Clinical trial results:
Evaluation of the effects of chronic treatment with venlafaxine (150 mg) and pregabalin (200 mg) on emotional indices of anxiety and panic induced by breathing carbon dioxide.

Summary

EudraCT number	2008-000971-15
Trial protocol	GB
Global end of trial date	26 August 2009

Results information

Result version number	v1 (current)
This version publication date	21 April 2019
First version publication date	21 April 2019
Summary attachment (see zip file)	Publication (VenPregab.pdf)

Trial information

Trial identification

Sponsor protocol code	P1V-ANX-CT01-07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	NHS REC reference: 08/H0308/298

Notes:

Sponsors

Sponsor organisation name	University of Bristol
Sponsor organisation address	One Cathedral Square, Bristol, United Kingdom, BS1 5DD
Public contact	Dr Alison Diaper, University of Bristol, alison_diaper@hotmail.com
Scientific contact	Dr Alison Diaper, University of Bristol, alison_diaper@hotmail.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 September 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 August 2009
Global end of trial reached?	Yes
Global end of trial date	26 August 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- To determine whether chronic (3 week) venlafaxine dosing reduces the anxiety symptoms induced by breathing a mixture of air and 7.5% carbon dioxide (CO2).
- To determine whether chronic (3 week) pregabalin dosing reduces the anxiety symptoms induced by breathing a mixture of air and 7.5% CO2.

Protection of trial subjects:

The Psychopharmacology Unit is experienced in managing and conducting human research in patient and healthy volunteer populations. Experience with the effects of inhaling 7.5% CO2 has been obtained from research completed over the last 8 years, using the procedure on hundreds of subjects.

The study was performed in accordance with ICH Good Clinical Practice, with approval from a Research Ethics Committee (Cambridge 2 Research Ethics Committee), relevant Health Service Trust regulatory approval (University Hospitals Bristol NHS Trust), and the Medicines and Healthcare products Regulatory Agency (MHRA). Approval in writing was received prior to starting the study.

Aspects of the Data Protection Act were adhered to. The case report forms were completed and stored appropriately. Data held on the computer were anonymised.

Volunteers were recruited using advertisements approved for that reason by the Ethics Committee.

After initial contact, the subjects received the Participant Information Sheet and were given at least 48 hours to read it and consider the implications of their participation in the study. They were given the time to raise any questions with the investigators prior to making the decision to participate. Each subject was then asked to give their written informed consent after one of the investigators had explained the nature, purpose and risks of the study, by signing the Informed Consent Forms.

A letter was sent to the subjects' general practitioners informing them of their patients' participation in the trial.

The study was of no direct benefit to the participants involved.

A medic was on call and available to all participants at all times, and two researchers administered the CO2 inhalations.

Background therapy: -

Evidence for comparator:

In the present study we will investigate the effects of two drugs prescribed to treat GAD, venlafaxine (Effexor®) and pregabalin (Lyrica®), both of which have different mechanisms of actions to the drugs already tested using the CO2 challenge. As both drugs require several weeks of dosing to be effective in treating GAD, the participants in this study will be given a CO2 challenge after chronic dosing. Consequently, participants will be treated for 3 weeks with either venlafaxine or pregabalin prior to undertaking the CO2 challenge test.

Venlafaxine is a bicyclic antidepressant, and is usually categorized as a serotonin-noradrenaline reuptake inhibitor (SNRI), however, it has also been referred to as a serotonin- noradrenaline-dopamine- reuptake inhibitor (Goeringer et al., 2001). It works by blocking the transporter "reuptake" proteins for key neurotransmitters affecting mood, thereby leaving more active neurotransmitter in the synapse. The neurotransmitters principally affected are serotonin and noradrenaline. Additionally, in

high doses it weakly inhibits the reuptake of dopamine (Wellington and Perry, 2001).

Venlafaxine is well absorbed with at least 92% of an oral dose being absorbed into the systemic circulation. The drug is extensively metabolized in the liver via the cytochrome P450 2D6 (CYP2D6) isoenzyme to O-desmethylvenlafaxine. This metabolite is equally potent as a serotonin-noradrenaline reuptake inhibitor as the parent compound, such that the differences in metabolism between extensive and poor metabolisers are not clinically important. Steady-state concentrations of venlafaxine and its metabolite are attained in the blood within three days and therapeutic effects are usually observed within 3-4 weeks. No accumulation of venlafaxine has been observed during chronic administration in healthy participants.

Actual start date of recruitment	03 November 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	60
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All respondents to the advertising underwent an initial telephone screening and sent a PIS. Those interested in participating attended for a screening visit to assess eligibility, and give informed to consent to participate if suitable. Participants then attended a baseline visit before for randomisation.

Pre-assignment

Screening details:

Physical examination, blood exam (biochemistry and haematology), height/weight/blood pressure, neuropsychiatric interview, ECG, alcohol breath test, pregnancy test, urinalysis and urine drugs of abuse test.

Pre-assignment period milestones

Number of subjects started	79[1]
Intermediate milestone: Number of subjects	Screening: 79
Number of subjects completed	60

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Not eligible: 19

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Subjects were found not eligible for the study at screening period.

Period 1

Period 1 title	Randomisation (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Blinding implementation details:

Participants were randomised to placebo (study arm A) or one of two active drugs (study arms B or C). Study drugs and randomisations were provided by Bilcare GCS (Europe) Ltd. Participants were allocated at random to one of the study arms below in the ratio 1:1:1, in blocks of 6. Both the venlafaxine and pregabalin tablets were over-encapsulated to give the same appearance as that of the red placebo capsule.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	DB size AA-el Swedish orange capsules
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Two capsules per day.

Arm title	Venlafaxine

Arm description:	
Venlafaxine	
Arm type	Experimental
Investigational medicinal product name	Venlafaxine
Investigational medicinal product code	
Other name	Venlafaxine 37.5mg tablets (Efexor, Wyeth)
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
75mg on days 0-2, 112.5mg on days 3-6, 150mg on days 7-21, 75mg on days 22-24 and 37.5mg on days 25-26. Dose one capsule twice a day, morning and evening.	
Arm title	Pregabalin
Arm description:	
Pregabalin	
Arm type	Experimental
Investigational medicinal product name	Pregabalin
Investigational medicinal product code	
Other name	Pregabalin 50mg capsules (Lyrica, Pfizer)
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
100mg on days 0-6, 200mg on days 7-21, 100mg on days 22-24 and 50mg on days 25-26. Dose one capsule taken twice a day, morning and evening.	

Number of subjects in period 1	Placebo	Venlafaxine	Pregabalin
Started	19	23	18
Health and compliance check A	19	18	18
Health and compliance check B	18	18	18
CO2 challenge	18	18	18
Follow up visit	19	18	18
Completed	18	18	18
Not completed	1	5	0
Adverse event, non-fatal	1	5	-

Baseline characteristics

Reporting groups

Reporting group title	Randomisation

Reporting group description: -

Reporting group values	Randomisation	Total	
Number of subjects	60	60	
Age categorical			
Placebo mean age 22.0, sd 2.47, venlafaxine mean age 22.8, sd 2.85, pregabalin mean age 24.4, sd 7.11.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	60	60	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	23.1		
standard deviation	± 4.68	-	
Gender categorical			
Placebo males 50.0%, venlafaxine males 66.7%, pregabalin males 44.4%.			
Units: Subjects			
Female	28	28	
Male	32	32	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	Venlafaxine
Reporting group description: Venlafaxine	
Reporting group title	Pregabalin
Reporting group description: Pregabalin	
Subject analysis set title	All subjects
Subject analysis set type	Full analysis
Subject analysis set description: n=54 completers	

Primary: Panic Symptom Inventory

End point title	Panic Symptom Inventory
End point description: The Panic Symptom Inventory (PSI) was used to rate panic anxiety and the associated symptoms of autonomic arousal, with the option of rating 0 = not at all, 1 = slight, 2 = moderate, 3= severe, 4 = very severe. The PSI was adapted from Clark and Hemsley (1982), and lists 34 items and has been used in studies of panic provocation (Nutt et al., 1990; Bell et al., 2002) and previous CO2 studies (Argyropoulos et al., 2002, Bailey et al., 2005).	
End point type	Primary
End point timeframe: Measured before and after each CO2 inhalation	

End point values	Placebo	Venlafaxine	Pregabalin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18[1]	18[2]	18	
Units: Score				
arithmetic mean (standard deviation)	20.1 (± 13.0)	18.1 (± 10.0)	18.2 (± 13.7)	

Notes:

[1] - 1 dropout replaced, therefore 18 in analysis.

[2] - 5 drop outs replaced, therefore 18 in analysis.

Statistical analyses

Statistical analysis title	Paired t test
Statistical analysis description: Paired t tests for placebo and venlafaxine, placebo and pregabalin, and venlafaxine and pregabalin showed the following results. At the Peak-Air time point, PSI scores on venlafaxine were significantly higher than on pregabalin (t=2.549, df=34, p<0.05). At the Peak-35% CO2 time point, PSI scores on venlafaxine were significantly higher than on pregabalin (t=2.235, df=34, p<0.05).	
Comparison groups	Venlafaxine v Placebo v Pregabalin

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05 [3]
Method	t-test, 2-sided

Notes:

[3] - At the Peak-35% CO2 time point, PSI scores on venlafaxine were significantly higher than on pregabalin (t=2.235, df=34, p<0.05).

Primary: Generalised Anxiety Disorder Inventory (GAD-C)

End point title	Generalised Anxiety Disorder Inventory (GAD-C)

End point description:

End point type	Primary

End point timeframe:

Before and after each CO2 inhalation

End point values	Placebo	Venlafaxine	Pregabalin	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18[4]	18[5]	18	
Units: Score				
arithmetic mean (standard deviation)	10.8 (± 7.9)	9.6 (± 5.0)	10.3 (± 7.8)	

Notes:

[4] - 1 dropout replaced, therefore 18 included in final analysis

[5] - 5 dropouts replaced, therefore 18 included in final analysis

Statistical analyses

Statistical analysis title	Paired t test

Statistical analysis description:

At the Peak Air time point, GAD-C scores on placebo were significantly higher than on pregabalin (t=2.059, df=28.4, p<0.05, and scores on venlafaxine were also significantly higher than on pregabalin (t=2.230, df=26.9, p<0.05). At the Peak 35% CO2 time point, GAD-C scores on venlafaxine were significantly higher than on pregabalin (t=2.145, df=34, p<0.05).

Comparison groups	Venlafaxine v Pregabalin v Placebo
Number of subjects included in analysis	54
Analysis specification	Post-hoc
Analysis type	equivalence
P-value	< 0.05 [6]
Method	t-test, 2-sided

Notes:

[6] - At the Peak 35% CO2 time point, GAD-C scores on venlafaxine were significantly higher than on pregabalin (t=2.145, df=34, p<0.05).

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From signing of informed consent form until last subject last visit (follow-up).	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	12.1
Reporting groups	
Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	Venlafaxine
Reporting group description: Venlafaxine	
Reporting group title	Pregabalin
Reporting group description: Pregabalin	

Serious adverse events	Placebo	Venlafaxine	Pregabalin
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 19 (0.00%)	0 / 23 (0.00%)	0 / 18 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Placebo	Venlafaxine	Pregabalin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 19 (84.21%)	17 / 23 (73.91%)	14 / 18 (77.78%)
General disorders and administration site conditions			
Headache			
subjects affected / exposed	11 / 19 (57.89%)	7 / 23 (30.43%)	10 / 18 (55.56%)
occurrences (all)	17	13	21
Insomnia			
subjects affected / exposed	5 / 19 (26.32%)	8 / 23 (34.78%)	2 / 18 (11.11%)
occurrences (all)	11	14	3
Fatigue			

subjects affected / exposed	3 / 19 (15.79%)	10 / 23 (43.48%)	5 / 18 (27.78%)
occurrences (all)	4	14	5
Feeling abnormal			
subjects affected / exposed	2 / 19 (10.53%)	6 / 23 (26.09%)	4 / 18 (22.22%)
occurrences (all)	3	6	4
Somnolence			
subjects affected / exposed	4 / 19 (21.05%)	3 / 23 (13.04%)	4 / 18 (22.22%)
occurrences (all)	5	3	4
Ear and labyrinth disorders			
Dizziness			
subjects affected / exposed	3 / 19 (15.79%)	6 / 23 (26.09%)	6 / 18 (33.33%)
occurrences (all)	4	7	15
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 19 (10.53%)	10 / 23 (43.48%)	3 / 18 (16.67%)
occurrences (all)	2	11	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 April 2008	Contact list - Changed Site Management Organisation to Funder Section 13.2.2 Serious Adverse Events (SAEs) - Removed the need to report SAEs to P1vital (funder) Section 18.2 On-Site Audits – Removed the need to inform P1vital (funder)
28 April 2009	• Change to inclusion/exclusion criteria. Currently the inclusion/exclusion criteria states that all resting blood pressure at screening should be between 100-140 mmHg systolic and 60-90 mmHg diastolic. Because of this tight range, we are excluding many fit participants with blood pressures outside of this range, when they are otherwise suitable for inclusion. We wish to add a statement to the inclusion/exclusion criteria which would mean that blood pressure results outside of this range should be subject to the judgment of the study physician as to the clinical significance of the results. If the study physician felt any out-of-range results were not clinically significant or relevant to the study, then s/he could then pass the participant fit to enter the study. As all participants will only be included on the study if deemed suitable by the study physician, there will be no additional risk to participants. The benefit of this amendment will be the inclusion of suitable participants who would otherwise fail screening unnecessarily. There will be no consequences to participants already on the trial, and no change to the evaluation of results.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22516666