stopped. There were no significant differences between pregabalin and placebo on any measure. Specifically, resting SBP, DBP, and HR, and standing DBP and HR were raised in the venlafaxine group compared with the placebo and pregabalin groups. Despite these significant increases, the values were not raised beyond prehypertensive ranges (defined as a DBP of 80–89 mmHg and an SBP of 120–139 mmHg; JNC 7, 2004) and therefore were not indicative of hypertension (defined as $\geq$90 mmHg DBP and $\geq$140 mmHg SBP by JNC 7 (2004) and by Feighner (1995) as increase from baseline of at least 15 mmHg and to 105 mmHg DBP, and an increase of at least 20 mmHg and to 180 mmHg SBP). In a meta-analysis of several patient studies, Thase (1998) concluded venlafaxine produced an increase in supine DBP, which was dose dependent but without increase below 300 mg/day. In our study, a maximum dose of only 150 mg/day resulted in significant resting and standing BP increases, compared with placebo. After only 1 week at a dose of 112.5 mg/day, compared with before dosing, the venlafaxine group had an average increase in SBP of 7.4 mmHg at rest and 1.9 mmHg after standing and DBP of 4.2 mmHg at rest and 3.2 mmHg after standing. This probably indicates the presence of some NA blockade effects at low doses, despite Stahl *et al*. (2005) considering a dose below 150 mg/day to be too low to have NA effects and Blier *et al*. (2007) finding no NA effects at doses of 300–600 mg /day. Analysis of the mean differences between resting and standing (meaning the change due to standing) BP showed no significant drug effects, and this may have been due to large variance in the data.

Studies that do report cardiovascular effects sometimes describe significant increases in DBP and HR but do not report significant changes in SBP (such as Brent *et al*., 2008). In the current study, increases in DBP and HR were found, supporting these findings; however, SBP increases were also noted. SBP effects of venlafaxine have been reported in the literature, largely in placebo-controlled studies. For example, a trend towards an increase in SBP after 6 weeks of doses up to 225 mg/day was shown by Nemeroff and Thase (2007) in a multicentre study of 96 depressed patients. Abdelmawla *et al*. (1999) found increases in SBP on both 75 and 150 mg/day after only 3 h in 15 healthy volunteers and suggested this may be indicative of NA reuptake effects. It is possible any CV effects of venlafaxine may only be detected correctly in placebo-controlled trials, where confounding factors are minimised.

The orthostatic challenges performed at each visit again demonstrated CV effects of venlafaxine. Participants in the venlafaxine group showed a larger drop in SBP, a lack of overshoot, a trend towards slower recovery to 50% and a significantly slower recovery to 100% SBP compared with pregabalin and placebo. Minimum HR was higher and HR ratio (the difference between minimum and maximum HR) was smaller in the venlafaxine group compared with pregabalin and placebo groups, indicating a smaller change in HR and therefore reduced HRV. There were no significant drug effects on DBP, although there was a non-significant trend towards a larger drop in DBP on venlafaxine compared with pregabalin.

The increased drop in SBP (and a trend towards increased drop in DBP) with venlafaxine during orthostatic challenge is likely to be due to the elevated SBP and DBP noted generally with this drug. Overshoot before recovery is due to vasoconstriction (baroreceptor reflex) evoked to facilitate blood return from the lower extremities where it was forced by gravity on standing. NA increases vasoconstriction (Abdelmawla *et al*., 1999), so it might be expected that venlafaxine administration would synergistically increase the overshoot. However, the results of the current study show a significantly smaller overshoot in the venlafaxine group compared with placebo and pregabalin groups. The venlafaxine group also took significantly longer to recover from the manoeuvre than the other groups. It is possible that this is a group difference that may have been apparent had the measures been taken at baseline.

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However, this is a pattern that has been seen with other NA-acting antidepressants such as the tricyclic antidepressants, and it may reflect a central as well as peripheral action of these drugs (Middleton *et al*., 1988). Also, both a loss of overshoot and increased time to recovery have also been reported in a study of the alpha-adrenoreceptor agonist clonidine, because of a central decrease in sympathetic function (Coupland *et al*., 1995b). However, the effects of venlafaxine may not just be due to NA reuptake blockade because overshoot was also altered in patients with panic disorder after taking selective serotonin reuptake inhibitors (Coupland *et al*., 2003).

The reduction of variability in HR during recovery may have been due to the secondary effects of BP overshoot; however, other studies have also found similar effects in their measure of HRV. A reduced HRV was found by Davidson *et al*. (2005) using paced breathing in their 3-week study of up to 225 mg/day of venlafaxine XR in depressed patients. Siepmann *et al*. (2007), in a similar 2-week study of healthy volunteers taking up to 150 mg/day, also found reduced HRV. HRV is mainly under parasympathetic control, and reduced HRV is associated with impairment of parasympathetic function (van Lieshout, 1989).

The clinical relevance of BP effects and changes to HRV in patients with depression, taking medication, but without significant cardiovascular problems is unclear. Reduced HRV is also found in anxiety disorders such as panic, generalised anxiety, social anxiety and obsessive–compulsive disorders (Pittig *et al*., 2013); however, the clinical relevance of HRV changes in patients with anxiety is also unclear (Tully *et al*. 2013). Increased BP may lead to hypertension, but where this has occurred with venlafaxine, reports have been limited to specific individuals within trials or case studies (e.g. Gründer *et al*., 1996; Pardal *et al*., 2001; Bradwejn *et al*., 2005; Sheehan *et al*., 2009). A reduced HRV may lead to cardiac arrhythmias, but this has only been shown in patients with coronary artery disease (Carney *et al*., 1995).

Our study did find CV effects of venlafaxine in healthy volunteers, supporting the recommendations of Feighner (1995), Johnson *et al*. (2006) and others for monitoring patients taking venlafaxine. These CV effects may explain the AEs of dizziness, light headedness and postural hypotension reported in this study and in most published studies of venlafaxine (e.g. Gründer *et al*., 1996, Sir *et al*., 2005; Nemeroff and Thase, 2007; Sheehan *et al*., 2009). A drop on standing of up to 40 mmHg SBP and 20 mmHg DBP is considered normal (Wieling *et al*., 1992). In the current study, variance is large, but on average, these criteria are exceeded in all groups including placebo, although to a greater extent by venlafaxine. This may be due to the beat-to-beat recordings being a more accurate method of measurement than by sphygmomanometer. Orthostatic hypotension can predispose someone to falls (particularly in the elderly; Ray *et al*., 1987). No falls were reported in the current study, but our sample consisted of young healthy volunteers. However, a study of an elderly sample found that the degree and timing of orthostatic hypotension did not significantly predict falls (Maurer and Cheng, 2004), which may indicate no link between postural dizziness and falls.

There are no publications associating pregabalin with CV effects. This is in accordance with the results of this study, which showed no significant difference between the CV effects of pregabalin compared with placebo. It should be noted that in a clinical situation, patients often receive a higher dose than the one used in this study; therefore, a higher dose of pregabalin may not be similarly free of CV effects. There were several reports of dizziness on pregabalin in our study, and it is cited as a common adverse effect in the Summary of Product Characteristics and in the British National Formulary. Hypertension and other CV effects are cited as less common.

There were limitations in this study. Doses of the active drugs may not have been comparable in terms of clinical efficacy. No baseline orthostatic challenge was performed, meaning comparisons with responses before drug administration was not possible. Individual differences in BP, already variable between measurements, meant a difficulty in obtaining accurate measurements with a Finapres. Artefacts were removed from analysis, but the nature of the recording leaves a vulnerability to hand movements. Participants were instructed to remain still but would occasionally move. Manoeuvres such as crossing ankles when supine and shifting standing positions would act as a muscle pump and increase BP. The study was well controlled with respect to using strict inclusion and exclusion criteria, and there were no significant differences between treatment groups on measures of gender, ethnic origin, age, usual caffeine and alcohol intake, usual amounts of smoking, body mass index, scores on mood and personality scales, and compliance (the number of drug capsules missed) (see main study, Diaper *et al*., 2013). Barantke *et al*. (2008) found gender differences in some measures of HRV. Although more men than women were included in the study (1.2:1), this was not significantly more. Imholz *et al*. (1990) and Stein *et al*. (1994) found no substantial differences in CV response between men

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and women. Menstrual cycle stages for women were not recorded in this study, but Claydon *et al*. (2006) showed no significant difference in head-up tilt tests of orthostatic tolerance in women during different menstrual stages.

In summary, these results confirm a lack of effect of pregabalin 200 mg/day on measures of BP and HR compared with placebo. However, venlafaxine up to 150 mg/day increased HR, DBP and also SBP, which is in accordance with similar placebo-controlled studies. Increase in SBP, increase in drop, reduced overshoot and increased time to recovery all point to NA effects of venlafaxine. Few differences were noted between each weekly orthostatic challenge, indicating no significant difference between doses of venlafaxine in this measure. Effects were present after only 7 days ingestion of 112.5 mg/day of venlafaxine. This study of healthy volunteers supports the presence of NA effects of venlafaxine, with parasympathetic effects of reduced variation in HR.

CONFLICTS OF INTEREST

Sue Wilson has provided consultancy services to Novartis and has received honoraria from Pfizer, Servier, and Lilly. Gerry Dawson, Colin Dourish, and Kevin Craig are directors and shareholders in P1vital Limited. David Nutt has provided consultancy services to Pfizer, GSK, Novartis, Organon, Cypress, Lilly, Janssen, Lundbeck, BMS, Astra Zeneca, Servier, Hythiam, and Sepracor; received honoraria from Wyeth, Reckitt-Benckiser, and Cephalon; received grants or clinical trials payments from MSD, GSK, Novartis, Servier, Janssen, Lundbeck, Pfizer, Wyeth, and Organon; and holds shares in GSK. There are no conflicts of interest declared for the remaining authors.

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