Sex influence on the clinical improvement of Major Depressive Disorder in patients treated with Venlafaxine

A prospective cohort Study

FINAL DEGREE PROJECT

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*"I would venture to guess that Anon, who wrote so many poems without signing them, was often a woman" **-Virginia Wolf***

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ABBREVIATIONS

5-HT: 5-hidroxitriptamine

AMHC: Adult Mental Health Centre

ANRI: Selective Norepinephrine Reuptake Inhibitor

BDNF: Brain-Derived Neurotrophic Factor

CBT: Cognitive Behavioural Therapy

CRP: C- reactive protein

ECT: Electroconvulsive Therapy

ESS: Epworth Sleepiness Scale

GC: General Coordinator

HDRS: Hamilton Rating Scale for Depression

HPA: Hypothalamic-Pituitary-Adrenal

HPT: Hypothalamic-Pituitary-Thyroid

IGF-1: insulin-like growth factor 1

IL-6: Interleukin 6

MAO: Monoamine Oxidase

MDD: Major Depressive Disorder

NA: noradrenaline

NaSSA: Norepinephrine and Specific Serotoninergic Antagonist.

NDRI: Norephinephrine and Dopamine Reuptake Inhibitor

NT: neurotransmitters

ODV: O-desmethylvenlafaxine

SARI: Serotonin Antagonist Receptor Inhibitor

SAS: Sympathetic autonomous system

SNRI: Serotonin-Norepinephrine Reuptake Inhibitor

SSRI: Selective Serotonin Reuptake Inhibitor

TNFα: Tumoral necrosis factor alfa

VEGF: vascular endothelial growth factor

ABSTRACT

BACKGROUND

Major Depressive Disorder (MDD) is a common severe disorder which consists of symptoms conditioning important disability and causes difficulties in the functioning areas such as social life or occupation. MDD has a very high prevalence being the most frequent mental disorder in Spain, and its prevalence is of 6,7%. It is as twice as prevalent in women as in men being 9,2% against 4%. This disorder has a multifactorial aetiology being genetic factors, stressful life events and socioeconomic factors the most relevant. There are some biological, social and psychological factors that may explain the difference in the prevalence between men and women. Those are hormonal factors, exposition to sexual abuse, being exposed to caretaker responsibilities and emotion-focused roles. To diagnose a patient of MDD the DSM-5 criteria are used. These criteria include all the symptomatology related to this disorder. Apart from the diagnostic criteria, there are some scales to assess the severity of the MDD episode. The most used is the Hamilton Depression Rating Scale (HDRS). There are three main strategies that have proven to be effective to treat an MDD episode: antidepressant drugs, psychotherapy and electroconvulsive therapy. Venlafaxine is a dual antidepressant drug; it is a 5-HT and Noradrenaline reuptake inhibitor. It is metabolised in the liver to its active metabolite O-desmethylvenlafaxine, and to a less active metabolite N-desmethylvenlafaxine by the enzyme CYP3A4. This enzyme has a higher expression in women than in men.

OBJECTIVE

The main objective of this study is to assess if the patient's sex influences the clinical improvement of depression in patients treated with Venlafaxine, and therefore if there is a relationship between the patient's sex and the clinical improvement.

DESIGN

The study is designed as a multicentre prospective observational cohort study that will be carried out in all the Adult Mental Health Centres (AMHC) of Girona province, in total seven centres will participate in this study.

PARTICIPANTS

In this study will participate all MDD patients of Girona province treated with Venlafaxine 225mg and aged between 30-50 years at the beginning of the study. This population will be divided into two groups: men and women. The two groups will be as equal as possible.

METHODS

Information will be recorded directly from the patient. To assess the clinical improvement a psychiatrist will perform the HDRS and will give punctuation to patients at the beginning of the study and every three months until they reach their first year of follow-up. After answering the HDRS, patients will be transferred to the nursery where a blood draw will be done to measure the blood levels of N-desmethylvenlafaxine. All these data will be analysed posteriorly.

KEYWORDS

Major Depressive Disorder, Sex, Venlafaxine, N-desmethylvenlafaxine, clinical improvement.

INTRODUCTION

MAJOR DEPRESSIVE DISORDER

Definition and epidemiology

Major Depressive Disorder (MDD), is one of the most important causes of disability worldwide which has increased mortality. It is a common pathology usually associated with severe and persistent symptoms conditioning important social role impairment.

MDD is defined by feelings of sadness and/or inability to feel pleasure, emptiness or hopelessness most of the day, nearly every day, causing difficulties in functioning areas such as social life or occupation, during at least two weeks (1,2). To diagnosticate the syndrome, these are the most characteristic clinical features among others included in DSM-5 criteria (see section "Symptomatology and diagnostic criteria").

Although being an episodic disorder if it is not well treated, it may stretch on for 5 months or even longer. Despite knowing this reality, there is a high rate of inadequate treatment. Because of this, over 50% of patients who have suffered an MDD, will have at least one relapse and more risk of perpetuating the symptomatology. (3,4)

MDD has a very high prevalence and it is twice as prevalent in women as in men. Evidence suggests that the gender ratio in depression is more pronounced in cultures with more traditional gender roles (4,5). Also, depressive symptoms have shown some cultural variation due to differences in ethnicity standards regarding acceptance and expression of emotional distress.

In Spain, depression has become a major health problem, especially in recent years. This increment supposes a high investment in health. Among all the mental health disorders, MDD is the most frequent in Spain with a prevalence of 6,7%, being for women twice as much as for men: 9,2% against 4%.

The prevalence is also different regarding the age group. For children under 12 years old, the prevalence is 8,2%. In adolescents under 19, about 14,6%. Prevalence begins to increase during university years being around 37,4%, and in elder people, the prevalence is among 34,5%. (5,6).

In Catalonia, among 2,77% of the population is visited once a year in an Adult Mental Health Centre (AMHC) of which 24,40% are treated for depression (7).

Aetiology and risk factors

Depression is a multifactorial disease linked to multiple biological, physical and behavioural factors:

Stressful life events

Such as the loss of a loved one, health threats, relational challenges or sexual abuse. They have an impact on emotion regulation, especially when they happen during adolescence. This emotional dysregulation has a strong influence on the degree of depressive symptoms during adolescence but also throughout our lives. It has been studied that those events affect people's emotions not only because of the stressful incident but especially due to the appearance of negative cognitive emotion regulation strategies such as self-blame, other-blame, catastrophizing and rumination about the episode(8).

Genetics

There is a concordance between genetic factors and MDD. Despite stressful life events are risk factors for depression, they are important but not enough for developing an MDD to appear. Even though some individuals are more vulnerable to stress than others, 75% of MDD are related to life events but the other 25% is due to other causes.

The gen 5HTT-PR is the gene transport region of 5-hydroxytryptamine (5-HT). Having some variant of that gene causes a higher probability for suffering an MDD due to stress issues. (9) Apart from that gene, some other genetic variants modulate the vulnerability to stress. The more studied are Brain-derived neurotrophic factor (BDNF), monoamine oxidase (MAO) and cortisol receptors. MDD has been associated with polymorphism in the glucocorticoid receptor gene NR3C1, the monoamine oxidase A gene, the gene for glycogen synthase kinase-3β (which has a key role in the phosphorylation and regulation of metabolic enzymes and many transcription factors), and a group-2 metabotropic glutamate receptor gene (GRM3). (4).

All of these genes are related to the neurobiology of depression (see "Neurobiology of depression" below).

Sex differences

As stated before, women have twice more risk to have a depressive episode than men. There are several social and psychological factors that may help explain this gender difference(3,10–12):

- Twice as many girls and boys are exposed to childhood sexual abuse
- During adulthood, women are more likely than men to be exposed to caretaker responsibilities.
- Acceptance of traditional roles imposed among girls, and its interference with some rewarding activities that are not considered "feminine".
- Hormonal differences: There is evidence that estrogen has an important role in women's depression. It has been studied that women tend to have more depressive episodes when going through a period of hormonal change, such as puberty, pregnancy and menopause.
- The attitude of gaining approval and closeness with interpersonal relationships can intensify reactions to interpersonal stressors, and it is more common in women.
- Social roles promote emotion-focused coping among women, which may then extend the duration of sad moods after major stressors.

Economic factors

Low socioeconomic status, particularly when assessed by indices of the material standard of living, is consistently associated with a higher prevalence of depression. This factor is important in the onset of MDD and in its maintenance. It seems that people suffering from financial strain are at higher risk of depression, as well as those becoming poor or unemployed. The prevalence of depression is double among those who are unemployed, 7,9%; compared to those employed, 3,1%. (5,13,14).

Having other mental health illnesses

Substance use, anxiety, and borderline personality disorders are among the most common. MDD that develops against the background of another disorder often follow a more refractory course, and with correct treatment of the underlying disorder may improve clinical symptomatology. (2)

Chronic diseases

Chronic illnesses are comorbid with mood disorders, especially with MDD. Not only they predispose to suffer this affection but also can elongate the episodes and consequently, they can cause a higher rate of persistent depression.

For example, there is a relationship between depression and biological indicators of systematic inflammation such as C- reactive protein (CRP), interleukin-6 (IL-6) and tumoral necrosis factor α (TNF α). (15,16). Also, endocrine abnormalities are being studied, especially hypothyroidism and Cushing's syndrome. It is believed that alterations in the Hypothalamic-Pituitary-Thyroid (HPT) and the Hypothalamic-Pituitary-Adrenal (HPA) axis can lead to depression. Some studies suggest adrenal corticoids may interfere differently in stress responses in women which makes them more likely to suffer from MDD (12,17). Coronary disease is also a known risk factor for an MDD episode, especially some months after the event. Other illnesses that are related to depression are diabetes, high blood pressure, asthma and arthritis, among others (18,19).

Neurobiology of depression

Neurotransmitters

There are several neurotransmitters (NT) related to MDD pathophysiology. Mood changes are due to alterations in the concentration of monoamines: serotonin or 5-hydroxytryptamine (5-HT) and noradrenaline (NA). 5-HT regulates multiple physiologic functions: appetite, sexual activity, pain sensitivity, body temperature, sleep and mood. Noradrenaline mediates interpersonal attitudes and moral judgement (20). Dysfunction of both 5-HT and NA brain circuits is related to depression. It is important to understand the role of these NT in the neurobiology of depression since the pharmacological treatment is based mainly in the reuptake of this NT.

Other NT have been related to mood disorders such as dopamine, an increase in the cholinergic-adrenergic quotient, and glutamate which apparently has an important role in the persistence of depressive symptomatology. Although glutamate is the main excitatory NT, having an excess of it can lead to neurotoxicity (21). Dopamine plays a major role in the sensitivity of the reward system in the brain, which is believed to guide pleasure, motivation, and energy in the context of opportunities to obtain a reward. In MDD episodes, dopamine usually is low (3,22).

Hypothalamic-Pituitary-Adrenal (HPA) axis

MDD is accompanied by dysregulation of the cortisol hormonal answer to stress, affecting the HPA axis. This axis controls human answer to danger among other things. It responds with an increase in cortisol release and activation of the sympathetic autonomous system (SAS) that prepares our body to fight or flight mode. A situation of chronic stress produces a chronic elevation of cortisol levels, which causes physiological exhaustion that leads to anxiety, low mood, lack of concentration, fatigue, pain and inhibition. In patients with MDD, there is an abnormal function of the HPA axis with a pathologic and sustained elevation of cortisol.

Cortisol does its neurotoxic effects by reducing Brain-Derived Neurotrophic Factor (BDNF) levels, especially during stressful events. The BDNF is a neurotrophic protein essential for neuronal plasticity and axon growing. Some brain regions such as hippocampus have a great number of cortisol receptors, which makes them very sensitive to its changes.

This HPA dysfunction is related to the monoamine system because 5-HT causes an important function in the plasmatic release of cortisol and in maintaining brain neurotrophic function.

Antidepressant drugs can increase monoamines level in neuronal synapse and are capable to reverse HPA anomalies and regulate BDNF concentrations and that's when remission of depression occurs.

There are three main categories of peripheral hormone-type factors, for which genetic variants are associated with major depressive disorder, and they are implicated in the pathophysiology of the illness:

1. Neurotrophic factors and other growth factors, including BDNF, vascular endothelial growth factor (VEGF) and insulin-like growth factor-1 (IGF-1).
2. Proinflammatory cytokines including interleukin-1β, interleukin-6, and tumour necrosis factor-α.
3. Impaired regulation of the HPA axis.

The three of them can reverse or attenuate during antidepressant treatment. (4)

Brain structures

Neural systems that are important to understand major depressive disorder include those that support emotion processing, reward-seeking, and regulate emotion, all of which are dysfunctional in the disorder. These systems include:

- Subcortical systems involved in emotion and reward processing (amygdala, ventral striatum).
- Medial prefrontal and anterior cingulate cortical regions involved in processing emotion and automatic or implicit regulation of emotion.
- Lateral prefrontal cortical systems (e.g. ventrolateral prefrontal cortex and dorsolateral prefrontal cortex) involved in cognitive control and voluntary or effortful regulation of emotion.

These systems are integrated as a medial prefrontal limbic network, including the amygdala, anterior cingulate cortex and medial prefrontal cortex that is modulated by serotonin neurotransmission, and a reward network centred on ventral striatum and interconnected orbitofrontal and medial prefrontal cortices that is modulated by dopamine. It has been studied that during MDD there is an

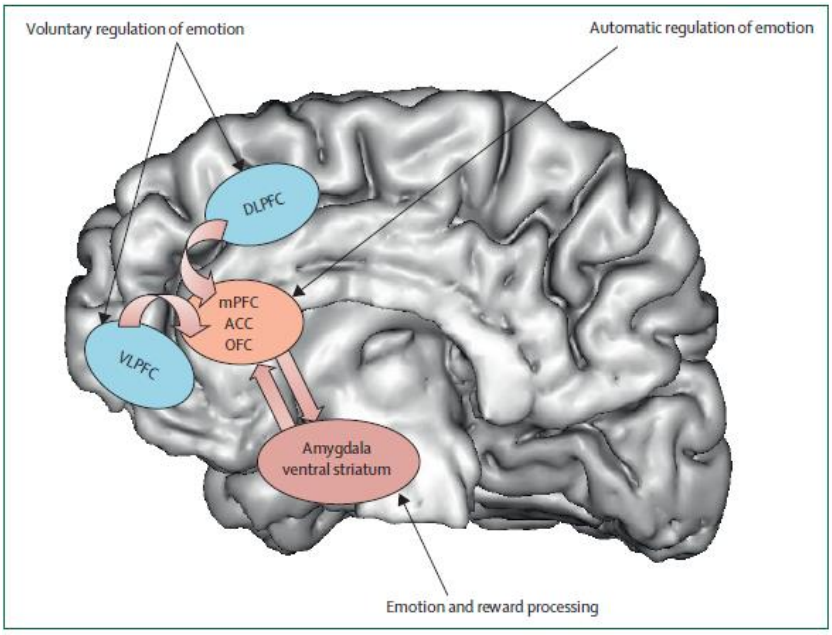

Figure 1. Neural systems of relevance to major depressive disorder. Extrated from (4). *DLPFC= dorsolateral prefrontal cortex. mPFC= medial prefrontal cortex. ACC= anterior cingulate cortex. OFC= orbitofrontal cortex. VLPFC= ventrolateral prefrontal cortex.*

abnormal increase of amygdala, ventral striatal and medial prefrontal cortex activity, mostly to negative emotional stimuli, such as fearful faces. Also, there is a reduced ventral striatal activity to positive emotional stimuli. (19, 20)

Symptomatology and diagnostic criteria

Depression is a disease that is related to sadness but goes far beyond it. In depressive disorder, sadness is not necessarily related to an external cause and, if there is any precipitating factor, sadness is clearly disproportionate to it and does not remit when it dissipates. In some cases, patients may manifest a global slowdown in body movements and thinking, so that they feel almost unable to perform daily tasks. These symptoms are known as severe melancholic symptoms. Other times, the perception of reality can be altered by the depressive state, presenting delusional symptoms: individuals feel fully convinced of being ruined, of being guilty of a crime or an unforgivable sin, for example. (21,24)

MDD symptomatology is included in the DSM-5 criteria. These criteria are used to diagnose the illness. They are cited below.

Major Depressive Disorder. Diagnostic Criteria
A. **Five or more** of the following symptoms have been present during a 2-week period and represent a change from previous functioning; at least one of the symptoms is either 1 or 2. 1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g. feels sad, empty, hopeless) or observation made by others (appears tearful). 2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation). 3. Significant weight loss when not dieting or weight gain (change of more than 5% of body weight in a month) or decrease or increase in appetite nearly every day. 4. Insomnia or hypersomnia nearly every day. 5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down). 6. Fatigue or loss of energy nearly every day. 7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick). 8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others). 9. Recurrent thoughts of death (not just fear of dying) recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
C. The episode is not attributable to the physiological effects of a substance or to another medical condition.
Note: Criteria A-C represent a major depressive episode. Note: Responses to a significant loss may include the feelings of intense sadness, rumination about the loss, insomnia, poor appetite, and weight loss, may resemble a depressive episode. Although such symptoms may be understandable or considered appropriate to the loss, the presence of a major depressive episode in addition to the normal response to a significant loss should also be carefully considered.
D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.
E. There has never been a manic episode or a hypomanic episode.
Note: This exclusion does not apply if all the manic-like or hypomanic-like episodes are substance-induced or are attributable to the physiological effects of another medical condition.

Table 1. Diagnostic criteria for Major Depressive Disorder. Adaptation from (2).

Within these criteria we have to evaluate different factors that can affect the development, course and severity of depression, including(25):

- The duration, number and intensity of symptoms and the comorbidity of these
- Psychosocial evaluation (social support and interpersonal relationships).
- Degree of dysfunction and/or associated disability
- Pre-treatment response
- Suicide risk: This aspect is key due to the great association between the major depressive episode and suicidal behaviour. People with depression have a suicide risk 20 times higher than the general population.
  The suicide risk assessment should consider:
  - Presence of previous suicide attempts
  - Substance abuse
  - Specific symptoms such as hopelessness, anxiety, agitation and suicidal ideation
  - Other risk factors such as comorbidity, chronicity, pain or disability, family history of suicide, social factors and a history of suicide in the environment.

Approximately, an MDD episode lasts from 6-8 months but can last up to 15-18 months.

To assess the severity of an MDD episode, the Hamilton Depression Rating Scale (HDRS) is a commonly used instrument. Although the HDRS form lists 21 items, the scoring is based on the first 17. It generally takes 15-20 minutes to complete the interview and score the results. Eight items are scored on a 5-point scale, ranging from 0 = not present to 4 = severe. Nine are scored from 0-2 (see Annex 1). Once the scale is completed, patients can be staged in different categories depending on the final score obtained (26,27). These stages are:

- Absence or remission of depression: below 7
- Light or minor depression: 8-13
- Moderate depression: 14-18
- Severe depression: 19-22
- Very Severe depression: scores above 23.

Major Depressive Disorder Treatment

Psychotherapeutic treatment

Psychotherapy can be defined as a comprehensive, deliberate and planned therapeutic treatment or intervention, based on a broad and specific training in behavioural alterations, diseases or broader needs for personal development, related to psychosocial and psychosomatic causes and factors.

In recent decades research in the field of psychotherapy has been increasing and in parallel, clinical practice guidelines on depression recommend its use, especially those developed specifically for depressive disorder (28).

Within these therapies, one of the most used is Cognitive Behavioural Therapy (CBT). It is the most studied and the most effective modality for this disorder. The intervention consists of the modification of dysfunctional behaviours and negative thoughts related to depression. The therapist adopts an educational style, seeking patient collaboration so that he can learn to recognize his negative thinking patterns and reassess him. The duration of the therapy usually ranges from 15-20 sessions of 50 minutes and approximately weekly and it is assumed that the duration of therapy can be prolonged in case of greater severity or associated comorbidity.

Group CBT is also used in patients with major depression. This is highly structured and has a strong psycho-educational component. It is usually organized in 12 sessions of two hours over 8 weeks(25).

There is evidence that many types of psychotherapeutic interventions have a moderate to large effect when compared to control conditions(29). For this treatment to be effective it is important to ensure a treatment fidelity of the patient(28,30).

Antidepressant drugs

Antidepressants are drugs aimed at improving symptoms associated with depression and there are different pharmacological groups classified according to their chemical structure and mechanism of action. Although there is a latency time at the beginning of its therapeutic effects that can be 2 to 4 weeks, the efficacy of the MDD drug treatment in adults is well documented, although there is controversy over which antidepressant is most suitable. In general, the more severe the symptoms of depression, the more benefit the drug treatment produces.

The classification of the different antidepressants marketed in Spain can be found in the following table.

Group		Mechanism of action	Main Side Effects of the group	Drugs
Classic antidepressants	MAO selective inhibitors	They decrease the metabolism of norepinephrine, dopamine and serotonin, which increase their extracellular concentrations by selectively inhibiting MAO	Sleeping disorders, dizziness, headache, dry mouth, nausea, paraesthesia, rash, agitation. (31)	**Moclobemide**
	Heterocyclics	Inhibit norepinephrine and serotonin reuptake.	Restlessness, dizziness, tremor, drowsiness, myoclonus, paraesthesia, muscle weakness, urination disorders, hot flashes, aggressiveness, dysarthria, accommodation disorders (32–35)	**Tricyclic: Imipramine, Clomipramine, Trimipramine Amitriptyline, Nortriptyline, Doxepin.** **Heterocyclics: Amoxapine, Mianserine, Maprotiline**
New Generation	SSRI	They inhibit the 5-HT reuptake receptor and potentiate serotonin effects.	Decreased appetite, hypersensitivity, hypothyroidism, nightmares, anxiety, libido decrease, increased sweating, diarrhoea, headache, arthralgia (36–39)	**Citalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Escitalopram**

New Generation	DNRI	It selectively inhibits the neuronal reuptake of catecholamines (norepinephrine and dopamine) with minimal effect on serotonin. It does not inhibit MAO.	Insomnia, anxiety, headache, hypertension, tinnitus, vision disturbances, tremor, changes in sense of taste, hives (hypersensitivity reaction)	**Bupropion**(40)
	SRNI	Enhancement of neurotransmitter activity in the central nervous system: inhibits the reuptake of serotonin and norepinephrine.	Dizziness, headache, decreased appetite, nausea, dry mouth, sweating, confused states, decreased libido, nervousness, drowsiness, paraesthesia, hot flushes, dysuria, pollakiuria, serotonergic syndrome. (41–43)	**Venlafaxine, Desvenlafaxine, Duloxetine**
	SARI	It is a sedative antidepressant with a mechanism of dual serotonergic action: in presynaptic it is a serotonin reuptake inhibitor and in post-synapse an antagonist of 5-HT2a receptors. It is used in sleep disorders because of its sedative effect.	tiredness, weakness, dizziness, pale skin, confusion, restlessness, sweating, tremor, heart rhythm disturbances. (44)	**Trazodone**
	NaSSA	It augments noradrenergic and serotonergic neurotransmission centrally. Serotonergic is due to blockade of 5-HT2 receptors.	Increased hunger and weight, sedation, drowsiness, headache, hypotension, lethargy, dizziness, tremor, orthostatic hypotension, constipation(45)	**Mirtazapine**
	ARNI	It is a selective and potent inhibitor of norepinephrine reuptake, does not affect dopamine and has a very weak effect on serotonin.	Insomnia, dizziness, dry mouth, constipation, nausea, hyperhidrosis, agitation, anxiety, dysgeusia, accommodation disorder, tachycardia, palpitations.(46)	**Reboxetine**

	Melatoninergic agonist	Melatoninergic agonist and a 5-HT antagonist. increases the release of dopamine and norepinephrine, especially the prefrontal cortex.	Headache, insomnia, drowsiness, dizziness, anxiety, increased liver enzymes, vomiting, weight gain. (47)	**Agomelatine**

Table 2. Antidepressants and its mechanism of action. Based on (24)

Electroconvulsive Therapy

Electroconvulsive Therapy (ECT) for the treatment of depression and other psychiatric disorders involves the application of electricity to the scalp in order to induce seizure activity. ECT increases cortical GABA concentrations and enhances serotonergic function. It also affects the HPA axis, normalizing the result of the dexamethasone suppression test. (48)

ECT has been reported to result in a prompt improvement in symptoms of depression in most patients treated. It is especially effective in the psychotic subtype of depression, with delusional or suicidal ideas, having a better remission rate than non-psychotic subtypes(49,50). Elder people have a higher rate of treatment-resistant depression and psychotic depression. Depressed elderly patients are treated with acute ECT more often than younger adults for several reasons: First, they often have poor tolerance to pharmacotherapy in the presence of comorbid physical problems, such as cardiovascular disease, and the related frequent use of multiple drugs. Second, severe depression leads more often to life-threatening conditions in frail elderly patients requiring fast treatment response. (51)

The decision to use ECT depends on several factors, including the severity and chronicity of the patient's depression, the likelihood that alternative treatments would be effective, the patient's preference, and a weighing of the risk and benefits. It is typically reserved for use after several medication trials, and after all the other therapies have failed, because of its relatively higher risk of side effects.

Some factors have been associated with reduced efficacy, this happens in a prolonged episode, lack of response to medication, and coexisting psychiatric diagnoses such as a personality disorder. People with an unstable cardiac disease such as ischemia or arrhythmias, cerebrovascular diseases such as recent cerebral haemorrhage or stroke, or increased intracranial pressure may be at increased risk for complications. ECT can be used safely in elderly patients and in persons with cardiac pacemakers or implantable cardioverter-defibrillators. ECT can also be safely used during pregnancy, with proper precautions and in consultation with an obstetrician (52,53).

ECT is performed while the patient is under general anaesthesia; therefore, all patients must undergo a full evaluation by an anaesthesiologist, including an assessment of the risk associated with anaesthesia, before the start of ECT(54). Patients have mask ventilation with supplemental oxygen. Neuromuscular blocking agents are administered to prevent skeletal muscle contraction and possible injury during tonic-clonic activity. The neuromuscular blocker more used is suxamethonium. (55) The electroencephalogram is monitored during ECT to confirm seizure activity and to document seizure duration. In addition, evidence of seizure motor activity is monitored.

Common electrode positions include bilateral, right unilateral, and bifrontal. Right unilateral and bifrontal placement may be selected to reduce the burden of side effects, whereas bilateral

placement may be selected if the right unilateral or bifrontal positions are unlikely to be effective. The ECT is measured in millicoulombs of charge delivered, the dose administered must be enough to induce seizure activity. Some medications (e.g., lithium, theophylline, and medications with anticonvulsant action) can interact with ECT, and they should be tapered or discontinued before ECT is initiated. Antidepressant drugs are often discontinued before the initiation of ECT.

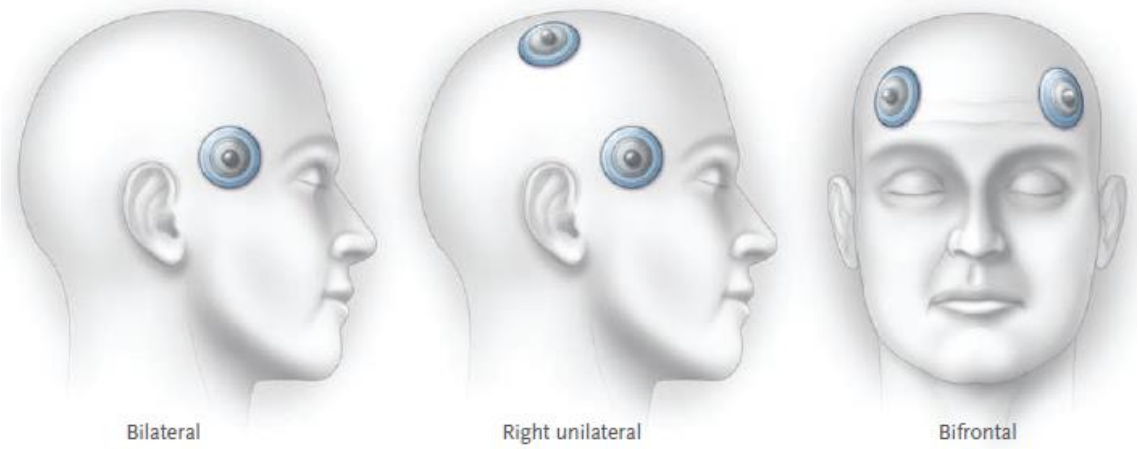

Figure 2. Standard Electrode Placements for ECT. Extracted from (46)

In the short term, ECT causes anterograde amnesia that typically resolves soon after ECT is completed. Postictal disorientation or even delirium may occur, but these conditions also tend to resolve within 1 hour after the procedure. Prolonged seizures during ECT are rare.

Retrograde amnesia is the most common persistent adverse effect of ECT. Shortly after ECT, most patients have gaps in the memory of events that occurred before treatment, and retrograde amnesia may extend back several months or years. Pre-existing cognitive impairment is predictive of amnesia after ECT, and amnesia is more likely in older adults. Other side effects of ECT include headache, muscle aches, nausea, and fatigue. (56)

All these three therapies (psychotherapy, pharmacological therapy and ECT) can be combined, usually, psychotherapy is combined with drugs, and ECT is used if these two fails to improve the clinical situation of the patient.

VENLAFAXINE

Pharmacodynamics

Venlafaxine is a dual antidepressant drug. The mechanism of action of Venlafaxine, and its main active metabolite, O-desmethylvenlafaxine (ODV) is a 5-HT and NA reuptake inhibitor. It also has reuptake effects of dopamine. It has no MAO inhibitory activity, and it also has virtually no affinity for benzodiazepine or opioid sensitive receptors (57).

The efficacy of venlafaxine for the major depressive episode has been demonstrated, both in short-term studies and in 26-week studies. The effectiveness of the drug in preventing recurrent depressive episodes and relapse has also been seen, especially when the patients continue their treatment during 6 months after the remission of the episode (58,59). A multinational study demonstrate that Venlafaxine is a more cost-effective treatment of MDD compared to the SSRIs and tricyclic antidepressants, this fact makes it a drug widely used in the clinical practice of our country, being in some areas the second antidepressant more used after the SSRIs (60,61).

Pharmacokinetics

Venlafaxine is extensively metabolized, mainly to the active metabolite ODV, which also has an antidepressant effect. The mean plasma half-lives +/- their standard deviation of Venlafaxine and ODV are 5 +/- 2 hours and 11 +/- 2 hours, respectively. The steady-state concentrations of venlafaxine and ODV are reached within 3 days of treatment with multiple oral doses. Venlafaxine and ODV show linear in the dose range of 75 mg to 450 mg/day. (41,42,62)

Absorption

Venlafaxine is well absorbed and extensively metabolized in the liver. ODV is the only major active metabolite. Based on mass balance studies, at least 92% of a single oral dose of venlafaxine is absorbed. The absolute bioavailability of venlafaxine is about 45%. Food does not affect the bioavailability of venlafaxine and ODV(41,62).

Distribution

Venlafaxine and ODV at therapeutic concentrations minimally bind to human plasma proteins. The volume of distribution for venlafaxine at steady-state is 4.4 +/- 1.6 l / kg after intravenous administration.

Metabolism

Venlafaxine undergoes extensive presystemic metabolism in the liver, primarily to ODV, but also to N-desmethylvenlafaxine, N,O-didesmethylvenlafaxine, and other minor metabolites.

The formation of ODV is catalysed by CYP2D6, an enzyme of the cytochrome P450 mixed-function oxidase system which is mainly expressed in the liver; this has been confirmed in a clinical study showing that patients with low CYP2D6 levels (poor metabolizers) had increased levels of venlafaxine and reduced levels of ODV compared to people with normal CYP2D6 (extensive metabolizers).

Although depending on the expression of CYP2D6 there can be different blood levels of Venlafaxine or ODV (being Venlafaxine levels higher and ODV levels lower in poor metabolizers and being Venlafaxine levels lower and ODV levels higher in extensive metabolizers) the differences between CYP2D6 poor and extensive metabolizers are not expected to be clinically important because venlafaxine and ODV both have an antidepressant effect, meaning they are pharmacologically approximately equiactive and equipotent.

The drug is metabolized to N-desmethylvenlafaxine a less active metabolite, mainly by CYP3A4. ODV is also metabolized to a less active metabolite, N, O-didesmethylvenlafaxine, by CYP3A4. (63)

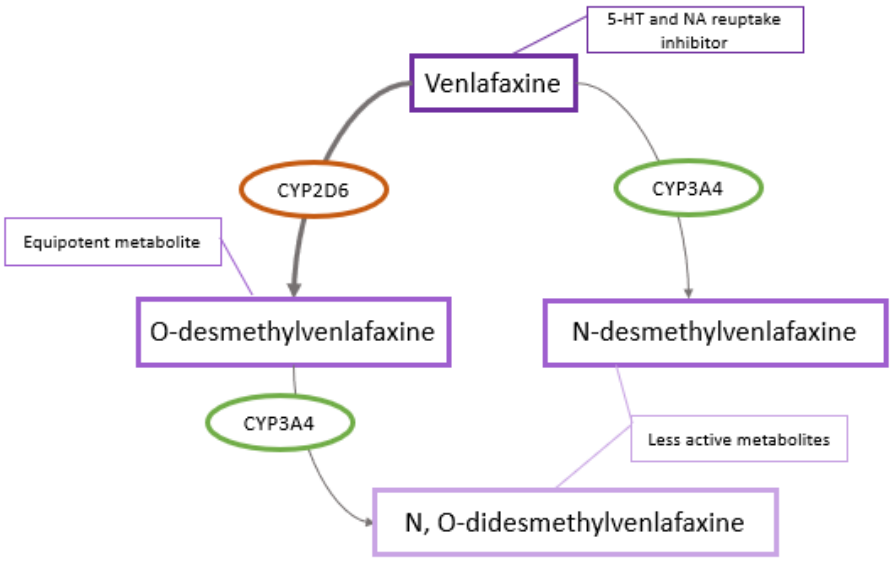

Figure 3. Venlafaxine metabolism and its enzymes. Based on (59)

CYP3A4

Cytochrome P-450 is a family of hemoprotein enzymes and is the main responsible for the oxidative metabolism of xenobiotics.(64) Of the P450 enzymes, the CYP3A subfamily is the most abundantly expressed, comprising approximately 30% of hepatic P450 and 70% of intestinal P450, and is involved in the metabolism of approximately 50% of drugs currently on the market. Four CYP3A isoforms have been identified in humans: CYP3A4, CYP3A5, CYP3A7 and CYP3A43. Of these, CYP3A4 has the greatest importance, as it exhibits the highest expression. It is highly expressed in the liver. (65)

CYP3A4 gen has a female-dominant expression, as determined by mRNA and protein levels compared to male samples, as well as the activities for more than ten clinically employed drugs (65–67). This has been studied in healthy people using CYP3A4-substrate drugs such as diazepam, seeing a higher clearance in women which persists even after adjustments for physiological factors, suggesting that the sex difference in pharmacokinetics of CYP3A4 is clinically significant (68). Women appear to have a two-fold higher CYP3A4 activity in their primary hepatocytes compared to men. Activity of CYP3A4 measured by in vivo elimination is higher in women than in men (69,70). It is speculated that this difference is due to sex hormones, and it has also been proven that the difference is bigger during pregnancy. Female sex hormones can increase the activity of CYP3A4. It is expressed at a higher protein and mRNA level in women than in men. This lead to sex differences in drug metabolism and pharmacokinetics.(66)

CYP3A4 is an enzyme that metabolises Venlafaxine to a much less effective metabolite, N-desmethylvenlafaxine. It has been showed that women have a higher concentration of N-desmethylvenlafaxine and higher ratio of N-desmethylvenlafaxine versus venlafaxine than men. (69,71) This could imply different clinical effectiveness of the drug and that is what this study is based on.

Excretion

Venlafaxine and its metabolites are excreted mainly by the kidneys. Approximately 90% of the drug is excreted in urine at 48 hours, mainly as conjugated ODV (26%) and unconjugated (27%), and other minor metabolites (27%). As intact Venlafaxine only 5% is excreted.

Situations that require dose adjustment(58,62)

- **Liver disease:** venlafaxine is mainly metabolized in the liver, so any hepatic disease can affect the dosage of this drug. Venlafaxine elimination half-life can increase in cirrhotic subjects. (see "Metabolism" section ahead).
- **Renal disease:** Venlafaxine elimination half-life can be prolonged, and clearance can be reduced in renally impaired patients, since Venlafaxine and its metabolites are excreted by the kidney. (see "excretion" section ahead).
- **Hypertension:** Venlafaxine treatment is associated with sustained hypertension and can elevate either systolic or diastolic blood pressure or both.
- **Drugs that inhibit Cytochrome P450 Isoenzymes:** Concomitant use of CYP3A4 inhibitors and venlafaxine may increase levels of Venlafaxine and ODV, so caution is advised if a patient's therapy includes a CYP3A4 inhibitor and Venlafaxine concomitantly.

Adverse effects

The most common adverse reactions reported are nausea, dry mouth, headache and sweating (including night sweats).

The most outstanding adverse effects compared to placebo treatment are: hypertension, nausea, weight loss, dizziness, drowsiness, dry mouth, nervousness, abnormal dreams, decreased libido, tremor, yawning, sweating, blurred vision, difficulty in accommodation. A severe adverse effect commonly seen in Venlafaxine is a QT interval prolongation, this makes it dangerous in case of overdose. So we have to be cautious when giving Venlafaxine in patients with autolytic behaviour, and evaluate this risk during the clinical interview.

JUSTIFICATION

Depression is a very common and invalidating mental disorder. In Catalonia, 24,40% of visits to an AMHC is due to depression (7). The prevalence of this is more frequent in women than in men, this being doubled in women. In Spain prevalence is 6,7%, being for women twice as much as for men: 9,2% against 4% (6). This prevalence has been associated with various causes: it has been shown that women suffer more depression in times of hormonal change: puberty, pregnancy and menopause. It has also been seen that psychosocial factors are of great importance in the prevalence of depression. These are the social roles of women as a caregiver and associated with femininity, differences in high job positions an unequal status and a higher risk of sexual abuse (3,11,12). These differences in the prevalence were the main motivation to do this study.

In these last twenty years, due to the pressure of WHO and Spanish legislation(72), it is mandatory that any clinical study that presents statistics on medications or diseases, presents its results analysed by sex. This initiative arose from the previous lack of participation of women in clinical trials. With this separation, it has been seen that apart from hormonal and psychosocial differences, there is a wide variety of responses to the treatment of certain drugs due to metabolic differences between sexes, and this differences also affect antidepressant drugs(67,69,70,74). One of the differences is the mentioned CYP3A4 enzyme, and its overexpression in women (65,66). This evidence is what gave us the idea to carry out this study, to understand if this difference in the enzyme could have any effect in clinical practice and in the treatment of depression on women, taking into account that its prevalence is higher than in men.

With the differences in the prevalence of the major depressive disorder and the metabolic differences cited, we might wonder if the treatment of depression is different depending on sex. Nowadays there is no treatment adjustment based on this parameter, and maybe we could treat better each individual if these sex differences are considered. Although some bibliography suggests that it is not necessary to adjust by sex(62,74), there are different studies that show that there are differences in metabolism and have shown it with differences in the plasma concentration of the drug and its metabolites(68,69,71,75).

In order to see if these differences could have an effect in the usual clinical practice on depression management, this observational study is designed to see if there are differences in the clinical improvement of depression in patients taking Venlafaxine, an antidepressant of new generation widely used in routine clinical practice, depending on the sex and metabolism of the drug.

HYPOTHESIS

Main hypothesis

The patient's sex determines a difference in the clinical improvement of MDD in patients treated with Venlafaxine 225 mg, due to the differences in drug metabolism and pharmacokinetics that exist between men and women, in this case, the difference in the expression of CYP3A4 which is overexpressed in women.

Secondary hypothesis

- There are different concentrations of N-desmethylvenlafaxine according to the patient's sex.
- Different concentrations of the metabolite N-desmethylvenlafaxine are related to a different clinical improvement.
- There is a difference in the effectivity of the Venlafaxine depending on which group of severity the patient is, according to the Hamilton Depression Rating Scale (HDRS), these groups are absence or remission, light or minor depression, moderate depression, severe depression, very severe depression.

OBJECTIVES

Main objective

The main objective of this study is to assess if the patient's sex influences the clinical improvement of depression in patients treated with Venlafaxine, and therefore if there is a relationship between the patient's sex and the clinical improvement.

Secondary objectives

- To analyse if the different concentrations of the metabolite N-desmethylvenlafaxine cause a variation in clinical improvement.
- To see the efficacy of Venlafaxine in our population of Study depending on HDRS group.
- To estimate the adherence to treatment with Venlafaxine based on sex.

METHODOLOGY

STUDY DESIGN

The study is designed as a multicentre prospective observational cohort study that will be carried out in all the Adult Mental Health Centres (AMHC) of Girona province. Centres participating are:

- Gironès i Pla de l'Estany AMHC (Girona)
- Baix Empordà AMHC (Platja d'Aro)
- Alt Empordà AMHC (Figueres)
- Garrotxa AMHC (Olot)
- Ripollès AMHC (Ripoll)
- Selva marítima AMHC (Blanes)
- Selva interior AMHC (Santa Coloma de Farners)

POPULATION OF INTEREST

The population of interest in our study will be MDD patients of Girona province treated with Venlafaxine 225mg. The participant centres will inform about the number of patients with MDD treated with Venlafaxine who have started treatment in the last month, and that meet inclusion and exclusion criteria. This population will be divided into two groups as equal as possible but divided into men and women.

Inclusion and exclusion criteria

The inclusion and exclusion criteria for this study are:

Inclusion criteria	Exclusion criteria
• Patients aged between 30-50 years at the beginning of the study. • The treatment must have been started a maximum of two months before the first review • Informed consent signature.	• Being on a decompensation of any other mental illnesses during the length of the study • Receiving other antidepressant drugs • Receiving psychotherapy or other non-pharmacological therapies for MDD. • Liver and kidney failure • Being or getting pregnant • Having a suicide attempt • Having a hospitalization with an impact on the patient's quality of life. • Impossibility for patient's follow-up • Not speaking Catalan, Spanish and English

Table 3. Inclusion and Exclusion criteria

Withdrawal criteria

- The treatment is not effective for the patient's MDD and needs other therapies.
- The treatment is finished before the 12 months of the study.
- Not participating in the study follow up.

SAMPLING

We will use a convenience sampling method, asking the mental health professionals of each centre in Girona province to give us a list of all the patients with MDD treated with Venlafaxine 225mg.

SAMPLE SIZE

Accepting an alpha risk of 0,05 and a beta risk of 0,2 in a two-sided test, 286 subjects are necessary for the first group and 286 in the second to find as statistically significant a proportion difference, expected to be of 0,25 in the women group, and 0,14 in the men group. It has been anticipated a drop-out rate of 30% due to abandonment of the study, treatment failures and other withdrawal criteria. All these measures have been done with the GRANMO (sample size and power calculator).

VARIABLES

Dependent

The main dependent variable will be the clinical improvement of MDD. It will be measured as a numerical discrete quantitative variable with the HDRS (see Annex 1).

In this study, a clinical improvement will be defined as a reduction of 5 points in the final score, since each stage consists of four points, so the reduction of at least 5 points guarantees a change of stage and a clinical improvement.

It has been demonstrated by some studies that women have overexpression of CYP3A4, one of the main enzymes that metabolize Venlafaxine. This enzyme activity will be measured with a blood concentration of N-desmethylvenlafaxine. To assess the relationship between clinical improvement and CYP3A4 metabolism, a blood sample will be taken from the patient, and we will use it to measure the concentration on N-desmethylvenlafaxine.

Independent

In our study, the independent variable is, first, the patient sex, due to its effects in the expression of CYP3A4, an enzyme important in the metabolism of Venlafaxine. It is a dichotomic qualitative variable.

The second independent variable is the depression group of the HDRS. One of my hypotheses is that there is a difference in the clinical improvement depending on the HDRS group.

This rating scale has five severity groups, depending on the final score obtained:

- Absence or remission of depression: below 7
- Light or minor depression: 8-13
- Moderate depression: 14-18
- Severe depression: 19-22
- Very Severe depression: scores above 23.

I will evaluate if these two variables are independent predictors of the dependent variables.

Covariates

- **Antecedent of a depressive episode**. It is supposed to be a confounding factor for MDD because it can mean the patient is having a recurrent MDD. It will be collected as a dichotomous qualitative variable: presence or absence of depressive episode on the past.
- **Socioeconomic factors:** Low income, unemployment and non-college education are factors of low socioeconomic status, and they may be confounding factors for MDD, because they can be accompanied by feelings of guilt or other emotions that can lead or enlarge the episode. The statistician will collect this data from the city census to stratify the results. It is a dichotomous qualitative variable: presence or absence of low socioeconomic status.
- **Substance abuse**: Addiction to any kind of drugs could be a confounding factor for MDD. It is related to a higher abandonment rate, and the episode can be more difficult to treat. It is a dichotomous qualitative variable: abuse of any drug (tetrahydrocannabinol, cocaine, alcohol, between others) or absence of drugs-abuse.
- **Antecedent of eating disorders:** It is supposed to be a confounding factor for MDD. It Is related to a higher abandonment rate, and the episode can be more difficult to treat. It is a dichotomous qualitative variable: presence or absence of any eating disorder (anorexia nervosa or bulimia).
- **Sleeping disturbances**: It may be a confounding factor for MDD. Sleeping has an important role in the limbic nervous system, and a lack of sleep can lead to a more complicated and resistant MDD. It will be measured with the Epworth Sleepiness Scale (ESS) (see annexe 2). It is an 8-item questionnaire that assesses subjective daytime sleepiness. The ESS assesses the likelihood of dozing in different common situations using a 4-point Likert response format (scored from 0 to 3 with higher scores indicate more severe sleepiness). Item responses are summed to obtain a total score ranging from 0 to 24, with a score greater than 10 indicating excessive daytime sleepiness. It will be measured as a dichotomous qualitative variable: a score greater than 10 defines a sleep disturbance, and lower than 10 means not having one.
- **Having illnesses with chronic systemic inflammation**: It is a confounding factor due to its comorbidity. It is a dichotomous qualitative variable: presence or absence of any chronic systemic inflammation: (rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis, lupus)

VARIABLE	TYPE	CATEGORY OF VALUES
Independent variable		
Sex	Dichotomic qualitative	Men/ Women
Depression group of HDRS	Ordinal qualitative	-Absence or remission -Light or minor depression -Moderate depression -Severe depression -Very severe depression
Dependent variable		
Clinical improvement of MDD	Discrete quantitative	Numerical
Blood levels of N-desmehtylvenlafaxine	Continuous quantitative	Numerical
Covariates		
Antecedent of a depressive disorder	Dichotomic qualitative	Yes/No
Socioeconomic factors	Dichotomic qualitative	Yes/No
Substance abuse	Dichotomic qualitative	Yes/No
Antecedent of eating disorders	Dichotomic qualitative	Yes/No
Sleeping disturbances	Dichotomic qualitative	Yes/No
Having illnesses with chronic systemic inflammation	Dichotomic qualitative	Yes/No

Table 4. Variables of the Study

DATA COLLECTION

Once we have the sample, will cite the patients to the AMHC to perform an interview. If the patient already had an appointment at the AMHC in the month in which the study begins, the appointment that the patient initially had will be left.

To perform this study, the information will be recorded directly from the patient. At the first follow up interview, once the psychiatrist is sure that patients are aware of having and MDD episode, and that they accept being treated with Venlafaxine and they tolerate the drug, we will proceed to explain the study to them. We will record personal patient data to see if they meet the inclusion and none of the exclusion criteria. If they meet these criteria, the patient will be given an explanatory sheet (see ANNEX 3) will all the information explained before and the informed consent (see ANNEX 4) in which they must sign that they have been well informed about the study and their agreement to participate in it.

Once the informed consent is signed, we will perform an interview based on the HDRS and we will assign the corresponding numerical value to the scale, so in the next follow up meetings of the study we can observe if there is any clinical improvement. The result of the HDRS will be noted in the Data Collection Sheet (see Annex 5) and will be uploaded to the SAP server, used in the AMHCs.

Subsequently, the patient will be transferred to the nursing sector where a blood draw will be performed. This blood sample will be sent from every AMHC to the laboratory, where they will measure the concentration of Venlafaxine and N-desmethylvenlafaxine. This will be compared with the patient's follow-up measurements. The blood samples obtained will be sent to the laboratory of Parc Hospitalari Martí i Julià, where the corresponding measurement of Venlafaxine and the metabolite of N-desmethylvenlafaxine will be carried out by an expert laboratory technician. We decided to hire a laboratory technician that will do the corresponding pharmacokinetic measurements in the Salt Hospital due to its proximity and therefore less transportation time and resources. The samples will be transported to Parc Hospitalari Martí I Julià by road vehicles. This must guarantee quality conditions. All transport of samples for clinical diagnosis are considered special shipping, which must maintain specific temperature and humidity conditions throughout the transportation and distribution chain. They must also ensure packaging that can withstand the usual shocks and loads of transport and transhipment between vehicles or containers.

Every N-desmethylvenlafaxine blood levels of each patient obtained in the laboratory will be noted in the Data Collection Sheet (see Annex 5) by the technician and uploaded to the SAP server.

After the first interview and blood draw, the patient will be cited every three months until they reach their first year of follow-up. In this follow-up consultations, the patient will have to answer the HDRS questionnaire and punctuation will be given each time, to assess if there is any clinical improvement. At the same follow-up visit, a new blood draw will be performed to be analysed in the laboratory and measure the drug metabolite.

All the measurements will be collected to analyse the results posteriorly so that every three months the Data Collection Sheet is updated to be posteriorly analysed correctly.

STATISTICAL ANALYSIS

DESCRIPTIVE ANALYSS

The dependent variables will be summarized by medians and interquartile range to analyse the HDRS, since it is a discrete quantitative variable, and by means and standard deviations to analyse N-desmethylvenlafaxine because it is a continuous quantitative variable. These summaries will be stratified by sex and depression group.

The main descriptive analyses (stratified by sex and HDRS group) will be repeated by the categories of the co-variables.

BIVARIATE INFERENCE

The association between the HDRS scale and sex and depression group will be assessed by means of the Mann-Whitney's test.

The association between the N-desmethylvenlafaxine and sex and depression group will be assessed using Student-t-test.

These analyses will be stratified by the co-variables.

MULTIVARIATE ANALYSIS

We will use multivariate analyses to assess the modification of sex and depression group on the dependent variables.

In the case of the HDRS we will estimate a logistic regression, where the dependent variable will be a clinical improvement (5 points or more), and the independent variables sex and HDRS group, as well as the interaction between sex and depression group, controlling for all the covariates.

In the case of the N-desmthylvenlafaxine we will estimate a linear regression, where the independent variables sex and depression group, as well as the interaction between sex and depression group, controlling for all the covariates.

We are interested in the estimators of the coefficients of sex, depression group and the interaction. When these are statistically significant, sex, depression group or both will be effect modifiers of the clinical improvement due to the drug.

WORK PLAN AND CHRONOGRAM

TEAM MEMBERS

The research team will be coordinated by the responsible investigator. This team will be formed by the project manager, study coordinators, psychiatrist of all the AMHCs of Girona province and a nurse from each centre, and a laboratory technician working in the Parc Hospitalari Martí i Julià.

- **Project manager/General coordinator (GC):** Responsible for, elaboration of the protocol, overseeing the study, coordination and formation of the research team, results interpretation, writing the conclusions and results publication and dissemination.
- **Study coordinators:** Competent authorities of every AMHC will be responsible for overseeing the study.
- **Co-investigators:**

- Psychiatrist: Responsible for providing the information of the study to the patients and select them if they meet the inclusion and none of the exclusion criteria. Also, they will have to fill the HDRS depending on the clinical interview of each patient and uploading the result to the Data Collection Sheet (see Annex 5).
- Laboratory technician: Responsible for analysing the blood samples of each patient and measuring the blood levels of Venlafaxine and N-desmethylvenlafaxine, and to upload the results to the Data Collection Sheet.
- Expert statistician: Responsible for the statistical analysis of the study.

WORK PLAN

The study is expected to last around 2 years. All the activities included in this study and carried out during this period will be organized in 5 stages.

Stage 1 – Preparation (December 2019- February 2020)

Time spent on performing the protocol. It took 3 months from December 2019 to February 2020. It has been done for the responsible investigator.

- **Activity 1:** Operative protocol elaboration.
- **Activity 2:** Definition of study variables for their further obtention.
- **Activity 3:** presentation of the protocol to the Clinical Research Ethical Committee (CEIC) for their approval.
- **Activity 4:** Once it is approved, we will proceed to ask the competent authorities of the participating centres for their authorisation to perform the study

Stage 2 – Coordination (February 2020 – March 2020).

Time spent to inform all the participating centres (AMHCs and Hospital Clínic de Barcelona) about the procedures and which task every centre must do. The time needed will be a month. It will consist of 3 meetings.

- **Activity 5:** Informative meetings with the competent authorities of AMHCs. The objective of these meetings is to inform the psychiatrist about the HDRS, and that they will have to program the visits every three months and fill the Data Collection Sheet (see

Annex 5). The main authority of every AMHC will have to upload the data collection sheet to the SAP server, with all the patient's medical records.

- **Activity 6:** Informative meetings with the laboratory doctors of Hospital Clínic de Barcelona. The objective of these meetings is to inform the laboratory doctors about the need for N-desmethylvenlafaxine measurements and how to manage them. They will have to fill the Data Collection Sheet. The main authority of the Hospital Clínic de Barcelona laboratory will have to upload the data collection sheet to the SAP server, with all the patient's medical records.
- **Activity 7:** Meeting with the investigators from both AMHCs and Hospital Clínic de Barcelona. This meeting is to coordinate the transport of the blow draws and to remind them of the need to fill the Data Collection Sheet and upload the results.

Stage 3 – Participant recruitment and data collection (March 2020 – May 2021)

This time will be used to obtain the study sample and proceed with the data collection. This will take 14 months to be done, from March 2020 to May 2021, the first two months will be to collect the sample and cite the patients, the next twelve months are the duration of the study.

- **Activity 8:** We will ask the AMHCs about all the patients between 30 and 50 years old that are diagnosed from MDD and that have been recently treated (in the last month) with Venlafaxine. In their next visit to the centre, patients will be offered to participate in the study if they fulfil the inclusion criteria and none of the exclusion criteria. We will explain all the information and they will receive the information sheet (see Annex 3). Once we confirm they understand the objective of the study and have all the necessary information, they will have to sign the informed consent (see Annex 4).
- **Activity 9:** After giving them the information, we will proceed to the clinical interview where the HDRS will be passed, and punctuation will be given. Once the interview is over, the patient will be sent to the nursery where they will have a blood draw done.
- **Activity 10:** The blood sample will be sent by road transportation to Hospital Clínic de Barcelona laboratory, where they will measure the blood concentration of Venlafaxine and N-desmethylvenlafaxine and will upload the data collection sheet to the server.
- **Activity 11:** The patient will be cited 3 months after this first interview, and we will do the same procedure mentioned in Activity 9 and 10. They will be cited every 3 months until a year has passed since the first visit, that means they will be evaluated at the 3rd month, the 6th month, the 9th month and the 12th month.

Stage 4 – Data analysis and interpretation (May 2021 – June 2021)

This time will be used to extract results and discuss them. A month is a time expected to do so.

- **Activity 12:** Once data collection is finished, the whole data will be organized. Then, a statistical analysis will be performed by a statistician.
- **Activity 13:** The statistical results obtained will be analysed and discussed by the research team.

Stage 5 – First data recompilation and analysis.

- **Activity 14:** We will begin to analyse the data from the 3rd, 6th and 9th month to start announcing to the medical community our study results. Afterwards, we will publish the final ones.

Stage 6 – Publication and dissemination of the research findings (June 2021 – November 2021)

This time will be used to share our conclusions and results with the medical community. It is expected to last 5 months.

- **Activity 15:** The obtained results after the study is finished will be edited, and an article will the redacted with all the conclusions and the appropriate structure
- **Activity 16:** Once the article is finished, we will send it to different journals for its publication.
- **Activity 16:** Dissemination of the findings. The team will attempt to display our results in conferences and courses related to mental health and depression, or in gender medicine conferences.

CHRONOGRAM

	19	2020											2021										
ACTIVITY	D	J	F	M	A	M	J	J	A	S	O	N	D	J	F	M	A	M	J	J	A	S	O	N
Stage 1 - Preparation																								
Activity 1																								
Activity 2																								
Activity 3																								
Activity 4																								
Stage 2 - Coordination																								
Activity 5																								
Activity 6																								
Activity 7																								
Stage 3 – Participant recruitment and data collection																								
Activity 8																								
Activity 9																								
Activity 10																								
Activity 11																								
Stage 4 – Data analysis and interpretation																								
Activity 12																								
Activity 13																								
Stage 5 – First data compilation and analysis																								
Activity 14																								
Stage 6 – Publication and dissemination of the research findings																								
Activity 15																								
Activity 16																								
Activity 17																								

ETHICAL CONSIDERATIONS

This study will be carried out in accordance with the four ethical principles of Beauchamp and Childress (no maleficence, beneficence, autonomy and justice) and with the requirements expressed in the Helsinki Declaration of Ethical Principles for Medical Research in Human Beings signed by the World Medical Association in 1964 and last revised in October 2013.

The study will also be submitted to the Clinical Research Ethics Commission (CEIC) of each of the participating centres. Moreover, the recommendations given by the committee will be considered to proceed with the study.

Before beginning any study procedure and for a patient to enter the study, they must have been informed correctly, have time to contemplate participation and freely read and sign the informed consent (see Annex 3 and Annex 4). Throughout the study, patients will always have their autonomy respected.

This protocol will be conducted according to the requirements expressed in the *"Orden SAS/3470/2009 de 16 de diciembre sobre EPAs observacionales, de Estudios postautorización de tipo observacional".* According to this law, the CEIC must accredit the study and ask the competent authorities of each centre for an authorization to proceed with the study. Once it is approved, the centre must be given all the study information.

Patient anonymity will be guaranteed to preserve patient confidentiality. Patient anonymity and rights will be based on the *"Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales. BOE núm.294, de 6 de diciembre de 2018".* It will also be regulated by the *"Ley 41/2002, de 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en materia de información y documentación clínica"* and *"Ley 15/2007, de 3 de julio, de Investigación biomédica".*

Patients data including names, surnames, addresses and clinical history information will remain anonymous after their introduction and processing into a database which will also be handled according to the mentioned Law and exclusively used for the development of the study. The data access will only be available for the research team. The access to this information for a third person will be allowed.

STUDY LIMITATIONS

The study population has patients treated with Venlafaxine 225 mg. This is a very restrictive treatment limitation, meaning that if the patient does not improve clinically, maybe it is due to an insufficient treatment dose or procedure.

As initially, we use a convenience sampling method, we could have a selection bias. We intend to avoid this bias using the inclusion criteria, so only the patients that fulfil these criteria and none of the exclusion criteria will be able to participate in the study. As we do not randomise the sample, we have tried to minimalize the effects of possible confounding bias by defining the plausible confounding factors described above as covariates.

Clinical improvement in HDRS may be due not only to the drug, but also to improvement in other parameters such as sleep, anxiety or appetite. Even so, this scale is still the most used for studies with antidepressants due to its great accuracy.

The second dependent variable, blood levels of N-desmethylvenlafaxine, will be measured in a blood sample that will be sent to Parc Hospitalari Martí i Julià, where a hired laboratory technician will analyse the blood draw. This increases the cost of the study due to the need of hiring a technician and the analytic procedures. It is expected that, if this study shows clinically relevant differences between sex, Venlafaxine metabolism and clinical improvement, this blood measurements would be done in Girona by their own technicians, either in Parc Hospitalari Doctor Martí i Julià laboratory or in Hospital Doctor Josep Trueta laboratory, without needing to hire one.

Even though some covariates are considered in this study, there may be more which could be confounding factors (having a stressful life event, ethnicity, among others) and they are not contemplated, because infinite variables could be considered. For this study, we have collected the most relevant ones and they will be analysed. Depression is a disorder with a multifactorial aetiology and it can have a different clinical improvement depending on different parameters, the most relevant is mentioned as covariates, but there are countless causes that can modify its course.

A prospective study like this has the added risk that some patients will be lost due to lack of compliance or loss of follow-up. Withdrawal and losses during the follow-up period could cause a selection bias. However, an abandonment rate has been estimated in the measurement of the sample, to avoid this bias.

This study is planned to be a multicentre study. Therefore, the interpretation of the results implies a certain degree of interobserver variability. For this reason, all the participant professionals of all centres will be trained about how to collect information, and they will have the HDRS with every item explained.

FEASABILITY

This prospective observational study will take place in the AMHC of Girona province. Psychiatrists and nurses participating in the study data collection are going to be paid their usual salary, and they are not going to get paid for participating in this study. The specialists that are going to be paid is the project manager, the statistical specialist and the laboratory technician that will be working in Parc Hospitalari Martí I Julià laboratory, and the transportation of the blood sample between AMHCs and the laboratory.

This study does not use a lot of material because the main dependent variable is passing the HDRS (see Annex 1) and it can be filled directly in the computer and posteriorly upload the punctuation in the SAP server, or if the psychiatrist prefers to print it, the cost will be 5 cents/page. The Information for the patient sheet and the informed consent sheet (see Annex 3 and 4) are going to be printed for the patient to read and to sign them. The cost will also be about 5 cents per page. The main expenses are due to the study of the second dependent variable, the blood levels of N-desmethylvenlafaxine.

The sample size is accurate with all the centre participating and the number of patients needed for this study realization is reasonable.

The duration of the study is adequate with the average duration of a major depressive episode, with enough time to assess whether there is the clinical improvement in the patients, as well as to evaluate inter-individual differences. The follow-up, being one year, allows not to lose too many patients since usual the follow-up of a patient with MDD can last even longer.

The means to carry out this project are available in Girona province. The main dependent variable is analysed in a clinical interview, and the blood samples will be drawn in each AMHC and analysed in Parc Hospitalari Martí i Julià. Although a laboratory technician will have to be hired to do the drug analysis, we believe that we have found the necessary means to carry out every aspect of this project.

In summary, this study has the right requirements that make its realization feasible and can be performed considering the location, the economic cost and the number of patients needed.

STUDY BUDGET

The budget of this study contains all the possible expenses that will be needed to realize it. We won't consider the expenses of the clinical practice that is normally performed in the Adult Mental Health Centres (AMHC).

PERSONNEL EXPENSES

The patients selected according to inclusion and exclusion criteria will be performed by the psychiatrist of the AMHC. This cost will not be included, because the follow-up consults are the usual clinical practice in the AMHC.

The extra personnel expenses will consist of paying a statistician that will be hired to perform the analysis of results. We have estimated approximately 30 hours of work will we needed to perform the statistical analysis. We will pay 40€ per hour so we estimate a cost of 1200€.

Another personnel expense will be the payment of the laboratory technician, which will be paid 35€ per hour. We calculate approximately 10 hours per week of work, so 40 hours per month. This laboratory work will be done 5 months according to the work plan (see Work plan and chronogram). So, the approximate cost of that will be of 7000€.

EXECUTION EXPENSES

The blood levels of Venlafaxine, according to the public prices of the "Institut Català de la Salut", a blood measurement of Venlafaxine costs 15,33€. We suppose that the measurement of N-desmethylvenlafaxine costs approximately the same, so we guess the cost of each analysis where we will measure Venlafaxine and N-desmethylvenlafaxine blood levels will be of 30,66€. So, considering that each patient (572 patients in total) will have an analysis done five times: in total will be 2860 measurements. It is also necessary to consider the possible repetition of the measurement by mistake or the need to repeat the test in some cases, we will consider 3000 measurements will be done, being the price of all the measurements about 91.980€

The articles and publications consulted for the development of this study have not entailed an additional cost.

Additional costs include the printing of the Information for the patient sheet (see annexe 3). Each page printing will cost 5 cents. At least 572 information sheets will need to be printed, and some extra sheets in case of need, so we will consider printing twice as many copies as necessary, approximately 1144 copies. The Informed consent sheet (see Annex 4) need to be printed three times as many copies as necessary because there has to be one copy for the patient, one for the doctor and we consider one more of it in case of loss and/or need of another one, so 1176 copies will be printed. In total, we'll print 2860 pages, and 0,05€ per cent, the cost will be of 143€.

PUBLICATION EXPENSES

The study will be published as a journal article. Considering the revision, the edition, the formatting and preparation of the digital data will cost approximately 3000€.

ÍTEMS	CATEGORY	COST
Personnel expenses	**Project manager**	3h x 52 weeks x 30€= 4680 €
	Laboratory technician	40h x 5 months x 35€ = 7000€
	Statistician	30h x 40€/h = 1200€
Execution expenses	**Blood levels measurements**	3000 x 30,66€ = 91.980€
	Printing expenses	2860 pages x 0,05€= 143€
Publication expenses	**Revision, edition, formatting…**	3000€
Total		**108.003€**

IMPACT ON THE NATIONAL HEALTH SYSTEM

Major Depressive Disorder (MDD) is a very common mental health disease with multifactorial causes, that affects a lot of people in our country. It is a severe disorder that can be invalidating and it is a very disabling and frustrating disorder for the patient, as they lose the illusion of doing their everyday life, lose the ability to feel pleasure, feels constantly sad or apathetic and patients even have thoughts of death. This disorder can affect negatively their personal, work and social life.

This disorder is more frequent in women than in men. This can be due to biologic and social differences between men and women. Since there is this difference in the prevalence of the disease, and there are differences in the metabolism of the drugs according to sex, it is important to consider if men and women need the exact same treatment or if sex is a determinant to adjust the MDD treatment in order to achieve better results in clinical improvement.

Venlafaxine is a dual antidepressant very commonly used in the pharmacological treatment of MDD. It's the second most used antidepressant after SSRIs treatment, and it has demonstrated to be effective in the treatment of this disorder. This drug is mainly metabolised in the liver to its active metabolite O-desmethylvenlafaxine (ODV), and to a less effective metabolite, N-desmethylvenlafaxine. The enzyme in charge to metabolise this none-effective metabolite is CYP3A4. This enzyme has shown to have greater exposure in women than in men, which can lead to thinking that women can have a lesser effect of Venlafaxine and a minor improvement in the clinical improvement in comparison to men.

Once the analysis of the results has been published, and if it is proven that the hypothesis is correct, it should be tested whether different doses of the drug applied according to sex can obtain a greater clinical improvement in women treated with Venlafaxine and equal the current effectiveness it has in men. This study can helps us to understand the clinical impact of metabolic differences in CYP3A4 according to sex.

This opens the doors to investigate the improvement of the effectiveness of antidepressant drugs according to sex and may lead to better pharmacological treatment of affective disorders, achieving greater clinical improvement of these pathologies in both men and women.

In conclusion, we believe that this study can have a great impact on our society as it will provide a useful tool for the depression treatment in the daily medical practice, and it can help in the future to adjust Venlafaxine doses to achieve better treatment and a better clinical improvement in women suffering from depression.

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ANNEXES

ANNEX 1: HAMILTON DEPRESSION RATING SCALE

PORFAVOR COMPLETE LA ENCUESTA CON LA INFORMACIÓN BASADA EN LA ENTREVISTA

Instrucciones: Marque la casilla correspondiente a lo que refiere el pacient. Asegúrese de responder en el espacio adecuado (del 0 al 4).

1- HUMOR DEPRESIVO		
0		Ausente
1		Estas sensaciones las expresa solamente si le preguntan como se siente
2		Estas sensaciones las relata espontáneamente
3		Sensaciones no comunicadas verbalmente (expressión facial, postura, voz, tendencia al llanto)
4		Manifiesta estas sensaciones en su comunicación verbal y no verbal en forma espontánea
2- SENSACIONES DE CULPA		
0		Ausente
1		Se culpa a si mismo, cree haber decepcionado a la gente
2		Tiene ideas de culpabilidad o medita sobre errores pasados o malas acciones
3		Siente que la enfermedad actual es un castigo
4		Oye voces acusatorias o de denuncia y/o experimenta alucinaciones visuales de amenaza
3- SUICIDIO		
0		Ausente
1		Le parece que la vida no vale la pena ser vivida
2		Desearía estar muerto o tiene pensamientos sobre la posibilidad de morirse
3		Ideas de suicidio o amenazas
4		Intentos de suicidio (cualquier intento serio puntúa 4)
4- INSOMNIO PRECOZ		
0		No tiene dificultad
1		Dificultad occasional para dormir, por ej. más de una hora para conciliar el sueño
2		Dificultad para dormir cada noche
5- INSOMNIO INTERMEDIO		
0		No hay dificultad
1		Esta desvelado e inquieto o se despierta varias veces durante la noche
2		Esta despierto durante la noche, cualquier occasion de levantarse de la cama se clasifica en 2 (except por motivos de evacuar)
6- INSOMNIO TARDÍO		
0		No hay dificultad
1		Se despierta a primeras horas de la madrugada, pero se vuelve a dormir
2		No puede volver a dormirse si se levanta de la cama
7- TRABAJO Y ACTIVIDADES		
0		No hay dificultad
1		Ideas y sentimientos de incapacidad, fatiga o debilidad (trabajos, pasatiempos)
2		Pérdidas de interés en su actividad (disminución de la atención, indecisión y vacilación).
3		Disminución del tiempo actual dedicado a actividades o disminución de la productividad
4		Dejó de trabajar por la presente enfermedad. Sólo se compromete en las pequeñas tareas, o no puede realizar estas sin ayuda

8- INHIBICIÓN PSICOMOTORA (LENTITUD DE PENSAMIENTO Y LENGUAJE, FACULTAD DE CONCENTRACIÓN DISMINUIDA, DISMINUCIÓN DE LA ACTIVIDAD MOTORA)		
0		Palabra y pensamiento normales
1		Ligero retraso en el habla
2		Evidente retraso en el habla
3		Dificultad para expresarse
4		Incapacidad para expresarse
9- AGITACIÓN PSICOMOTORA		
0		Ninguna
1		Juega con sus dedos
2		Juega con sus manos, cabello, etc.
3		No puede quedarse quieto ni permanecer sentado
4		Retuerce las manos, se muerde las uñas, se tira de los cabellos, se muerde los labios.
10- ANSIEDAD PSÍQUICA		
0		No hay dificultad
1		Tensión subjetiva e irritabilidad
2		Preocupación por pequeñas cosas
3		Actitud aprensiva en la expressión o en el habla
4		Expressa sus temores sin que le pregunten
11- ANSIEDAD SOMÁTICA (concomitantes fisiológicos de ansiedad) como: • Gastro-intestinales: Boca seca, diarrea, eructos, indigestion, etc. • Cardiovasculares: palpitaciones, cefaleas • Respiratorias: hiperventilation, suspiros • Frecuencia de micción incrementada • Transpiración		
0		Ausente
1		Ligera
2		Moderada
3		Severa
4		Incapacitante
12- SÍNTOMAS SOMÁTICOS GASTROINTESTINALES		
0		Ninguno
1		Pérdida del apetito pero come sin necesidad de que lo estimulen. Sensación de pesadez en el abdomen
2		Dificultad en comer si no se le insiste. Solicita laxantes o medicación intestinal para sus síntomas gastrointestinales
13- SÍNTOMAS SOMÁTICOS GENERALES		
0		Ninguno
1		Pesadez en las extremidades, espalda o cabeza. Dorsalgias. Cefaleas, algias musculares.
2		Pérdida de energía y fatigabilidad. Cualquier síntoma bien definido se clasifica en 2
14- SÍNTOMAS GENITALES (tales como: disminución de la libido i trastornos menstruales)		
0		Ausente
1		Débil
2		Grave
15- HIPOCONDRÍA		
0		Ausente
1		Preocupado por si mismo (corporalmente)
2		Preocupado por su salud
3		Se lamenta constantemente, solicita ayuda

16- PÉRDIDA DE PESO (RELLENAR a O b)					
a) Segun el paciente:			**b) Segun medidas semanales**		
0		No hay pérdida de peso	0		Pérdida de peso inferior a 500 gr
1		Probable pérdida de peso relacionada con la enfermedad	1		Pérdida de más de 500 gr. en una semana
2		Pérdida de peso definida por el paciente	2		Pérdida de más de 1 Kg. en una semana
3		No evaluado	3		No evaluado

17- INTROSPECCIÓN (insight)		
0		Se da cuenta que esta deprimido y enfermo
1		Se da cuenta de su enfermedad pero atribuye la causa a la mala alimentación, clima, exceso de trabajo, virus, necesidad de descanso, etc.
0		No se da cuenta que está enfermo

	PUNTUACIÓN TOTAL

ANNEX 2: EPWORTH SLEEPINESS SCALE

Valore las situaciones asociadas a la somnolencia:

Sentado y leyendo		
	Sin posibilidad de adormecerse	0 puntos
	Ligera posibilidad de adormecerse	1 punto
	Posibilidad moderada de adormecerse	2 puntos
	Posibilidad alta de adormecerse	3 puntos
Viendo la televisión		
	Sin posibilidad de adormecerse	0 puntos
	Ligera posibilidad de adormecerse	1 punto
	Posibilidad moderada de adormecerse	2 puntos
	Posibilidad alta de adormecerse	3 puntos
Sentado inactive en un lugar público		
	Sin posibilidad de adormecerse	0 puntos
	Ligera posibilidad de adormecerse	1 punto
	Posibilidad moderada de adormecerse	2 puntos
	Posibilidad alta de adormecerse	3 puntos
Tumbado por la tarde para descansar		
	Sin posibilidad de adormecerse	0 puntos
	Ligera posibilidad de adormecerse	1 punto
	Posibilidad moderada de adormecerse	2 puntos
	Posibilidad alta de adormecerse	3 puntos
Sentado y hablando con otra persona		
	Sin posibilidad de adormecerse	0 puntos
	Ligera posibilidad de adormecerse	1 punto
	Posibilidad moderada de adormecerse	2 puntos
	Posbilidad alta de adormecerse	3 puntos
Sentado tranquilamente después de una comida (sin consume de alcohol en la comida)		
	Sin posibilidad de adormecerse	0 puntos
	Ligera posibilidad de adormecerse	1 punto
	Posibilidad moderada de adormecerse	2 puntos
	Posibilidad alta de adormecerse	3 puntos
Sentado en un coche, detenido durante unos pocos minutos por un atasco		
	Sin posibilidad de adormecerse	0 puntos
	Ligera posibildiad de adormecerse	1 punto
	Posibilidad moderada de adormecerse	2 puntos
	Posibilidad alta de adormecerse	3 puntos

ANNEX 3. INFORMATION FOR THE PATIENT

FULL D'INFORMACIÓ AL PACIENT

Bon dia/Bona tarda,

Agraïm la seva col·laboració en l'estudi que realitzem a totes les comarques de la província de Girona. Aquest estudi està contribuint a millorar els coneixements que tenim sobre el tractament de la depressió amb el fàrmac Venlafaxina, i a millorar el coneixement sobre les diferencies en el metabolisme del fàrmac entre sexes.

Els investigadors d'aquest estudi estem molt interessats en conèixer el paper que pot tenir el sexe del pacient en la milloria clínica de la depressió. Per aquest motiu hem format un grup de recerca que incorpora a psiquiatres i infermeres de tots els Centres de Salud Mental d'Adults de la província de Girona.

Amb aquest document la nostra intenció és que vostè rebi la informació correcta i suficient perquè pugui avaluar i decidir per vostè mateixa si vol participar en aquest estudi. Per a això, llegiu aquest document amb atenció i després podrem aclarir els dubtes que li hagin pogut sorgir.

Títol de l'estudi

Sex influence on the clinical improvement of Major Depressive Disorder in patients treated with Venlafaxine. A prospective cohort study.

Lloc de realització

L'estudi es durà a terme a tots els Centres de Salud Mental d'Adults de Girona:

- CSMA Gironès I Pla de l'Estany (Girona)
- CSMA Baix Empordà (Platja d'Aro)
- CSMA Alt Empordà (Figueres)
- CSMA Garrotxa (Olot)
- CSMA Ripollès (Ripoll)
- CSMA Selva marítima (Blanes)
- CSMA Selva interior (Santa Coloma de Farners)

Participació voluntària

Vostè ha de saber que la seva participació en aquest estudi és voluntària I pot decidir no participar o canviar la seva opinió un cop hagi acceptat i retirar el seu consentiment en qualsevol moment. Això no suposarà cap perjudici per a vostè ni per la seva atenció sanitària.

Objectius de l'estudi

Aquest estudi pretén valorar si hi ha una diferencia en la millora clínica de la depressió en funció del sexe, en pacients que estan sent tractats amb Venlafaxina, degut a diferències entre ambdós sexes en l'expressió d'un enzim que metabolitza el fàrmac.

Les dades es recolliran amb un qüestionari que li farà el seu psiquiatra a la consulta, del qual se'n traurà una puntuació numèrica. Després de la consulta se li realitzarà una analítica de sang, en la que es mesurarà la concentració d'un metabòlit del fàrmac, el qual ens ajudarà a veure

com funciona l'enzim. Un cop recollides les dades, es pretén comparar el valor numèric del qüestionari i la concentració del metabòlit en sang amb l'obtingut en les visites subseqüents.

Descripció de l'estudi

Aquest estudi té una durada aproximada de dos anys. El seguiment de cada pacient es realitzarà un cop el consentiment informat sigui signat.

El seguiment d'aquest estudi consistirà en una visita als 3 mesos d'haver començat, als 6 mesos, als 9 mesos i als 12 mesos. En aquesta visita el seu psiquiatra li realitzarà un qüestionari que vostè haurà de respondre amb la major sinceritat possible, i posteriorment el/la visitarà el personal d'infermeria on li faran una extracció sanguínia per a mesurar la concentració del metabòlit del fàrmac.

Un cop s'hagin recollit totes les dades necessàries per a la realització de l'estudi, aquestes es descriuran i analitzaran estadísticament. Per últim, l'equip d'investigació avaluarà la informació obtinguda per tal de determinar la seva rellevància i utilitat de cara a la dosificació i ajustament del tractament amb Venlafaxina en pacients amb episodis depressius majors.

Beneficis i riscs derivats de la seva participació en l'estudi

Com se li realitzarà una extracció sanguínia periòdicament al principi de l'estudi i als 3, 6, 9 i 12 mesos, vostè ha de conèixer que tot i ser infreqüents existeixen els següents riscs o complicacions:

- Infecció
- Sagnat excessiu pel punt de punxada
- Formació d'hematomes
- Dolor
- Col·lapse venós
- Reaccions vasovagals
- Ansietat

És possible que en aquest estudi no obtingui un benefici immediat però és important la seva participació de cares a poder millorar amb la dosificació del fàrmac i el tractament personalitzat.

Confidencialitat/Protecció de dades personals:

Sol·licitem el seu permís per a realitzar-li l'entrevista pertinent i les analítiques i utilitzar les dades obtingudes únicament per la realització d'aquest estudi, de forma totalment confidencial i sense accés a les mateixes per part de tercers d'acord amb la legalitat vigent (Llei Orgànica 3/2018, de 5 de desembre, de Protecció de Dades Personals i Garantia dels Drets digitals). Les dades recollides en l'estudi estaran identificades mitjançant un codi, que no inclogui informació que pugui identificar-lo, i només el seu metge de l'estudi/col·laboradors podran relacionar aquestes dades amb vostè i amb la seva història clínica.

Si vostè decideix retirar el seu consentiment per participar en aquest estudi, cap dada seva serà afegida a l'estudi.

Revisió de l'estudi

L'estudi serà revisat i aprovat pel Comitè Ètic d'Investigació Clínica d'aquest Centre de Salut Mental d'Adults. Aquest comitè té la responsabilitat de garantir que els estudis acompleixin les normes vigents i els protocols de bona pràctica clínica i ètica.

Despeses i compensació econòmica

En el cas que participi en l'estudi, no tindrà cap despesa ocasionada per participar-hi. També l'informem que no està prevista cap compensació econòmica per la seva participació en l'estudi.

Més informació

Per a més informació, pot posar-se en contacte amb l'investigador principal de l'estudi, les dades del qual li facilitarem, o una vegada començat l'estudi amb la terapeuta que se li hagi assignat.

Li agraïm la seva participació.

ANNEX 4. INFORMED CONSENT

CONSENTIMENT INFORMAT DE L'ESTUDI

TÍTOL DE L'ESTUDI: Sex influence on the clinical improvement of Major Depressive Disorder in patients treated with Venlafaxine. A prospective cohort study.

INVESTIGADOR PRINCIPAL:

CENTRE/SERVEI:

Jo, El Sr/La Sra……..amb DNI……

Afirmo que:

- He rebut i llegit el full informatiu que se m'ha lliurat.
- He pogut fer totes les preguntes necessàries respecte a l'estudi i han estat respostes de manera satisfactòria.
- He rebut suficient informació sobre les característiques i objectius de l'estudi, els possibles riscos i la importància de la meva contribució per a l'avanç de la medicina.
- He estat informat per l'investigador ..... de les implicacions i la finalitat de l'estudi i declaro que:
    - Comprenc que la meva participació és voluntària
    - Comprenc que puc retirar-me de l'estudi quan vulgui sense haver de donar explicacions
    - Presto lliurement la meva conformitat per a participar a l'estudi.

Consento expressament a participar en l'estudi i entenc que la meva participació permet expressament el tractament de les meves dades personals i de salut, i manifesto que les dades facilitades per l'estudi són certes.

A dia ..... de ..... del .....

Signatura:

Nom i cognoms del participant: .....

ANNEX 5. DATA COLLECTION SHEET

FULLA DE RECOLLIDA DE DADES DELS PACIENTS

PROJECTE: Sex influence on the clinical improvement of Major Depressive Disorder in patients treated with Venlafaxine. A prospective cohort study.

DADES DEL PERSONAL SANITARI

Informació del psiquiatra del Centre de Salud Mental d'Adults.

Nom del Psiquiatra	
Centre de Salut Mental	
Data de l'entrevista clínica	
Número de col·legiat i signatura	

Informació del metge de laboratori del Parc Hospitalari Doctor Martí i Julià

Nom del metge de laboratori	
Data de l'estudi farmacològic	
Número de col·legiat i signatura	

DADES DEL PACIENT

NOM I COGNOMS					
Identificació numèrica del pacient					
Data de naixement	……./……../……..	**Dia inclusió**	……./……../……..	**Sexe**	Home [__] Dona [__]

Marcar amb una creu la casella si el pacient compleix les dades. Aquestes dades s'han d'obtenir de l'entrevista clínica inicial amb el psiquiatre.

Té un antecedent d'episodi depressiu major	
Fa un abús de substancies (alcohol, tetrahidrocannabinol, cocaïna...)	
Té un antecedent d'un trastorn de l'alimentació	
Pateix d'un trastorn de la son	
Pateix d'una patologia inflamatòria sistèmica crònica	

Dades recollides a la primera visita, als 3, 6, 9 i 12 mesos.

	1a visita	3 mesos	6 mesos	9 mesos	12 mesos
Data de l'actualització					
Puntuació de l'escala de depressió de Hamilton					
Nivells en sang de Venlafaxina					
Nivells en sang de N-desmetilvenlafaxina					