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# Depression and Serotonergic Changes during the Climacteric and Postmenopausal Stages: Hormonal Influences

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Additional information is available at the end of the chapter

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## Abstract

Depression is a psychiatric disorder that affects a high percentage of women. Most of the depression disorders turn up during the premenopause and perimenopause stages when the hormonal oscillations make an impact in the brain function principally on the serotonergic system, which is related to neurobiology of depression. 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors change on functionality and density in afferent areas related to emotional modulation and increased serotonin clearance, and the binding potential of serotonin transport has been related to the underlying mechanism of the depression during the climacteric or postmenopausal stage. Some findings have been proven on preclinical studies. These studies on animals have recognized how estrogen treatment activates intracellular signaling pathways as mitogen-activated protein (MAP)/extracellular signal-regulated kinase (ERK), tyrosine kinase brain-derived neurotrophic factor receptor (TrkB), insulin-like growth factor-1 receptor (IGF-1R), phosphatidylinositol 3-kinase (PI3)/serine/threonine-specific protein kinase (Akt), and metabotropic glutamate receptor 1 (mGluR1) which interact with the serotonergic system to allow establishment of the estradiol effects on mood regulation. Thus, the interaction between the woman's reproductive status and the serotonin changes could be useful to create prevention strategies, early diagnosis, and medical treatment of climacteric and postmenopausal women with depression, in order to improve their quality of life.

**Keywords:** depression, menopause, climacteric, 5-HT<sub>1A</sub> receptor, 5-HT<sub>2A</sub> receptor, estradiol

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1. Introduction

Depression is one of the most common psychiatric disorders that affect approximately 4.84% people around the world, and it is considered to be one of the principal causes of disability worldwide [1]. According to the Global Burden of Disease study report in 2015 [2], the highest rates of disability-adjusted life years (DALYs) worldwide are established on women aged 15–49 years with 5.65%, followed by 50–69 years old women with 2.98% and 70 years old with 1.26%. DALYs represent the years of life that are adjusted by a certain level of disability experienced during a particular period of time, related to depressive disease. It supports studies which demonstrate that most of the depression disorder comes out during the premenopause and perimenopause stages.

During the beginning of menopausal stage or in the postmenopausal stage, women are more susceptible to suffer depression disorder with more severe and longer symptoms [3, 4]; severity of depression has been related to the ovarian hormone oscillating levels in the premenopause and very low levels in early postmenopause, specifically with estrogens [5].

The climacterium stage is a period of time that includes the perimenopause, premenopause, and menopause (see **Figure 1**); in this stage the women estrogenic oscillating, produces a dysfunction on the serotonergic neurotransmission system which is related to the high prevalence of depression in such stages compared with women in postmenopausal stage. However, this relationship seems to be controversial because not all the studies reported an increased prevalence of depression in the climacteric stage, when women’s groups from different ethnic cultures, ages, school grade, and civil status, among others, were evaluated. These divergences on the clinical study results could be partially justified by different neurochemical changes related to the effects of estradiol on serotonergic system and the influence of these changes on the establishment of depression during the different stages of the climacteric period. For example, on early premenopausal stage, there is a decrease on the 5-HT1A autoreceptors in raphe, which is a brain structure responsible for the serotonin (5-HT) synthesis, and an increase on the 5-HT1A postsynaptic receptors located on the hippocampus (both receptors enable the antidepressant clinically effective, as the selective inhibitors of the serotonin, e.g., the fluoxetine) related to the high hormonal concentration compared with postmenopausal women [6].

				Climacterium						
				Premenopause	Perimenopause					
STAGE	REPRODUCTIVE				TRANSITION TO THE MENOPAUSE			POSTMENOPAUSE		
Phase	Early	Peak	Late		Early	Late	Menopause	Early	Late	
Duration	Variable	Variable	Variable	Variable	Variable	1 - 3 years	1 year	1 year	3-6 year	Till the end of life

**Figure 1.** Classification of the reproductive phases of the woman. This classification is an abstract of the reproductive stage of women with their approximate duration. Ovarian function markers and hormonal levels can help to make a correct classification. Modified from [57].

Thus, this can be related with the different antidepressant responses along the climacteric and postmenopausal stages.

The 5-HT<sub>2A</sub> receptors located on brain areas such as prefrontal cortex contribute on regulating the release of the 5-HT to areas that modulate the amygdala reactivity, brain structure involved to the emotional regulation. Treatment with 17 $\beta$ -estradiol for postmenopausal women increases the 5-HT<sub>2A</sub> receptors in prefrontal cortex [7]. However, the possible association between the establishment of depression in different climacteric and postmenopausal stages with the 5-HT<sub>2A</sub> receptor's activity has not been explored. Nevertheless, the preclinical data support the involvement of these receptors on the regulation of the depression disorder [8, 9].

On the other hand, in healthy postmenopausal women, there is a relation between personality features such as extroversion, aggressiveness, and neuroticism with the serotonin transporter (5-HTT). 5-HTT promotes polymorphism with "s" allele, which implies 5-HTT low expression and an increase in the impulsivity. Likewise, this trait is related with monoamine oxidase A (MAO-A) polymorphism that produces an increase of climacteric and depressive symptoms [10, 11]. In contrast, women under 50 years old with the "l" allele 5-HTT present a better antidepressant response and neural protection against the suicide attempt [12]; however, this response disappears when there is a low hormonal activity during menopausal stage [13].

Therefore, the main objective of this work is to collect and review scientific data not only clinical but also preclinical data that allow us to explain the knowledge about the impact of hormonal change experienced during climacteric and postmenopausal stages and how it affects serotonin neurotransmission that may contribute to the establishment of the depression disorder and the therapeutic response to antidepressant drugs.

## **2. Influence of hormones on the depression disorder establishment**

Some researches point out a high vulnerability to suffer depression disorder on the women reproductive stage, related to the hormonal changes, as a decrease on the estradiol levels and an increase on the follicle-stimulating hormone (FSH) levels on the perimenopausal [3, 14, 15] throughout different reproductive stages it is set basically two different aspects about the hormonal influences, principally estradiol with the increasing risk to set out depressive symptomatology. The first one establishes that low hormonal concentrations on estradiol and progesterone during the earlier follicular stage of the menstrual cycle of the earlier productive stage of a woman are related to premenstrual dysphoric syndrome characterized among some other symptoms by depression and anxiety [16]. The second one suggests that oscillations on the hormonal levels on early stages of the menopause transition are determinant to increase the risk of having some depressive incidences. The same effect is observed on women who had been throughout menopause by surgical procedure, thus, became on the decrease of the hormonal levels, and also there is a surgical post-period where they show hormonal oscillations because the renal glands try to supply the hormonal

lost, but it is important to mention that women who had been in a surgical procedure, such as oophorectomy on early age, indicate an increased probability to depression disease with severe and longer symptoms compared to women with a natural menopause [17].

There is a relationship at the establishment on depressive symptomatology with FSH or high luteinizing hormone (LH) levels and low inhibin B levels; this is a glycoprotein hormone secreted by theca and granulosa cells from the pre-antral and antral follicles that was responsible for the inhibition of FSH production at the level of the pituitary gland and a huge variability on estradiol levels, which occur during the menopause transition that includes women on the premenopause and perimenopause [2, 3]. Likewise, there is a FSH levels increasing and an abrupt fall of the estrogen levels after 12 months of menopause considered as early postmenopausal [18] pattern, which is independently from the sample analyzed on the late premenopausal and postmenopausal stage. Those hormonal variations are related to a rise on depression prevalence for 10 years before and 8 years after the last menstrual cycle and fall on the late postmenopausal period [4]. The above suggests that alterations in the feedback of the hypothalamic-pituitary-gonadal axis consequence of changes on the concentrations of ovarian hormone through the climacteric and postmenopausal stages, carry out a fundamental place on women's emotional stability, through the regulation of brain plasticity and neurochemical changes.

It has been established an association between a delay in appearance of menopause transition, in a period of two more years than average with 2% of decrease on the risk of a depression disease during the postmenopause, and also a reduction of the 50% to suffer depression disease on women who have menopause after 40 years old compared with early menopause on women before that age. It is suggested that those findings could be attributed to longer exposure to the endogenous estrogens that develop a neural protection and antidepressive effect [19]. This effect seems to be associated with the cerebral changes that induce the hormonal diminution according to the age of the woman.

The antidepressant effect on hormone replacement therapy (HRT) or estrogenic therapy on menopausal women is controversial. The estrogen supply such as 17 $\beta$ -estradiol (100  $\mu$ g/day) has a lack of antidepressant effects on depressed women during the postmenopausal period on the late stage; it is to say that, 17 years after the menopausal stage, they show a FSH ( $\geq 40$  pg/ml) and estradiol ( $\leq 19.7$  pg/ml) hormonal concentrations [20]. This lack of antidepressant effect is also observed in postmenopausal women in the early phase, approximately 6 months to 3 years after menopause, with hormonal concentrations of FSH  $\geq 35$  pg/ml and estradiol  $\leq 40$  pg/ml, when 50  $\mu$ g/day or 84  $\mu$ g/day of estradiol was administered [7, 21]. The loss of estrogen efficacy against depression in women with postmenopausal may be associated with the downregulation of  $\alpha$ - and  $\beta$ -estrogenic receptors at the brain level, caused by continued decrease of plasma estradiol concentrations. In contrast, antidepressant effects have also been reported in postmenopausal women with replacement treatments with bioidentical hormones (80% estriol/20% estradiol; 0.25 to 0.5 mg) and/or progesterone (20 to 60 mg), by transdermal injection in a volume of 1 ml/day for a period of 8 weeks. These women present an improvement in the depressive and anxiety symptoms according to Hamilton scales, at 2 months of treatment and annually until 36 months. Treatment with bioidentical hormones improved the health and quality of life of



women without reports of adverse side effects. However, these women cursed postmenopausal, after an oophorectomy with a mean age of  $52.3 \pm 9.6$  years and the time that elapsed since the surgery was not described, so it cannot be specified whether it was in the early or late stage of postmenopause [22]. This suggests that the type of molecule used for hormone replacement therapy and probably the age at which it is given could determine therapeutic success, a possibility that remains to be explored.

Changes in plasma levels of FSH on the establishment of depression in women with natural menopause are also seen in women with oophorectomy [23]; since the ovaries are removed, there is an abrupt cessation in the production of testosterone that is aromatized to estrogen and estradiol, which results in a dysfunction in the hypothalamic-pituitary-gonadal axis increasing FSH and LH levels, with the consequent decline of estradiol and progesterone levels [24]. These changes in hormone levels undergoing surgery take from 2 to 3 months to stabilize and are associated with a decrease in depressive symptoms [23]. Women undergoing menopause induced by surgeries such as hysterectomy and/or oophorectomy increase up to four times the probability to suffer postsurgery depression [25]. However, women who have undergone some depressive episode prior to surgery report a decrease in postoperative depressive symptomatology [25]. This may reflect a paradoxical effect. Some of the answers might be in the interrelation between estrogen and the serotonergic system.

### **3. Serotonergic alterations during the climacteric and postmenopause related with depression**

A study by Stein et al. [6] detected an increase on 5-HT<sub>1A</sub> receptor levels in the hippocampus and a decrease in the dorsal nucleus raphe of premenopausal women at early ages ( $24.1 \pm 2.6$  years) compared to postmenopausal women ( $55.2 \pm 4.8$  years). In this same study, they identified higher concentrations of progesterone, estradiol, dehydroepiandrosterone sulfate (DHEAS), and cortisol in premenopausal women compared to postmenopausal women. This suggests that these hormones could be involved in the regulation of the expression of 5-HT<sub>1A</sub> receptors in different brain areas in women who travel through the climacteric, intervening in the establishment of depressive disorders of this stage, as well as in the different therapeutic responses to antidepressant drugs, and probably contributing to the effect of drug resistance, depending on the levels of receptors affected by oscillations on concentrations of hormones, mainly produced by the ovaries.

Studies made with positron emission tomography with [carbonyl-C<sup>11</sup>] WAY-100635 show that in the dorsal nucleus raphe, a structure highly involved in the regulation of serotonergic neurotransmission and therefore with a high density of 5-HT<sub>1A</sub> receptors, there is 1.5 times more 5-HT<sub>1A</sub> receptors in the luteal phase than in the follicular phase in healthy women, whereas this proportion is not observed in women with premenstrual dysphoric disorder [26], so a dysfunction like this could be a factor underlying to the establishment of depressive symptoms. Although Drevets et al. [27] reported a reduction in 5-HT<sub>1A</sub> receptors in the raphe (41.5%) and neocortical and limbic areas (25–33%) in depressed patients [27]. In this study the

sex of the patients was not discriminated, and only from 4 to 7% of the patients were women and do not described the age neither conditions of the reproductive phase, so these results should be taken with reservation.

Moses-Kolko et al. [28] reported that in depressed women going through premenopause and postmenopause, there is a 15% decrease in 5-HT<sub>1A</sub> receptors in the orbitofrontal cortex compared to adult men with depression. The foregoing after performing an endocrine standardization to minimize the influence introduced by endogenous hormonal fluctuations and reproductive stage. They also detected an increase in the potential binding to 5-HT<sub>1A</sub> receptors in women, as age increases. They estimate that there is a 4.5% reduction per decade of age in the number of 5-HT<sub>1A</sub> receptors in the raphe in women. The 5-HT<sub>1A</sub> receptors have an age-dependent increase in neocortical regions in women, associated with decreased estrogen. In the same study, they identified that increase in 5-HT<sub>2A</sub> receptors is associated with the establishment of disorders such as neurosis, depression, suicide, and eating disorders [28], suggesting that age tends to reduce these receptors, since they are expressed in the neuropil of pyramidal neurons located mainly in the neocortex which are related to the release of glutamate and gamma-aminobutyric acid (GABA) regulating the postsynaptic excitatory impulses that project to the hippocampus and spinal cord neurons [29]. So, it is hypothesized that its reduction associated with age may be related to sleep disorder, cognition, and mood disorders [30].

#### **4. Serotonergic changes associated to antidepressants and hormone replacement in the climacteric and postmenopause**

The HRT in women undergoing climacteric, with 17 $\beta$ -estradiol by means of transdermal patches at a mean dose of 93  $\mu$ g/day, causes an increase in plasma levels of estradiol from 14.7 pg/ml at baseline versus 176.5 pg/ml, after 10.2 weeks of treatment. This increase in estrogen levels has been related to the establishment of antidepressant effects after HRT [7]. However, several studies suggest that estrogens have the capability to produce a modulating effect on the serotonergic system that contributes to the establishment of the antidepressant effect (see **Table 1**).

In surgically postmenopausal women (58.4 age and 7.5 years after oophorectomy) and, therefore, with very low plasmatic concentrations of estradiol, the treatment with estradiol reduces the potential binding of 5-HTT in brain structures, such as in the amygdala, in the frontal cortex, and in various cortical regions. While the treatment with estradiol and testosterone reduces it in the parahippocampal gyrus, insular cortex, caudate nucleus, and thalamus [31]. Hence, the hormonal treatment reduces the efficiency of 5-HTT and increases the availability of 5-HT in the synaptic cleft on structures involved in the emotion modulation. This fact could be associated to an improvement in depressive symptomatology of these women measured with Beck Depression Inventory test [31]. However, some studies indicate that estrogen therapy in postmenopausal women does not produce antidepressant effects [21, 24], probably due to the downregulation of estrogenic receptors, associated with chronic decrease of

*Changes associated to condition without pharmacological treatment*

Condition (average age)	Serotonergic system	Hormonal changes	References
Premenopausal women (24.1 ± 2.6 years) vs. postmenopausal women (55.2 ± 4.8 years)	↑ 5HT1A receptor levels in the hippocampus ↓ 5HT1A receptor levels in the dorsal raphe	↑ Levels of progesterone, estradiol, dehydroepiandrosterone sulfate (DHEAS), and cortisol	[6]
Premenopausal depressed women (<50 years) Postmenopausal depressed women (>50 years)	↓ Postsynaptic 5-HT1A receptors in neocortical regions Increasing age was associated with ↑ postsynaptic 5-HT1A receptor binding potential in neocortical regions Significant decline in 5HT2A receptor binding potential relative to age (8% per decade)	Low estradiol concentrations and low 5HT1A receptor binding potential	[28]

*Changes associated to condition and estrogen replacement therapy*

Condition (average age)	Serotonergic system changes	Regimen of treatment and/or changes associated to treatment	References
Surgically postmenopausal women (58.4 ± 4.7 years) Hysterectomy and bilateral oophorectomy	↓ The binding potential of 5-HTT in the amygdala, parahippocampal gyrus, insular cortex, and frontal cortex and in various cortical regions	Positive correlation between estradiol levels and the binding potential of 5-HTT in putamen, frontal cortex, and amygdala Negative correlation between testosterone levels and the binding potential of 5-HTT in the anterior cingulate cortex, hippocampus, caudate nucleus and thalamus	[31]
Postmenopausal women (54.5 years, 44–68 age range)	↑ 5-HT2A serotonergic receptors mainly in brain areas such as the right inferior prefrontal cortex, anterior cingulate cortex, and medial and inferior frontal gyrus	Transdermal patch (17β-estradiol, 0.075–0.15 mg; mean dose=0.084 mg for a mean of 10.2 weeks Negative correlation between estradiol levels and 5HT2A receptors	[7]
Postmenopausal women (55 ± 4.8)	No significant differences in 5-HT1A binding potential values	Combination 17β-estradiol valerate (Progynova® 21 mite; 2 mg/day, v.o.) and micronized progesterone (Utrogestan®, 200 mg/day, v.o.) for 67 ± 8 days Increase in estradiol and progesterone plasma levels	[56]
Female rats (2–3 months) Five postovariectomy days	↓ The time of 5-HT1A receptor desensitization of 7 days with fluoxetine and 2 days with estradiol + fluoxetine	17β-Estradiol-3-benzoate (0.01 mg/0.4 ml/kg, s.c.) plus fluoxetine (10 mg/2 l/kg, s.c.)	[37]
Female rats (2 months) Two months of postovariectomy	↑ 5-HT level in raphe	Estradiol benzoate (2.5 µg/kg/0.1 ml, s.c., day of ovariectomy; 5 µg/kg/0.1 ml, s.c., weekly; 20 µg/kg/0.1 ml, s.c. day of the test) + Progesterone (2 mg/kg/0.1 ml, s.c., 48 hours before the test)	[40]



*Changes associated to condition and estrogen replacement therapy*

Condition (average age)	Serotonergic system changes	Regimen of treatment and/or changes associated to treatment	References
Female rats (1–2 months) 2–3 weeks of postovariectomy	Slowing of the 5-HT clearances, as well as an inhibition of the ability of fluvoxamine (SSRI antidepressant) to slow the clearance of 5-HT	Acute administration of both 17 $\beta$ -estradiol in the CA3 region of the hippocampus and systemic administration of estradiol benzoate (25 $\mu$ g/100 $\mu$ l, s.c., 48 hours before progesterone) + progesterone (500 $\mu$ g/100 $\mu$ l, s.c., 24 hours before the test)	[41]
Female rats (2–3 months) 2–3 weeks postovariectomy	Canceled the antidepressive-like effect of fluvoxamine (10 mg/kg) in forced swim test	Estradiol benzoate (25 $\mu$ g/100 $\mu$ l, s.c., 74–75 hours before the test and 24 hours before progesterone) + progesterone (500 $\mu$ g/100 $\mu$ l, s.c., 24 or 74–75 hours before the test)	[42]
Female rats (4 months) Two weeks of postovariectomy	Inhibits the 5-HTT	Estradiol (20 pmol) in the CA3 region of the hippocampus but not in 10 months in females, even at <40 pmol doses	[51]

5-HTT, serotonin transporter; 5-HT, 5-hydroxytryptamine;  $\uparrow$ , increase;  $\downarrow$ , decrease; SSRI, selective serotonin reuptake inhibitors

**Table 1.** Clinical and preclinical studies of the relation between serotonergic system and hormones.

concentrations of estradiol in the postmenopausal stage. This hypothesis is based on the fact that estrogenic antidepressant treatment on perimenopausal women produces therapeutic effects [32], probably because they still have considerable concentrations of estradiol, compared to postmenopausal women, which contribute that they do not present important neurochemical changes on estrogen receptors. In support, depressed postmenopausal women treated simultaneously with the combination of antidepressant serotonin-specific reuptake inhibitor drugs, such as fluoxetine with estrogen, showed significantly greater improvement of both mood and quality of life compared to fluoxetine monotherapy [33]. Pointing out that estrogen by itself probably does not produce antidepressant effects, the reduction that exerts on the potential binding of 5-HTT is enough to increase synaptic 5-HT concentration, a synergistic effect on serotonergic system of both estrogen and fluoxetine, which contributes to the establishment of the antidepressant effect. Paradoxically, the combination with tibolone, a synthetic steroid, does not produce synergistic antidepressant effects with fluoxetine [34]. The above suggests that substituents on steroid molecules could be a determinant in the potential interrelation in therapeutic efficacy between steroids and the serotonergic system.

On the other hand, some studies observed an increase on hypersensitivity of postsynaptic 5-HT<sub>2A</sub> receptors on the basis of neurobiological depression [35, 36]. The 5-HT<sub>2A</sub> receptor is related to regulating the 5-HT release on the protection of neurons which are located on the prefrontal cortex, thus, to help the regulation easier to the amygdala's reaction and some other behaviors related. The administration of 150 mg/day of clomipramine for 3 weeks, tricyclic antidepressant, results a descend of 5-HT<sub>2A</sub> receptor's occupation on neocortex area,

calculated by positron emission tomography (PET) which coincide with depression scores significantly improved, denoting the probability of the clomipramine's interaction with those receptors or may cause modified signal mechanism of these receptors [37].

There is a relationship with ovarian hormone and the 5-HT<sub>2A</sub> receptors. Kugaya et al. [7] developed a study on postmenopausal women, classified by the concentrations of FSH  $\geq 30$  UI/L. Those women were treated with 17 $\beta$ -estradiol HRT for almost 3 months; by PET that 5-HT<sub>2A</sub> serotonin receptors increased principally on brain areas such as prefrontal cortex and anterior cingulate cortex, related to increase of plasmatic estradiol density, this study did not mark any changes related to the effects on the mood but could be the result related to the test characteristics and the few subjects of study [7].

## 5. Preclinical studies of serotonergic changes associated with hormones and ovariectomy

Studies made in rodents have also shown the interrelation between estrogen and serotonergic system. Coadministration of estradiol with fluoxetine has been shown to contribute to 5-HT<sub>1A</sub> receptor desensitization [38], which is associated with antidepressant effect in humans and in rats evaluated in behavioral despair models [38]. In addition, this combination of estradiol with fluoxetine inhibits 5-HTT and increases de novo brain serotonin synthesis by activating tryptophan hydroxylase enzyme [39]. At the same time, it increases the number and sensitivity of the 5-HT<sub>1A</sub> receptors, mainly in the dorsal nucleus raphe of rats. This could be related to the antidepressant effect produced by estradiol.

It has also been detected that acute administration of estradiol on ovariectomized rats increased the turnover of serotonin, by increasing serotonin and its metabolite, 5-hydroxyindoleacetic acid (5-HIAA) in amygdala and striatum involved in the mood regulation. While chronic for 16 days, estradiol and progesterone administration has been found to increase serotonin mainly in the dorsal raphe of the ovariectomized rats [40].

Benmansour and collaborators' research group [41] has explored the signaling mechanisms involved in the interaction of estradiol and serotonergic systems in rats. Both acute administration of 17 $\beta$ -estradiol in the CA3 region of the hippocampus and systemic administration of estradiol benzoate cause slowing of the 5-HT clearances, as well as an inhibition of the ability of fluvoxamine to slow the clearance of 5-HT [41]. These effects are mediated by estrogen receptors  $\alpha$  and  $\beta$ . The slowing of the 5-HT clearance was due to activation of  $\beta$ -estrogen and/or GPR30. Meanwhile, the blockade of fluvoxamine's inhibitory effect on 5-HT clearance was mediated by  $\alpha$ -estrogen [42]. Both of them used different signaling mechanisms. The estradiol-induced slowing of serotonin clearance by means of activation of receptors of  $\beta$ -estrogen required MAPK/ERK1/2 signaling pathways and involved interactions both with tyrosine kinase BDNF receptor (TrKB) and insulin-like growth factor-1 receptor (IGF-1R). The effect of estradiol to prevention of the ability of fluvoxamine to slow serotonin clearance, through receptors of  $\alpha$ -estrogen, required MAPK/ERK1/2 and PI3K/Akt signaling pathways as well as interactions with both IGF-1R and mGluR1 [43]. All these ways are etiologically implied to depression.

In this context, the ERK signaling cascade is activated by antidepressant clinically effective as fluoxetine [44] and the systemic blockade of the MAPK pathway in mice produced depressive-like behavior in several animal models of experimental depression as well as inhibits the antidepressant effect of desipramine and fluoxetine in the forced swim test, a main model of depression [45]. On the other hand, the action of BDNF, which has been implicated in the mechanism(s) of action of the antidepressant (see Ref. [46]), is mediated through its high-affinity tyrosine kinase receptor B (TrkB), whose activation is required for antidepressant-like effect [47].

The acute intraventricular administration of IGF-1 produced antidepressant-like effects in mice evaluated in the tail suspension and forced swim tests [48], an effect detected after 3 days of the administration with participation of 5-HT [49]. The antagonism of the mGluR produced antidepressant-like effects in the forced swim test, probably through the intracellular signaling pathways described above [50]. Therefore, there is evidence about the interaction with the estrogens and the serotonergic system on the regulation on the depression disorder not only removing them but also influencing them by the other neurotransmitter systems and other kinds of receptors.

We have already mentioned the difference between the plasmatic estradiol levels during the climacteric stage that is related to the establishment of the depression disease and the antidepressant responses. We have also mentioned that estradiol slows the clearance of 5-HT and at the same time disables the same effect produced by fluvoxamine per se. In this sense during the rat estrous cycle, it has been shown that both estrous and diestrus phases are characterized by low estradiol levels in comparison to the proestrous phase; the fluvoxamine increases the clearance time of 5-HT, but not in the proestrous phase [41]. Rats with 2–3 postovariectomy weeks, it is observed that fluvoxamine increases the clearance time of 5-HT, the same effect caused by the estradiol benzoate treatment. However, the pretreatment with estradiol benzoate blocks the fluvoxamine effect [41].

Additionally evaluated the estradiol effect on the 5-HTT functionality, through time a clearance of the 5-HT, in different ages and postovariectomy time identifying that microinjection of 20pmol of estradiol on CA3 region in the hippocampus to inhibit 5-HTT in young adult rats (4 months age) after 2 weeks from the postovariectomy, but had not effect in middle-age rats (10 months), even with the use of <40 pmol dosage. While fluvoxamine reduces the clearance of 5-HT on rats about 10 months aged with 2 weeks, 4 and 8 months postovariectomy the same way as the 4 months rats [51]. Additionally, they detected that 5 µg/day of estradiol for 2 weeks subcutaneously via implantation of osmotic minipumps produces antidepressant effects on forced swim test on 4-month aged rats but not in 10-month aged rats both with 2 weeks of postovariectomy. Nevertheless the dosage of estradiol for 10 µg/day produces an antidepressant effect after 2 weeks of the postovariectomy procedure, but not at 4 months of postovariectomy in 10-month aged rats. The same dosages produced the same antidepressant effect on older rats (14 months of age) after 2 weeks of postovariectomy. The authors conclude that the lack of an antidepressant effect in estradiol is due to the 4-month hormone withdrawal and not to an age effect. Also in the same study, they reported that 2 weeks of treatment with sertraline, an antidepressant selective serotonin reuptake inhibitors (SSRI), on

rats from 4 to 10 months of age with 2 weeks, 4 months, and 8 months of postovariectomy produce antidepressant effect in the forced swim test. In this study, it is concluded that the age influences the potency of estradiol on the 5-HTT, but its effects were strongly reduced if the period of postovariectomy is longer. On the other hand, the treatment with sertraline inhibited the 5-HTT and produced antidepressant-like effects without affected either by age or length of hormonal depletion [51].

In support to clinics finding about 5-HT<sub>2A</sub> receptors above mentioned some animal studies it has been observed that the administration of 5-HT<sub>2A</sub> receptor antagonist, i.e., ketanserin (0.1 mg/kg, i.p., 14 days) produces antidepressant effects in forced swim test and anxiolytic effect in elevated plus-maze test both in the proestrous and estrous phases of estrous cycle, characterized by high concentrations of progesterone and estradiol. In contrast, produces anxiogenic effect in phases with reduce concentrations of estradiol [52]. It is suggested that 5-HT<sub>2A</sub> receptors play different roles on the modulation of anxiety and depression associated with the alterations of hormonal concentrations during the ovarian cycle. In contrast, ketanserin administered in the same doses (0.1 mg/kg, i.p.) for 7 days in male rats produces an antidepressant-like effect, and together with the antidepressant fluoxetine (5 mg/kg, i.p., 7 days), it potentiates the antidepressant effect in forced swim test [53]. This suggests that the effect of ketanserin on females goes beyond changes in hormonal concentrations, which requires exploration.

Previous searches suggest that different hormonal levels, which vary through different reproductive statuses on women, may cause some changes on serotonergic system. For example, density and potential binding of the 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors, as well as the potential binding of the 5-HTT in different brain structures linked to the mood changes, may contribute to the depression establishment. Those disruptions on the serotonergic system may influence or modify negatively the success of therapeutic response treated with antidepressant drugs or HRT; there is one possibility that must be explored.

### 5.1. Pharmacological response prediction: 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors

Pharmacological compounds that take action on 5-HT<sub>1A</sub> receptors such as SSRI are clinically effective antidepressants but require a period of 3–6 weeks of treatment to establish the therapeutic effects [54]. Additionally, 50 to 70% depressed patients respond to the first pharmacological treatment, and less than 40% get a total remission [54]. Combination of SSRI with 5-HT<sub>2A</sub> receptor antagonist makes the latency period shorter for the establishment of antidepressant effect [55]. This fact suggests that the stimulation of 5-HT<sub>1A</sub> receptors by SSRI and the inactivity of 5-HT<sub>2A</sub> receptors, which are part of the serotonin release on limbic areas, produce synergism effect. Therefore, the alteration in the expression of receptors in different brain areas, associated with variations of hormones such as estradiol, mainly in the stages of the climacteric, can influence the pharmacological response to antidepressants.

There are controversial data related to regulatory mechanism, which are exerted to antidepressant treatments on the 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptor density. A study developed by



Kranz et al. [56] did not detect differences on the 5-HT<sub>1A</sub> receptor density on structures such as the hippocampus, the frontal cortex, and the raphe on postmenopausal woman [56]. After the administration of HRT with 17 $\beta$ -valerate ester alone or combined with progesterone, no matter the fact exist, a significant increase of estradiol and progesterone, an effect that has been identified on postmenopausal women [28]. This suggests that plasma concentrations of estradiol that are still elevated in premenopausal women compared to postmenopausal women seem to determine the 5-HT<sub>1A</sub> receptor expression on the estrogenic treatment response.

## 6. Final comments and conclusion

Variations in the levels of ovarian hormones that occur throughout the stages of climacteric and postmenopause severely impact women's mood. The depression is found mainly in the stages with continuous hormonal oscillations like perimenopause and premenopause. However, the relationship between hormonal and serotonergic systems in the climacteric and postmenopausal stages needs to be explored. The neurochemical and neurophysiological modification consequence of the oscillating hormonal levels leads to alterations in the cerebral neurotransmission functioning, mainly on the serotonergic system of the 5-HTT, 5-HT turnover, and 5-HT<sub>1A</sub>/5-HT<sub>2A</sub> receptors. This affects the pharmacological response to antidepressant treatments, both with estrogen therapy and with SSRI or tricyclic drugs in the different climacteric and postmenopausal stages.

The limitation on the studies have contributed to the establishment of these hypothesis emerged by the reduced length of women included in the studies and the wide range of ages which is used, because these incorporate women who are in different stages and different reproductive status and also women going through induced oophorectomy postmenopausal on early ages. Also, the lack of quantification of the hormonal levels, principally estradiol, FSH, and the ovarian function markers such as inhibin B, antral follicle count, anti-Müllerian hormone, and the estradiol levels. There is a direct relationship between advanced age and elevated serum basal levels which is associated with poor ovarian response. However, additional studies are needed to support these findings because it should let us categorize effectively those women on their reproductive stage. Thus, it allows us to establish a correct reciprocity between the serotonin changes and evaluated stages.

In addition, some limits in the imaging studies (e.g., PET), which are difficult to correct analysis on small brain structures or markers used, are not always selective to serotonin receptors, principally 5-HT<sub>2A</sub> receptors. It is also necessary to extend the researches related to serotonin changes on women with some depressant disorder, as major depression on all the reproductive stages, because some recent studies are only used to evaluate the symptomatology improvement on menopause, as somatic, urogenital, or physiologic symptomatology. On the last one, the symptomatology causes low motivation but without depression diagnosis, which limits the exploration of the neurochemical alterations that underlay to the depressive disorder on many different reproductive stages.

There are two areas that have been explored yet; the first one is nonsymptomatic women, thus, probably related to the hormonal levels through the reproductive stages and the correlation with



brain serotonergic function, and also women through oophorectomies on early ages or ovarian failure (both under 40 years old). Women through an abrupt fall on ovarian hormone and some studies point out a high prevalence of depressive disorder longer and severe. Data may contribute to possible genetic factors, biological, psychosocial, and environmental, which are related to the establishment of the depressive disorder on different climacteric and postmenopausal stages.

In conclusion, depression associated to climacteric and postmenopausal stages involves changes in the serotonergic system, which includes an increase in the 5-HT clearance, turnover of 5-HT, and affinity of 5-HTT, as well as increased expression of 5-HT1A and 5-HT2A receptors in different brain regions (i.e., prefrontal cortex and hippocampus). All these changes seem to be a result of the oscillations in the ovarian hormone concentration characteristics of the climacteric and postmenopausal stages.

## Conflicts of interest

The authors declare no conflicts of interest.

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