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Chapter 9

Anxiety in Natural and Surgical Menopause — Physiologic and Therapeutic Bases

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Additional information is available at the end of the chapter

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Abstract

Generalized anxiety disorder is one of the most common psychiatric disorders, affecting a high percentage of human beings around the world. This emotional disorder possesses marked gender differences and occurs more often in women than in men, in a proportion of 2:1. Accompanying the reproductive cycle of women are significant fluctuations in plasma and brain steroid hormone concentrations, including oestradiol, progesterone, and allopregnanolone, among others. These hormonal changes are related to some illnesses and with the development of anxiety and mood swings occurring in the premenstrual and postpartum period, and particularly during the menopause. Menopause is a clinical term used to indicate the cessation of the woman's reproductive ability that occurs naturally, but also may be surgically induced by bilateral oophorectomy, with or without the removal of the Fallopian tubes and uterus. Natural menopause includes specific periods related to the physiological and hormonal changes produced by ovarian failure, it is usually a natural stage that occurs to women in midlife, during their late 40s or early 50s, indicating the end of the reproductive period in the woman. During the menopause transition years, women experience changes in the production of ovarian hormones, which are associated with significant changes in the physiological, emotional, and affective processes. Unfortunately, surgical menopause occurs at an early age, and produces similar physiological and psychiatric disorders, but they are more severe in this instance. In both cases, typical symptoms associated with menopause critically

deteriorate the mental health of the women. In this way, the therapeutic management of clinical symptoms of menopause include replacement hormone therapy, the use of anxiolytic and antidepressant drugs, and other natural alternatives based on the use of chemical compounds obtained from plants such as soya. However, a general effective treatment for menopause symptoms does not yet exist. For this reason, experimental studies have proposed ovariectomy in rats as a potential tool to study the effects of a long-term absence of ovarian hormones associated with surgical menopause, which also allowed the study of substances with potential therapeutic application to ameliorate typical symptoms associated with surgical menopause. The aim of this chapter is to review the participation of ovarian hormones in the regulation of emotional and affective disorders in women with natural or surgical menopause; particularly their anatomical pathways, neurotransmission systems, and the resulting behavioural patterns. Finally, preclinical and clinical research suggested that long-term absence of ovarian hormones associated with natural or surgical menopause is the principal cause of physiological and psychiatric disorder in the women; therefore, oestrogenic compounds seem to play an important role in the maintenance of the brain structures that regulate anxiety, mood, memory, and cognitive functions in menopausal women.

Keywords: Anxiety, natural menopause, surgical menopause, oestrogens, experimental model, ovariectomy

1. Introduction

Generalized anxiety disorder is one of the most common psychiatric disorders, affecting a high percentage of the general population around the world. This psychopathology possesses marked gender differences and occurs more often in women than in men [1]. During the reproductive cycle of women, fluctuations occur in plasma and brain steroid hormone concentrations, including oestradiol, progesterone, and allopregnanolone: a reduced metabolite of progesterone. These hormonal changes are related to some illnesses and the development of anxiety and mood swings [2].

Low concentrations of steroid hormones are associated with irritability, anxiety, or depressive symptoms, and occur during the premenstrual, post-partum, and climacteric or post-menopausal periods. In particular, natural or surgical post-menopause is mainly characterized by a reduction of both oestradiol and progesterone because of failing ovarian function. These hormonal changes are associated with a major incidence of vasomotor symptoms, vaginal dryness, osteoporosis, cognitive deterioration, and hot flashes accompanied by perspiration, palpitations, irritability, anxiety, and mood swings. Unfortunately, emotional and affective alterations associated with the long-term absence of ovarian hormones are more severe in women who have undergone surgical menopause than women who experienced natural menopause. Disturbingly, surgical menopause is occurring more frequently in young women,

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in an economically productive stage, which impacts on the economy, on their quality of life, and, unfortunately, on their mental health [3].

Treatment of anxiety and depressive symptoms associated with the long-term absence of ovarian hormones produced by natural or surgical menopause, includes the use of benzodiazepines (i.e., diazepam), some selective serotonin reuptake inhibitors (i.e., fluoxetine or paroxetine), and hormone replacement therapy (i.e., oestrogens, or a combination of oestrogens plus progestagens), among others. Hormone replacement therapy has been used to ameliorate physiological, behavioural, and emotional alterations in post-menopausal women; for example, to reduce bone loss, hot flashes, irritability, and mood swings [4, 5]. Nevertheless, hormone replacement therapy is associated with several side-effects limiting their long-term use in vulnerable women. In this way, some investigations focusing on finding new therapeutic alternatives have explored the effects of some vegetables such as soya that contains high concentrations of the phyto-oestrogens genistein, daidzein, glycitein, and their conjugate metabolites. In some reports, there is evidence that phyto-oestrogens produces physiological effects similar to that produced by endogenous oestrogens. Apparently, these effects occur through actions on the oestradiol receptor-β [6, 7], which has been involved in the anxiolytic-like effect of endogenous and synthetic oestrogens at the experimental level.

To study the effect of the long-term absence of ovarian hormones associated with surgical menopause in the women, ovariectomy in rats has been used at a preclinical level as a potential tool to explore alterations in diverse organs and systems [8]. A rat experiencing a long-term absence of ovarian hormones induced by ovariectomy is considered as an early model of surgical menopause, which has allowed studying changes in cardiovascular, reproductive, motor, and bone systems, as well as changes in the sensitivity of neurotransmitter receptors in the brain. These changes in the brain impact negatively on the behaviour of the rats, producing higher indicators of anxiety-like behaviour and despair [6, 9]. Such facts support the hypothesis that rats with a chronic absence of ovarian hormones induced by ovariectomy could help us to understand the anxiety and mood swings typical of women who have undergone surgical menopause, as well as to screen new substances that could ameliorate anxiety symptoms in this particular group of women.

The aim of this chapter is to review the participation of ovarian hormones in the regulation of emotional and affective disorders in women experiencing natural or surgical menopause, particularly their anatomical pathways, neurotransmission systems, and the resulting behavioural patterns. Additionally, the principal pharmacological therapies used to ameliorate physiological and psychological symptoms in natural and surgical menopause will be discussed.

2. Natural and surgical menopause

Menopause is a clinical term used to indicate the cessation of a woman's reproductive ability. It may occur naturally, but also may be surgically induced by bilateral oophorectomy (removal of ovaries), with or without removal of the Fallopian tubes (salpingo-oophorectomy), and

uterus (hysterectomy). Natural menopause includes specific periods (Figure 1) related with the physiological and hormonal changes produced by ovarian failure (Table 1). Menopause is usually a natural stage that occurs to women in midlife, during their late 40s or early 50s, indicating the end of the reproductive period in the woman [2]. During the menopause transition years, the women experiment fluctuations in the production and release of ovarian hormones, which produces significant changes in the physiological and affective processes. Not every woman experiences bothersome levels of these effects; it varies greatly from person to person and also depends of their lifestyles. Most women experience that their menstrual periods are gradually becoming less frequent, and that the timing of the start of the flow is usually less predictable.

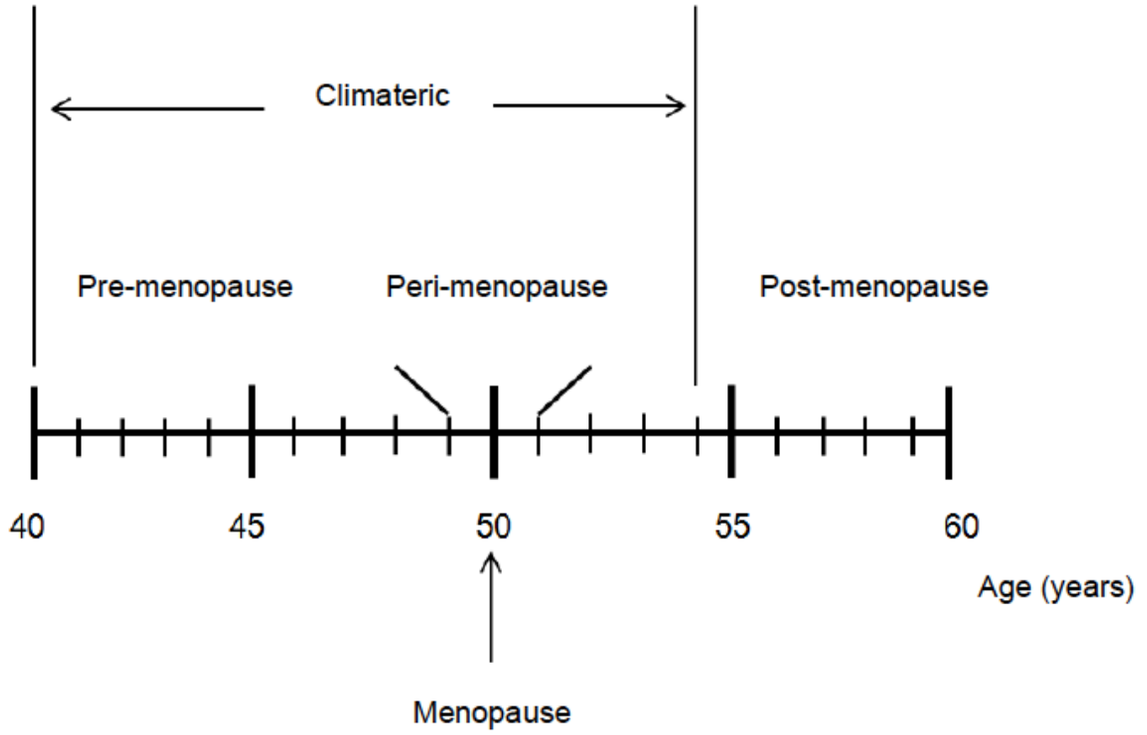

Figure 1. Scheme illustrating the different phases that characterized the end of the reproductive period in women, under natural conditions.

The beginning of menopause (the last period from natural causes) typically occurs in an age range between 40 and 61 years, [10] with an average age for the last period of 51 years [12]. The average age of natural menopause in the majority of women occurs at 51 years [11], however, in some countries (i.e., the Philippines and India), the median age of natural menopause occurs earlier, at 44 years. [13]. Nonetheless, the World Health Organization indicates that the menopause occurs at the average age of 45–55 years around the world.

During natural or surgical menopause there are significant reductions of ovarian hormones' concentrations, particularly oestradiol, progesterone, and their metabolites. This influences

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the beginning of menopausal symptoms, including bone density loss and vasomotor alterations, accompanied by irritability, anxiety, and depression in some cases [2, 6, 14, 15]. Natural menopause is caused by follicular atresia in which there are ovarian follicles that do not respond to gonadotrophynes; for this reason, the ovaries lose their function, ovulation ceases, and the reproductive period of the woman ends. In this state, the oestrogen concentrations are lowest, increasing the follicular stimulant hormone (FSH) and luteinizing hormone (LH) in a minor proportion [16].

Term	Description
Premenopause	Is a term used to mean the years leading up to the last menstrual period, when the concentrations of ovarian hormones are already becoming more variable and lower, and the effects of hormone withdrawal are present.
Perimenopause	It term refers to the menopause transition years, a span of time both before *and* after the date of the final menstrual period; which can last for four to eight years. It period may occur during six to ten year, ending approximately 12 months after the last menstrual period.
Menopause	Clinically, menopause is defined as the last menstrual flow period. It is necessary taken in count that this moment may only be identified retrospectively, once 12 months have gone without experiment any menstrual flow. Commonly, menopause is used to referrer to menopause transition years, but not the last menstrual period.
Postmenopause	This term include the period after 12 months without menstrual flow, assuming that women still have a uterus, and are not pregnant or lactating. Physiologically, this period is characterized by very high follicular stimulant hormone concentration (FSH) at plasma level. Thus postmenopause is all of the time that follows the point when her ovaries become inactive, evidenced by last menstrual period.

Table 1. Terms associated with natural menopause

On the other hand, surgical menopause is associated with sudden and complete reduction of oestradiol, progesterone, and testosterone plasma concentrations [17], which predisposes the appearance of physiological and psychiatric alterations, such as occur in natural menopause, but with greater intensity.

3. Anxiety disorders and mood swings associated with natural or surgical menopause in women

Menopause is a stage of biological development of women that implies physiological, psychological, and social changes. During menopause, women are vulnerable to cognitive and

physical impairment as well as psychiatric illnesses as anxiety and depression. Hot flushes; night sweating; skin dryness and mucosa; even vaginal dryness; sleep disorders; and cognitive and behavioural changes are symptoms that deteriorate a woman's quality of life [18]. Mild anxiety and stress vulnerability are common in premenopause; while anxiety, depression, and irritability are more intense during perimenopause [19]. Anxiety disorders tend to be more chronic compared to mood disorders (i.e., depression) in a woman suffering during the menopause [20]. It is noteworthy that emotional and affective disorders are more severe in cases of surgical menopause compared with natural menopause, apparently due to the drastic suppression of hormonal production and the psychosocial context of the surgery and related illness.

During natural menopause, ovarian hormones biosynthesis (i.e., oestrogens and androgens) becomes gradually reduced, while surgical menopause is characterized by a drastic hormonal suppression. This reduction of hormone concentrations influences the impairment in neuronal functioning responsible for a predisposition to develop anxiety disorders and changes in general mood, mostly in woman with records of psychiatric illness. Women who had experienced disorders such as premenstrual syndrome or dysphoric premenstrual syndrome in their life, experience menopause with a certain degree of liberty and comfort with respect to their sexuality; on the other hand, women with records of psychiatric disorders can experience emotional and affective disorders more severely [21].

It has been found that between the ages of 42 to 52 years, women with high levels of anxiety during premenopause continue to experience this during menopause. Premenopausal woman with low levels of anxiety can be more susceptible to increased levels of anxiety during and after menopause transition [22]. Consistent with that findings, Jafari et al., 2014 [23], found that post-menopausal women, between the ages of 45 and 55, have high levels of anxiety compared to premenopausal women between 35 and 45.

Some authors have suggested that transition to menopause is the stage with the most risk of developing or increasing the symptoms of anxiety. Anxiety disorders such as panic disorder, social phobia, or generalized anxiety do not vary with the different stages of menopause [24]. However, studies showed that during the perimenopause, anxiety symptoms are higher than symptoms in pre- and post-menopause. Approximately 74% of women undergoing natural menopause experience hot flushes [24], which are associated with the development of anxiety symptoms. It is still controversial if anxiety develops before or in consequence of the vascular symptoms (i.e., hot flushes and night sweating) that characterized menopause.

Respecting the severity of the symptoms associated with menopause, there exists a considerable variation between samples. African-American women report similar symptoms of anxiety and panic attacks, but a higher degree of severity in vascular motor symptoms (i.e., hot flushes in the chest and head, palpitations, and sweating) when compared with Asiatic women [25]. This difference in symptoms has been associated with lifestyles and nutrition as well as particularities in metabolic activity and the disruption of some neurotransmission systems in the brain [26], but it is not yet clear if anxiety precedes vascular symptoms or vice versa. On the other hand, a close negative relation between the severity of anxiety and depression symptoms and quality of life has been reported. In this sense, post-menopausal women with

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a low quality of life showed a higher index of anxiety and symptoms of depression than pre-menopausal women with a good quality of life [23].

Symptoms of anxiety, irritability, depression, bluntness, mnesic disease, impairment of general capacity, and sleep disorders are the most frequent motives in women with perimenopause to attend to medical consultation [18]. It is common that women that refer to psychological discomfort in medical consultation during the whole menopause span are also the women that show less self-esteem and a low personal satisfaction [23]. Additionally, there is a relation between hormone levels and psychological wellbeing in menopausal women. For example, depression seems to increase when hormonal fluctuations occur in perimenopause, possibly as result of a lack of regulation of oestrogens over serotonergic activity and other neurotransmission systems in the brain [21]. Variations in circulating levels of androgens are related to mood disorders in young post-menopausal women, establishing a direct relation between androgen concentrations and symptoms of anxiety and depression in post-menopause [27].

Panic disorder is one of the most common anxiety disorders during menopause; it can develop once menopause has been completely established. Such disorder is more frequent in women with evident physical symptoms during menopause. In three groups of women classified in different ages (i.e., 50 to 59, 60 to 69, and 70 to 79 years old), panic attacks were more frequent in women between 50 to 59 years old. This group probably experienced perimenopause with variations in ovarian hormones production, an increased vulnerability to psychological stress, and somatic symptoms that can be more intense, which can increase the probability of developing anxiety. Other factors include negative experiences in life, general physical impairment, and comorbidity with other illness [28]. For example, women from 51 to 83 years old experienced at least one episode of panic attacks during the six months previous to suffering from a cardiovascular disorder, with a prevalence of 10%. It seems that anxiety is a risk factor that increases morbidity and mortality associated to cardiovascular illness in post-menopausal women [29].

Obsessive-compulsive disorder (OCD) is a mental illness associated with different events in the reproductive life of a woman. There are reports of a 47% of incidence of OCD during menopause while this percentage decreases considerably in post-menopausal women to 9 %. Although there are studies about the relation of menopause and OCD, the data are contradictory [30]. One research on women suffering natural or surgical post-menopause measured prevalence and comorbidity of OCD, the prevalence of OCD was about 7.1% and the more common obsessions was cleanliness, while the most common compulsions were cleanliness/washing. Comorbidity for the different disorders was 63.2 %, with comorbidity and generalized anxiety being the most frequent [31].

In relation to panic disorder (PD), some studies have related PD with vascular disturbances in perimenopausal women that attended medical consultation, with a prevalence of 18%. However, this research did not specify how it determined menopause onset; it seems the researchers used only verbal reports of patients [32], so these results must be interpreted carefully.

Concerning surgical menopause, very little literature about anxiety attacks and this kind of menopause exists. One medical case reported that a woman with a surgical extirpation of ovarian developed physiological and psychological changes similar to those of natural menopause, but also immediately developed symptoms of severe anxiety that impaired her quality of life [33]. The emotional and affective symptoms associated with surgical menopause vary between individuals, but it has been reported that bilateral extirpation of ovaries before natural menopause is related to the development of anxiety disorders and the increase of cognitive impairment risk, compared with women that experience natural menopause [34].

In summary, reported data associating anxiety disorders to natural or surgical menopause are still contradictory, perhaps due to differences between the populations of study and the variations in criteria for measuring both menopause and anxiety. Some studies report that symptoms of anxiety increase during perimenopause and decrease later in post-menopause [35]. Other studies suggest that anxiety symptoms are not directly related to a particular stage of menopause [36]. For example, Freeman et al. (2005) [37] reported that previous medical records of depression and stress vulnerability are strong predictors of anxiety during menopause, while Moilanen et al. (2010) [36] only related the lifestyle (i.e., obesity, sedentary lifestyle, and alcohol consumption) with the predisposition to suffer anxiety episodes during natural menopause. Besides, most of the investigations do not offer solid data about prevalence of anxiety disorders that fulfil the diagnostic criteria. It seems that most of the few studies comparing natural and surgical menopause have found a relation between vascular alterations and symptoms of anxiety; however, this relationship is not definitive since it must be assured that somatic and psychological symptoms were not confused with anxiety symptoms in these studies' particular populations. At the time of writing, predisposal factors of emotional and affective alterations during natural or surgical menopause have not been clearly identified, but it seems evident that during menopausal stages there is an increased vulnerability to stress which increases the prevalence of anxiety and depression symptoms that impair quality of life during natural or surgical menopause. This makes necessary specific studies with standardized criteria for measuring the factors that produce these disorders in order to design therapeutic strategies, including pharmacological treatments that improve the quality of life of women suffering natural or surgical menopause.

4. Pharmacological treatment of anxiety disorders in menopausal women: Benefits versus side-effects

Despite the evidence that in natural and surgical menopause there is a high incidence of anxiety and depression disorders, there are few controlled studies evaluating the efficacy of pharmacological treatments in this particular population, while there is a worryingly high frequency of self-medication using anxiolytic drugs in menopausal women. Treatment selection for controlling the symptoms of menopausal women requires establishing a balance between the benefits on mood and the potential risks to health. It is very important to consider the clinical background of the patient; in cases of young women who have undergone surgical menopause

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at an early age (24 to 38 years old), efficiency of the pharmacological response can vary compared with women who experienced natural menopause.

The therapeutic treatment for the control of symptoms of anxiety includes hormonal replacement therapy, antidepressant with anxiolytic activity, and some therapies based on the use of chemical compounds isolated from vegetables (i.e., soya), which have shown certain anxiolytic potential (Table 2).

Type of Therapy	Condition (Average age)	Dosage	Therapeutic effects	Side-effects	Reference
Hormonal Ethinyl estradiol	Bilateral oophorectomy (24 year)	(3.9 mg / week; td; 3 mouth)	Without Anxiolytic effects	Increased risk of endometrial hyperplasia and cancers other, venous thromboembolic events and stroke (Hickey et al., 2005).	[34]
	Bilateral oophorectomy (46 year)	(3.9 mg / week; td; 3 month)	Anxiolytic		[34]
	Hysterectomy and bilateral oophorectomy	(3.9 mg / week; td; 6 mouth)	Anxiolytic		[41]
Tibolone	Hysterectomy and bilateral oophorectomy (47 year)	(2.5 mg/day; v. o.; 6 month)	Anxiolytic	Increased risk of stroke in women over 60 years (Cummings et al., 2008). Nausea, headache, breast tenderness, weight gain, bloating (Gupta et al., 2013).	[41, 43]
	Hysterectomy and bilateral oophorectomy (50 year)	(2.5 mg/day; v. o.; 12 month)	Anxiolytic		[87]
	Natural menopause	(2.5 mg/day; v. o.; 3 month)	Anxiolytic		[42]
Estradiol valerianate-dehydroepiandrosterone enanthate (Gynodian Depo)	Hysterectomy with bilateral oophorectomy (35-45 year)	(4 mg/200 mg/ month; i.m.; 3 month)	Anxiolytic	Pruritus, eczema, urticaria, skin reactions at the site of injection, hair loss, erythema nodosum, acne (PLM, 2015).	[86]
17β-estradiol	Natural menopause	(50 mg/day; t.d.; 3 month)	Anxiolytic	Increased risk of venous thromboembolic events (Canonico et al., 2007),	[42]

Type of Therapy	Condition (Average age)	Dosage	Therapeutic effects	Side-effects	Reference
				cerebrovascular accidents and myocardial infarction (Welty, 2003).	
	Hysterectomy and bilateral oophorectomy (48 year)	(2 mg/day; v.o. ; 6 month)	Anxiolytic		[43]
	Hysterectomy and bilateral oophorectomy (50 year)	(50 mg/day; t.d.; 12 month)	Anxiolytic		[87]
Conjugated equine estrogen (Premarin)	Total abdominal hysterectomy/ bilateral salpingo-oophorectomy (48-51 year)	(0.625 mg/day; v.o.; 12 month)	Anxiolytic	Increased risk of myocardial infarction, breast cancer and strokes, besides headache and nausea (Gupta et al., 2013).	[46]
Dehydroepiandrosterone (DHEA)	Total abdominal hysterectomy/ bilateral salpingo-oophorectomy (48-51 year)	(25 mg/day; v.o.; 12 month)	Anxiolytic	Acne and hair loss (Welty, 2003).	[46]
Testosterone (gel hidroalcoholyc TESTOGEL®)	Natural menopause (50-65 year)	(50 mg/day; t.d.; 3 month)	Anxiolytic	Headache, weight gain, facial hair, increased appetite (Nathorst-Böös et al., 2006).	[88]
Antidepressant Venlafaxine	12 month of amenorrea (45-55 year)	(450 mg/day; v.o.; 6 month)	Anxiolytic	Dry mouth, altered appetite, abdominal discomfort, decreased libido, insomnia, headache and nausea (Hickey et al., 2005; Iglesias et al., 2009; Handley et al., 2015).	[54]
Paroxetine	Natural menopause (62 year)	10 mg/day; 1 week and the subsequent dose of 20 mg/day; 6 months.	Anxiolytic	Decreased libido, insomnia, headache and nausea (Hickey et al., 2005; Handley et al., 2015).	[89]
Phytoestrogens Red clover extracts (MF11RCE,	>12 month of amenorrea (40 year)	(80 mg/day; v.o.; 3 month)	Anxiolytic	Without effects.	[38]

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Type of Therapy	Condition (Average age)	Dosage	Therapeutic effects	Side-effects	Reference
containing isoflavones)					
Phytoestrogens					
PHYTO SOYA, capsules containing 17.5 mg isoflavones	Postmenopausal period	35 mg/day; v.o.; 4 months	Anxiolytic	Without severe side effects.	[59]

Table 2. Pharmacological treatment of anxiety disorders in menopausal women.

5. Hormonal replacement therapy

Reduced oestrogen concentrations during menopause impacts different biological systems, including the central nervous system. The psychiatric disorders most common during menopause include loss of motivation, lack of mental concentration, irritability, aggression, mood swings, mental tension, anxiety, and depression disorders. Anxiety in particular occurs mainly in women who have been susceptible to suffering anxiety during their whole life. It is well known that exogenous administration of oestrogens or progesterone not only prevents the common symptoms of menopause [5], but is also able to improve the mood and emotional state, and reduce the symptoms of anxiety [38, 39]. In this sense, the use of oestrogens to treat anxiety is preferable to the use of psychopharmacological drugs.

Rocca and collaborators (2008) [34] reported that women who experience surgical menopause at an early age are not responsive to the treatment with oestrogens for symptoms of generalized anxiety, while women suffering during a natural menopause but who experienced surgical extirpation of the ovaries were sensitive to treatment with ethinyl oestradiol (3.9 mg/week) which significantly decreased the symptoms of anxiety [40, 41]. This finding suggests that physiological and neurochemical conditions associated with the reduction of hormonal levels in natural and surgical menopause are age-dependent, and impacts on the establishment of anxiolytic effects of oestrogenic therapy.

Clinical studies agree that chronic administration of 17β-oestradiol to women with natural [42] or surgical menopause [43] is effective in reducing symptoms of anxiety. However, some studies relate the use of 17β-oestradiol with an increase in the risk of developing venous thromboembolism [44], strokes, and myocardial infarction in women both with and without a family history of this illness; apparently, the use of a transdermal patch with oestrogens minimizes the secondary effects but unfortunately also minimizes therapeutic effects [45].

Therapy with equine conjugate oestrogens at a dose of 0.625 mg/day also produces significant anxiolytic effects, in the same way that 25 mg/day of dehydroepiandrosterone (DHEA) does; both treatments significantly reduce genitourinary, vasomotor, psychological, vaginal dryness symptoms, and improve libido [46]. Unfortunately, the use of oestrogens alone or in combi-

nation with medroxyprogesterone acetate (synthetic progestin) used to ameliorate the symptoms associated with the menopause, also has side-effects and increases the risk of heart attacks, breast cancer, and strokes. Other symptoms include headaches, nausea, and (in the case of DHEA) secondary effects of an androgenic kind such as acne and hair loss [45, 46].

On the other hand, there are different alternative drugs for oestrogenic therapy when it is contraindicated, for example gonadomimetics such as Tibolone. This drug is a synthetic steroid from which three metabolites are produced: 3 alpha-OH-tibolone, 3 beta-tibolone with oestrogenic activity, and the isomer tibolone, which exerts a weak influence on progestegenic and androgenic activity. Tibolone, 2.5 mg/day, reduces the symptoms of generalized anxiety in menopausal women, who had undergone a hysterectomy or bilateral oophorectomy [41, 43] and in women experiencing a natural menopause [42]. It seems that these anxiolytic effects could be associated with an increase of β–endorphin concentrations in blood and the pituitary gland [47].

Collateral effects of the oestrogenic therapy include vaginal bleeding in women that still have a uterus, which in some cases determines the use of Tibolone [48], given that it not only produces anxiolytic effects but also reduce symptoms at vegetative and cardiovascular levels. Additionally, it also reduces triglyceride, total cholesterol, and bad cholesterol (LDL) levels, while increasing good cholesterol (HDL) levels, reduces loss of bone density, and increases libido in post-menopausal women [46]. Data available about the chronic use of Tibolone show that it can reduce the risk of bone fractures, and breast and colon cancers, but also increases the risk of strokes in women older than 60 [49].

Hormonal replacement therapy, in general, is contraindicated in women with hepatic and cardiovascular illness, and with records of thrombovascular or cerebrovascular disease, as well as breast and cervical cancer. Nevertheless, it exists as a treatment option with excellent clinical results.

6. Antidepressants

Women suffering during the menopause have reduced serotonergic activity associated with low concentrations of steroid hormones, which is associated with the symptoms of anxiety and depression [50]. The reduction in oestrogenic levels during menopause could alter the availability of cerebral tryptophan used in serotonin synthesis, allowing the establishment of psychological symptoms typical of menopause. In consequence, the use of Selective Serotonin Reuptake Inhibitors (SSRI) can control the symptoms of anxiety and depression in menopausal women [50].

The use of SSRI to control symptoms of anxiety and depression in menopausal women includes mainly paroxetine, fluoxetine, sertraline, citalopram, and venlafaxine, which are also used to control vascular symptoms, and mainly hot flushes. Usage of these drugs has an appropriate tolerance and security window, with the exception of some adverse effects including the reduction of libido, insomnia, headache, and nausea [51, 52].

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Venlafaxine is used for treatment of anxiety disorders most common in menopause, such as generalized anxiety, panic attacks, and social phobia. Very few studies evaluate the effects of antidepressants in women experiencing menopause and diagnosed with some anxiety disorder, due to the fact that frequently symptoms of anxiety can be confused with emotional disturbances characteristic of menopause, such as palpitations, irritability, and sweating [53].

One study by Iglesias et al. (2009) [54] including women between 45 to 55 years old experiencing natural menopause, showed the anxiolytic effect of venlafaxine (450 mg/day/six months). Despite the use of relatively high doses compared to the standard dose (150 mg/day), no potentially dangerous secondary effects were reported, with the exceptions of mouth dryness, appetite changes, abdominal discomfort, headaches, and, in some cases, sexual dysfunction.

7. Alternative therapies

The collateral effects produced by hormone replacement therapy and the lack of controlled studies evaluating the therapeutic effect of antidepressants in women suffering menopause have encouraged research into new alternative therapies that control the symptoms characteristic of menopause but which few or no undesirable side-effects. At the time of writing, the use of chemical compounds obtained from plants (i.e., phyto-oestrogens) has been evaluated as a potential therapeutic option due to the oestrogenic activity over β-oestrogen receptors in the osseous system, reproductive system, and central nervous system [55, 56]. Although phyto-oestrogens seem to be less potent than conventional oestrogens [57] some preclinical and clinical studies support its potential use in therapeutic treatment of osteoporosis, vascular disorders, and the symptoms of anxiety and depression [38].

Some clinical studies have reported that isoflavones are effective in improving classical menopause symptoms, including those related to anxiety and mood swings. The phyto-oestrogens from magnolia bark extract significantly reduces the relevant psycho-affective symptoms, particularly anxiety, irritability, and insomnia in menopausal women, with a scarcity of side-effects [58].

In women experiencing natural menopause, the therapeutic effect of isoflavones synthetized from extracts of red clover (*Trifolium pratense*) was studied. The administration of 80 mg/day of isoflavones during three months (MF11RCE capsule with 40 mg of isoflavones biochanin A, formonometin, genistein, and daidzein) in women experiencing natural menopause reduced the symptoms of generalized anxiety 76% measured by the Hospital Anxiety and Depression Scale (HADS) and compared with basal measures, while with the Zung's Self Rating Depression Scale there was a reduction of 80.6% of symptoms with respect to basal [38]. It is noteworthy to point out that women who received a placebo also significantly reduced the symptoms of anxiety, but only 21.7% with respect to basal. These authors suggest that isoflavones isolated from red clover are efficient in treating the symptoms of anxiety and depression in women experiencing menopause.

On the other hand, Albert et al. (2001) [59], in a multicentric, open, prospective, observational, and nonrandomized clinical trial involving 190 post-menopausal women, tested the effect of a preparation rich in isoflavones (PHYTO SOYA, capsules containing 17.5 mg isoflavones) on symptomatology derived from the lack of oestrogens (i.e., hot flushes, sleep disorder, anxiety, depression, vaginal dryness, loss of libido, and bone pain). Each patient received 35 mg of isoflavones per day in two doses, during four months of treatment. In this study, most of the women reported a statistically significant decrease in all evaluated parameters, including a significant reduction of symptomatology of anxiety and depression, without severe side-effects and with excellent tolerance. Nonetheless, more data from a double-blind, randomized study performed with 50 women (with an average age of 53.3 ± 3.1 years) with menopausal symptoms, the administration of the phyto-oestrogens genistein and daidzein during three months produced significant reductions in hot flushes only, but not in anxiety, insomnia, or vaginal dryness [60]. In this way, diverse studies of menopausal women have reported a particular effectiveness of phyto-oestrogens in the control of vasomotor symptoms, principally in the control of hot flushes [61–63], but few have demonstrated effectiveness in the control of anxiety and depressive symptoms [38, 58, 59]. There are in fact few studies that explore the clinical relevance of phyto-oestrogens in the control of emotional and affective disorders in menopausal women, which limit the wide use of these substances in the treatment of anxiety and depressive disorders. Considering the controversy of the effectiveness of phyto-oestrogens in the management of physiological and psychiatric disorders associated with the menopause, additional studies are needed to further address the complex array of factors that may affect efficacy, such as dose, isoflavone structure, baseline of typical symptoms in the menopause, and treatment duration [61]. Only then will it be possible to consider phyto-oestrogens as a safe and efficacious alternative for treating symptoms associated with menopause and to remove the present barrier to recommending its use for treatment.

8. Ovariectomized rats as an animal model for surgical menopause

Surgical menopause in women is produced by ablation of the ovaries (oophorectomy) with or without the uterus, which produces a similar symptomatology to that observed in natural menopause, but with an increase in intensity. In this way, bilateral ovariectomy in rats has been proposed as a tool to reproduce physiological and emotional alterations related with the reduction of ovarian hormones (Table 3), as occurring in women subjected to surgical menopause; in other words, that surgical manipulation of rats is proposed as an experimental model to study emotional and physiological changes that occur in women [8].

Some experimental studies of ovariectomized rats show a body-weight gain [64] and reduction of bone density as in osteoporosis [65], similar to that identified in menopausal women as a consequence of the long-term absence of ovarian hormones, in particular oestradiol, progesterone, and their reduced metabolites [65]. In this state, other physiological alterations that produce atrophy of the skin and mucosa also occur [66], such as hair loss, deterioration of attention and concentration capacity, reduced memory capacity, and loss of libido [67, 68]. The absence of oestrogens disrupts the immune, motor [69], and cardiovascular systems [70]; in

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Weeks post ovariectomy	Effects	References
1	Reduced activation of glutamatergic receptors in the basolateral amygdala.	[75]
1-2	Reduced density of dendritic spines and synaptophysin in pyramidal neurons in the CA1 layer of the hippocampus.	[90]
3	Reduced density of dendritic spines in the CA1 layer of the hippocampus.	[67]
4	Reduced expression of mRNA of α2 and α3 subunits in the amygdala $GABA_A$ receptors.	[75]
4	Reduced expression of mRNA of the tryptophan hydroxylase enzyme and the serotonergic transporter (SERT) in the dorsal raphe nucleus.	[79]
4	Reduced concentration of serotonin in the hippocampus and nucleus accumbens.	[76]
5	Reduced thickness of the CA1 layer in the hippocampus and the cerebral prefrontal cortex.	[91]
6	Reduced concentration of dopamine in the central nucleus of the amygdala.	[92]
8	Reduced expression of mRNA of estrogen receptors (ERα y ERβ) in the hippocampus and cerebral cortex.	[74]
9	Reduced density of dendritic spines in the cerebral prefrontal cortex.	[93]
12	Anxiety-like behavior was higher in 12-weeks postovariectomized rats than 3-weeks postovariectomized rats in the burying behavioral test	[8]
12	Higher anxiety-like behavior in the elevated plus maze, which was reduced by phytoestrogen genistein treatment.	[6]
1-15	Anxiety-like behavior increase progressively after ovariectomy, it was higher from nine weeks post ovariectomy.	[9]
18	Reduced activity of the tryptophan-2-hydroxylase enzyme in the brain.	[78]

Table 3. Cerebral and anxiety-like behavior changes associated with ovariectomy in the rat.

addition, an increase in emotional (i.e., anxiety) and affective (i.e., depression) alterations that negatively impact on women's quality of life also occurs. It has been suggested that these alterations are related to the long-term absence of ovarian hormones, which play an important role in the regulation of diverse physiological processes in gastrointestinal [71], metabolic, and bone [64, 65] systems, as well as in the regulation of emotional and affective states. All those alterations of the different systems are produced at the experimental level through the ablation of the ovaries in the rat; therefore this surgical manipulation has been considered as an appropriate model to study medical alterations occurring in women undergoing surgical menopause [6, 8, 58, 62].

In rats, the long-term absence of ovarian hormones produced by ovariectomy reduces GABAergic neurotransmission in diverse brain structures [72]. It also produces a reduced sensitivity of the $GABA_A$, possibly associated with a reduced expression of mRNA of $\alpha 2$ and $\alpha 3$ subunits of this receptor [73]. As mentioned above, this is important because the $GABA_A$ receptor is the action site of clinically effective anxiolytic drugs such as benzodiazepines; those molecular modifications in the $GABA_A$ receptor could explain the reduced effectiveness of anxiolytic pharmacological therapies in menopausal women.

On the other hand, ovariectomies performed on rats reduce the density of oestrogen receptor α and β in the hippocampus [74]; in addition, reduced activity of glutamate receptors in the basolateral amygdala also occurs [75], and these neurochemical changes are accompanied by an increase in anxiety-like behaviour. While administration of an agonist of the glutamate receptors produces an anxiolytic-like effect in the ovariectomized rats, it is dependent on the availability of oestrogens in the basolateral amygdala [75].

Likewise, the ovariectomy of rats reduces the monoaminergic neurotransmission affecting the production and release of norepinephrine, dopamine, and serotonin in the brain [76]. It has been proposed that reduced monoaminergic neurotransmission in the hippocampus and accumbens nucleus could be related to the presence of anxiety-like behaviour, while administration of oestrogenic compounds in ovariectomized rats produces anxiolytic-like effects [77], possibly associated with the reactivation of brain neurotransmission. Some investigations indicate that the lower concentration of oestrogens in the brain associated with ovariectomy reduces the activity of the enzyme tryptophan hydroxylase-2, which reduces the availability of serotonin and their transportation in the dorsal raphe nucleus [78]. Administration of oestrogenic compounds in ovariectomized rats, on the other hand, produces anxiolytic-like effects [79].

The rats with a long-term absence of ovarian hormones produced by ovariectomy are more vulnerable to environmental stressors. In this case, rats with long-term ovariectomies subjected to chronic mild stress show more anxiety-like behaviour than rats with short-term ovariectomy in the elevated plus-maze, indicating that the frame time in the absence of ovarian hormones plays an important role in response to stress. Vulnerability to stress in ovariectomized rats is associated with a reduced cellular proliferation in the dentate gyrus [79], and reduced density of dendritic spines in CA1 pyramidal neurons [80]. These neuroanatomical changes at brain level are proposed as part of the neurobiological substrate of the altered stress response and higher predisposition to develop emotional (i.e., anxiety) and affective (i.e., depression) disorders [67] in women experiencing both a natural or a surgical menopause.

In rats with the long-term absence of ovarian hormones induced by ovariectomy, it has been possible to study the same emotional and affective changes as occur in women as a result of surgical menopause. Rats with 12 post-ovariectomy weeks show higher anxiety-like behaviour than rats with three post-ovariectomy weeks [8]. Interestingly, this anxiety-like behaviour is reduced with anxiolytic drugs (i.e., diazepam), some natural chemical compounds (i.e., isoflavones), or some extract of plant (*Montanoa tomentosa*). In rats with long-term absence of ovarian hormones produced by ovariectomy, the effect of several doses of isoflavone genistein (0.25, 0.5, and 1.0 mg/kg) during four consecutive days was explored. This treatment schedule

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produces an increase in the time spent in exploration of an illuminated compartment and the number of explorations towards this compartment in the light/dark test: a validated model to screen drugs with a potential anxiolytic effect. These changes in rat behaviour are an indicator of a reduced anxiety-like behaviour, such as occur in this experimental model when anxiolytic drugs like diazepam are evaluated [6]. Interestingly, the anxiolytic-like effect produced by the isoflavone genistein is antagonized by tamoxifen, a non-selective antagonist of the β-oestradiol receptors [7]. The aforementioned facts support the idea that isoflavones activate the β-oestrogen receptor which play a important role in the anxiolytic effects produced by natural oestradiol and other oestrogenic synthetic compounds [81]. In this way, these data support the hypothesis that phyto-oestrogen could be a possible therapeutic alternative in the natural management of anxiety disorders in menopausal women. In support, clinical studies have shown that administration of 34–100 mg/day of isoflavones from soya reduces the typical symptomatology of menopausal women: principally, vasomotor problems [82]. In other studies, the administration of isoflavones to menopausal women also reduces symptoms of anxiety and depression disorders [38, 58, 83].

In an early study, the effect of an aqueous extract of *Montanoa tomentosa* in rats with a long-term absence of ovarian hormones was evaluated [84]. In this study, the acute administration of the extract produced a significant reduction of anxiety-like behaviour when rats were evaluated in the elevated plus maze. These findings are interesting because the traditional use of this plant extract had been recommended in the ancient traditional medicine from México, as it was described in the *Badianus Codex* or *Libellus de Medicinalibus Indorum Herbis* (1552). It supports the potential use of this extract in the future as a natural alternative to ameliorate anxiety symptoms related with changes in ovarian hormones [84, 85].

In short, the aforementioned data indicate that ovariectomy in rats produces long-term behavioural and physiological changes that mimic the symptoms that occur in women who have undergone surgical menopause, and permit the exploration of possible therapeutic alternatives at an experimental level to ameliorate emotional and affective disorders associated with the long-term absence of ovarian hormones.

9. Conclusion

Anxiety disorders are strongly associated with natural and surgical menopause, principally due to the prolonged absence of oestrogen concentration levels in plasma and the brain. Anxiety is related to hot flashes in most of clinical studies. Finally, preclinical and clinical research suggested that the long-term absence of ovarian hormones associated with natural or surgical menopause is the principal cause of physiological and psychiatric disorder in the women; therefore, oestrogenic compounds seem to play a important role in the maintenance of the brain structures that regulate anxiety, mood, memory, and cognitive functions in menopausal women. Despite advances in the development of diverse therapeutic schedules to ameliorate typical physiological and psychiatric symptoms associated with natural or surgical menopause, we still lack of an efficient treatment to ameliorate symptoms of menopause. The actual therapeutic schedules are partially effective, but they produce some side-

effects that limit their use in sensitive women. In consequence, alternative therapies based on the use of natural products, such as isoflavones, are in an experimental phase, but the data suggest that they could be used in the future as alternative therapies to ameliorate symptoms of natural and surgical menopause.

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