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Effectiveness of the Dual Serotonin Norepinephrine Reuptake Inhibitor Venlafaxine in Depressed Patients

Submission date	Recruitment status	[ ] Prospectively registered
07/09/2005	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
29/09/2005	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
29/09/2006	Mental and Behavioural Disorders	[ ] Record updated in last year

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
N/A

Study information

Scientific Title

Study objectives
Tyramine is well known by clinicians for its capacity to increase blood pressure, typically in patients treated with monoamine oxidase inhibitors. The finding that pretreatment with reserpine, which induces a depletion of catecholamines, abolishes the effect of Tyramine on blood pressure suggests that Tyramine acts indirectly as a sympathomimetic agent. It has been shown that Tyramine is taken up in NE neurons by the NE transporter and that by stochiometric displacement, it then releases NE from intraneuronal stores (Hoffman and Lefkowitz 1990). Blood pressure is increased by the release of NE; therefore, blood pressure serves as a simple and reliable index of the action of Tyramine. The Tyramine test (Ghose and Turner 1975) consists of measuring the transient increase in the blood pressure of patients after a Tyramine load. It can be carried out either by determining the dose of Tyramine required to induce a fixed increase in systolic blood pressure (SBP) (for example, 30 mmHg,) or by measuring the effect of a fixed dose of Tyramine. Pretreatment with Tomoxetine (now called Atomoxetine), a relatively potent and selective inhibitor of NE uptake, has been reported to decrease the transient elevation in blood pressure produced by Tyramine administration (Zerbe et al. 1985). In recent work, we have demonstrated that transient blood pressure elevation in response to Tyramine is reduced by pretreating subjects with Desipramine, Nortriptyline, Clomipramine and Reboxetine, three NE uptake inhibitors, but not by pretreating with Paroxetine, a selective 5-HT uptake inhibitor (Blier et al. 1997; Slater et al. 2000; Turcotte et al. 2001). In the proposed study, if treated subjects decrease their pressor response to Tyramine, it will be interpreted as evidence of NE uptake inhibition.
In this study, the 5-HT content of the whole blood will be used as an index of 5-HT uptake in depressed patients and will be measured before and after each week of treatment. Since more than 90% of the 5-HT in the blood is in platelets, it is not necessary to correct this value for the platelet count. Notably, Flament et al. (1987) found that the mean level of 5-HT did not change significantly after 5 weeks of placebo whereas it dropped by 95% after 5 weeks of treatment with clomipramine. In this study, the use of each subject as his own control will allow the use of covariance analysis, increasing the likelihood of detecting a statistically significant difference between the different groups at the end of the treatments.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Not specified

Study type(s)
Treatment

Participant information sheet

Health condition(s) or problem(s) studied
Major Depression

Interventions
This is a three-arm, randomized, parallel study designed to assess the inhibition of NE and 5-HT uptake by Venlafaxine, Paroxetine and Atomoxetine. Approximately 40 depressed patients will be randomized to one of three treatment groups with the goal of having at least 10 subjects complete the study in each group. The investigators involved in the Tyramine test or the collecting of biochemical data will be blind to the medications used by patients. This study will be conducted on an outpatient basis.

Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
Venlafaxine, Paroxetine and Atomoxetine

Primary outcome measure
The primary objective of this study is to find evidence of a dose-dependent inhibition of NE reuptake starting of Venlafaxine at 150 mg/day.

Secondary outcome measures
A secondary objective of this study is to show a lack of effect of Paroxetine on NE reuptake at doses of up to 50 mg/day. Another secondary objective is to show a lack of effect of Atomoxetine on 5-HT reuptake and a similar action of higher doses of Venlafaxine and Atomoxetine on NE reuptake. A third secondary objective is to show a marked effect of Paroxetine and Venlafaxine on 5-HT reuptake starting at low doses.

Overall study start date
01/08/2004

Completion date
30/04/2005

Eligibility

Key inclusion criteria
1. Male or female patients between 18 and 65 years of age
2. Diagnosis of major depression according to the Diagnostic and Statistical Manual of Mental

Disorders, Fourth Edition (DSM-IV) (American Psychiatry Association, 1994) using the Structured Clinical Interview for Depression (SCID) (Spitzer 1992)
3. Initial global score 18 on the 17-item Hamilton depression rating scale
4. Written informed consent signed by the patient

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
40

Key exclusion criteria
1. Evidence of significant physical illness contraindicating the use of Venlafaxine, Paroxetine or Atomoxetine found on physical or in the laboratory data obtained during the first week of the study
2. Evidence of suicidality or severity of depression precluding safe participation in the study
3. Mental retardation (IQ lower than 80) rendering the response to investigators unreliable
4. Pregnancy, or absence of adequate contraceptive method in women with childbearing potential
5. Concurrent use of psychotropic medication such as antipsychotics, mood stabilizers or regular use of high doses of benzodiazepines
6. Lack of response or intolerance to optimal doses of Paroxetine, Venlafaxine or Atomoxetine
7. Participation in another clinical trial within 30 days of entry into the current study

Date of first enrolment
01/08/2004

Date of final enrolment
30/04/2005

Locations

Countries of recruitment
Canada

Study participating centre
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Sponsor information

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Industry

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Funder(s)

Funder type
Industry

Funder Name
Wyeth Pharmaceuticals

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration