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Estrogen and Transdiagnostics: A Systematic Review

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Abstract

Objective: To evaluate, through systematic review, whether the role of estrogen influences the onset of disorders in anxiety and depression. Data Sources: The search was performed in two databases, ISI Web of Science and PubMed, using the terms estrogen, anxiety and mood.

Study selection: The search produced 1060 references. Those that were repeated or not written in English were excluded. After analysis of the abstracts, 38 were selected to have their texts read, of which 18 were chosen for the execution of this review.

Data collection: The PubMed and ISI Web of Science articles were extracted in June 2015. Moreover, the study was also restricted to articles that involved adult patients and were elaborated between 2005 and 2015.

Results: There were six case-control observational studies, followed by four randomized clinical trials. The results in smaller quantities in the review were: three retrospective cohort observational studies and three cross-sectional studies, followed by one prospective cohort observational study. A letter to an editor was also included. The result that stood out in the review was the finding that women are twice as likely to suffer from disturbances of anxiety or mood, such as generalized anxiety disorder, panic disorder, post-traumatic stress disorder and bipolar disorder.

Conclusion: Some women there is a greater vulnerability to hormonal oscillations of estrogen (in pre-menstrual and postpartum periods and in the pre-menopause) leading to the aforementioned disorders.

Keywords: Estrogen; Mood disorders; Anxiety disorders

Introduction

The estrogen hormone is defined as being responsible for the control of ovulation and for the development of feminine characteristics. It works like a kind of energy supplement. It is a known fact that women are more likely to report symptoms of depression and anxiety during premenstrual, postpartum and perimenopausal periods, when estrogen levels are low [1,2]. Moreover, neuroimaging studies show greater activation of neural networks involved in fear when women are scanned during the early follicular phase of their menstrual cycle (low estrogen levels) than when they are scanned mid-cycle (high estrogen levels) [3,4]. Hence, natural fluctuations of estrogen across the reproductive cycle may factor into the disproportionate incidence of PTSD in women.

The explanation for clinical differences observed between men and women might be seen, in part, in the structural and functional differences of brain regions such as amygdala, hippocampus and medial prefrontal, which contain elevated levels of estrogen receptors. Studies show that women are twice as prone to suffering from fear and anxiety disorders [5-7]. Generalized anxiety, panic and post-traumatic stress disorders are highly prevalent in this female physiological framework. One reason for this is the difference in ovarian hormones which oscillate in women during their reproductive life and alter the emotional process [5].

Apparently, some women are more susceptible to hormonal changes, for example, during pre-menstrual periods, in the post-partum period and pre-menopause, as there is an alteration in the production of this hormone, enabling an increase or a reduction. Among these women a drastic reduction in estrogen levels may increase the risk of experiencing anxiety and symptoms of depression [6,7]. Furthermore, studies indicate that, as well as regulating the reproduction and modulation of sexual behaviour, estrogen also affects various other bodily systems such as the cardiovascular and musculoskeletal systems. It is highlighted in the research that estrogen can exercise an anti-inflammatory effect on the brain [8,9]. The objective of this study is to perform a systematic review, making reference to the scientific literature on female patients with estrogen fluctuations which individuals influence the occurrence, intensity, expression of different disorders of mood or anxiety (transdiagnostic).

Sources

Searches were carried out in the ISI Web of Science and PubMed databases, utilizing the terms "estrogen", "anxiety disorder" and "mood disorder". The search was performed in May and June of 2015, with a temporal restriction of 10 years (2005-15) in both databases. Articles that were reviews or repeated were excluded, as were studies that were not available in English.

Study Selection

A total of 1060 references were found, 673 on PubMed and 387 on ISI Web of Science, among which 11 were duplicates and 52 were in languages other than English. Of the remaining 997 references, 118 were excluded by prior review, 114 for having incoherent abstracts, 727 by title and 20 by eligibility, leaving a total of 16 articles to compose this review. The eligibility criteria were the hormone physiological relation with the prevalence of the anxiety and mood disorders.

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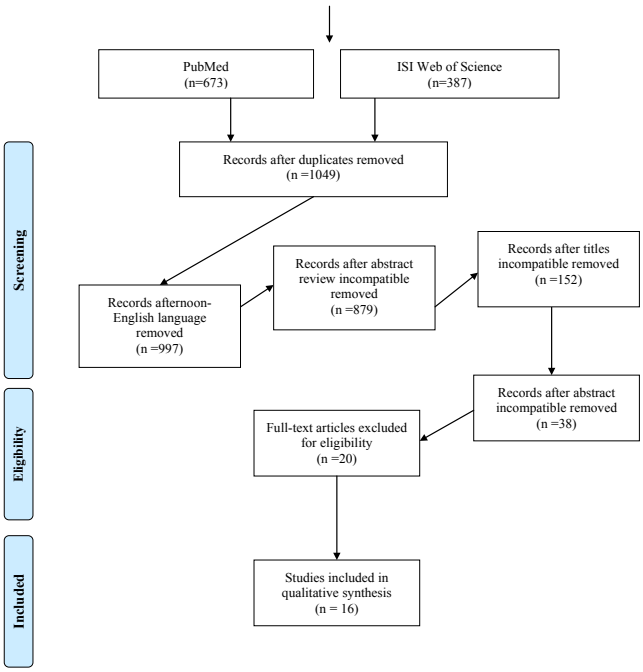

Figure 1: Articles selection in mental disorders in patients with less estrogen.

The flow chart is presented in Figure 1. Noteworthy among the published articles are those which expound on the influence of alterations in the production of estrogen on levels of anxiety and mood. The data of the 16 studies found on the theme is presented in Table 1. The results are presented after classification of the studies in accordance with the adopted design: 3 cross sectional observational studies, 3 retrospective cohort studies, 1 prospective cohort study, 5 case-control studies and 4 randomized clinical trials.

Results

Case-control studies

In 2010, Milad et al. [10] carried out a study in which they investigated the influence of sex and the phase of the menstrual cycle on recall of fear extinction in women in two different phases of the menstrual cycle (initial follicular [the beginning of the cycle] and final follicular [mid-cycle]) and in men. During the acquisition of fear on day 1, the men presented significantly greater conditioned responses than the women; though there was no difference between those at the beginning of the menstrual cycle and those in the middle of the cycle. On day 2, women at the beginning of the cycle and the men expressed a greater extinction of the memory of fear than women in the middle of the cycle. This data confirms sexual differences in the acquisition of conditioned fear, suggesting that hormones in the middle of the cycle tend to diminish the response on day 1.

In 2010, Huo et al. [11] carried out haplotype analyses of estrogen receptors alpha and beta (ESR1 and ESR2) in 91 women with prospectively confirmed Premenstrual Dysphoric Disorder (PMDD) and 56 controls. The objective was to investigate possible sources of genetic susceptibility to affective dysregulation are induced by normal levels of sexual steroids. However, the results of this study indicate that exposure to normal levels of gonadal steroids can trigger a depressed mood in women with PMDD, but not in those without a history of PMDD.

In 2011, Alonso et al. [12] carried out a study whose objective was to investigate whether variants in genes of estrogen receptors ESR1 and ESR2 may contribute to genetic susceptibility to Obsessive-Compulsive Disorder (OCD). This was done through a case-control association study which used an approach of extensive linkage between disequilibrium and mapping of the respective genotypes. A haplotype analysis was performed whereby the allelic combination rs488133 *C-rs2234693*C*G-rs9340799 (coinciding with the protector combination which was found for the three SNPs) was significantly associated with the messenger RNA levelsER1 ($p = 0.01$).

In 2012, Glover et al. [13] developed a study which indicates that women are twice as likely to develop post-traumatic stress (PTSD) than men. The results show that all the groups had equivalent levels of fear conditioning. Nevertheless, it was shown that there were significant interaction effects on extinction between highs and lows of E2 and a diagnosis of PTSD [$F(1.71) = 4.55$, $p<0.05$]. Among the women with low levels of estrogen, fear-potentiated startle was higher for the PTSD group during extinction when compared with traumatized women of the control group [$F(1.38) = 5.04$, $p<0.05$]. This effect was absent in the high E2 group.

Date	Author	Sample	Design	Summary
2005	Trent D. Lund [22]	8	Randomized Clinical Trial	The DPN treatment of rats reduced anxiety related behavior in elevated + maze. The difference was significant (P 0.01) in comparison with the treatment control.
2006	Mohammed R. Milad [37]	42	Case-Control	The analysis of variance (ANOVA) did not show a significant effect in the group on the level of shock selected at the beginning of the cycle (2.00; 0.29), in the middle of the cycle (1.86 0.18) and in masculine (2.20 0.32) participants, f (2.39) 0.537, p 0.59.
2010	Liang Huo [11]	147	Case-Control	The results of individual and family studies on PMDD suggest that it is a hereditary disorder. In thepre-menstrual period, menstrual and neurotic symptoms had different genetic and environmental determiners such that the hereditariness of the SNP wasaround 56%.
2008	Antonella Gasbarri [15]	56	Prospective Cohort	The obtained results show that the rate of errors in the follicular phase were significantly greater in comparison to the menstrual phase for facial expressions of sadness, [$F(2.53) = 3.00$, $p <0.04$] and disgust, [$\sum f(2.53) = 4.393$, $p <0.02$]. [$\sum f(2.445) = 3.29$, $p <0.002$]
2008	John Studd [23]	50	Randomized Clinical Trial	There was a remission in depression in 17 of the 25 patients undergoing treatment (68%) and in 5 of the 25 patients receiving placebo (20%). This improvement occurred regardless of the DSM-IV diagnosis.
2011	P. Alonso [12]	508	Case-Control	A haplotype analysis was carried out and it was discovered that the allelic combinations rs488133 * C-rs2234693 * C- s9340799 * G (coinciding with the protector combination which was found for the three SNPs) was significantly associated with the levels of mRNA ER1 ($p = 0.01$).

2010	Rossella E. Nappi [19]	138	Cross-sectional	As far as the psycho-relational variables were concerned, the state of anxiety (1) and the Zung depression score (2) were negatively correlated with the full FSFI score in LMT (1: r = - 55; P = 0.000/2: r = - 6; p = 0.0001) and in EPM (1: r = - 32;. P = 0.009/2: r = - 28; p = 0.03); the state of anxiety was also significant in EMT (r = - 32; p = 0.009).
2011	Joanne Ryan [16]	1092	Retrospective Cohort	The results were similar for rs 9340799 (interaction p = 0.019), in which the allele was associated with a reduction in the risk of phobia for HT users only [HT users, OR: CI 0.29, 95%: 0.12-0.71, p = 0.0064; Non-users, OR: 0.95, IC 95%: 0.61-1.49, p = 0.83].
2012	Ebony M .Glover et al. [13]	81	Case-Control	The effects of significant interaction between high and low E2 groups and a diagnosis of PTSD were studied [F (1.71) = 4.55, p <0.05]. It was observed that this effect was absent in the group with high E2.
2012	Lisette Graae [17]	884	Retrospective Cohort	After correction for multiple tests, RS 6023059 showed a statistically significant association with the illness (corrected p value = 0.023; (OR) 0.681, 95% confidence interval (CI) 0,570-0,814) in no material bipolar disorder material in females.
2013	Ebony M. Glover, PhD [14]	72	Case-Control	Effects of estradiol levels (E2) on conditioned discrimination of a traumatized clinical sample: (A) Percentage of fear-potentiated startle for the different types of test in all groups. The women in the E2 group showed significant discrimination (p <0.05). The women in the E2 group showed high robust discrimination (p <0.01).However, contrary to the data on startle, women in the phase of low E2 also demonstrated significant inactive discrimination and inhibition (p <0.001).
2013	Michael C. Craig [26]	61	Randomized Clinical Trial	In summary, there is no preliminary support for the use of estrogen therapy in the treatment of postnatal depression, but there is still enough available evidence to justify the widespread use of hormonal treatment for postnatal depression in clinical practice.
2013	Suwaporn Daendeea [25]	88	Randomized Clinical Trial	Two variants of ANOVA revealed that in the midbrain expressions of ARNm of GABAA sub-units 2 and 3 were greater in groups of OVX rats in comparison with E2 groups [2: F (1.22) = 4.81, P = 0.0435; 3: F (1.32) = 5.0, P = 0.0341] one day after the ovariectomy for the expression of the gene of GABAA sub-units 2, 3 and 4.
2014	Nancy F. Woods [18]	130	Retrospective Cohort	High levels of estrogen (OR = 0.016) significantly reduce the probability of being in the high severity group of hot flushes (class 1), while the women with higher levels of FSH (follicle stimulating hormone) (OR = 2.870) were significantly more likely to be in this group.
2014	Nehle Parand Avar [20]	300	Cross-sectional	The highest frequency of psychosomatic disturbance was related to sexual in capacity (33.7%).
2014	Xianglan Wang [21]	48	Cross-sectional	The bi-variate Pearson correlation analysis showed a positive relationship between the average FA value of the left insula and levels of E2 plasma (r = 0.453, p = 0.026. Significant correlations were not found between E2 plasma and significant values of FA in the midbrain (r = -0.284, p = 0.178) or the left thalamus (r = -0.071, p = 0.741).

Table 1: Studies published on estrogen and transdiagnostics.

In 2013, Glover et al. [14] studied the hypothesis that women with low levels of estrogen would show deficits in the inhibition of fear in relation to those with high levels of estrogen. In both samples, it was verified that low estrogen in women during their cycle was associated with impaired inhibition of fear. In regard to limitations, this study indicated that in the clinical sample, the group with low estradiol was, on average, older than the group with high estradiol, due to the random approach to recruitment. Participants were not excluded based on their hormonal status or for being in the menopause.

Prospective cohort studies

In 2008, Gasbarri et al. [15] carried out a study on physiological hormonal fluctuations during the menstrual cycle, post-partum and during the menopause, which have been implicated in alterations in mood, cognition and also in affective disorders. The obtained results show that the rate of errors in the follicular phase was significantly higher in comparison to the menstrual phase, when identifying facial expressions of sadness, [F (2.53) = 3.00, p <0.04] and of disgust, [F (2.53) = 4.393, p < were found 0.02]. The analysis of response times for each facial expression with emotional valence demonstrated a significant difference between the follicular and the luteal phase in relation to expressions of sadness [F (2.445) = 3.29, p<0.002].

Retrospective cohort studies

In 2011, Ryan et al. [16] investigated whether variations in the ESR1 and ESR2 genes were associated with specific anxiety disorders in post-menopausal women and evaluated the potential modifier effect of hormonal treatment (HT) on these associations. The most common anxiety disorders were phobia (14.2%) and generalized anxiety disorder (GAD, 8%). There was also evidence of a significant gene-environment interaction, where only the women using HT had a reduced risk of phobia with the ESR1 gene variants.

In 2012, Lisette Graae [17], with the aim of investigating whether binding sequence variations of Estrogen Receptors (ER) to DNA may be involved in mood disorders, carried out a study of all the genome of bindings of DNA-ER in patients diagnosed with major depression or bipolar disorder. The association studies were conducted separately for each genre and the results for various tests were corrected using the Bonferroni method. In bipolar disorder among women, a significant association result was found for rs6023059 (corrected p-value = 0.023; probability ratio (OR – odds ratio) 0.681, confidence interval of 95% (CI) 0.570-0.814). Thus, women with a specific genotype of this SNP may be more vulnerable to fluctuations in the level estrogen, which may, in turn, act as a triggering factor for bipolar disorder.

In 2014, Woods et al. [18] having low levels of estrogen and high levels of follicle stimulating hormone (FSH) as a base, significantly associated them to high severity of hot flushes against the low severity group. Low levels of epinephrine and high levels of norepinephrine increase the probability of high severity hot flushes against low severity. Low levels of adrenaline were significantly associated with belonging

to the moderate severity group against the low severity group. Cortisol and testosterone were not related to symptoms of high levels of estrogen (OR = 0.016) and significantly reduced the probability of being in the hot flushes group (group 1), while women with higher levels of FSH (OR = 2.870) were significantly more likely to be in the hot flushes group.

Cross-sectional studies

In 2010, Nappi et al. [19] developed an observational cross-sectional study aiming to analyse the effects of hormonal and psycho-relational variable son sexual function during the transition between the menopause and the beginning of post-menopause in women with hot flushes. The sample was composed of 138 women and involved assessments of anxiety, depression and eating disorder, which, as with evaluations of marital adjustment, did not present differences between the menopause sub-groups. Both the levels of free testosterone (FT) ($p = 0.01$) & dehydroepiandrosteronesulfate (DHEAS) ($p = 0.03$) were slightly reduced in early post-menopause (EPM) when compared to early menopausal transition (EMT), as were the levels of estradiol (E2) ($p = 0.001$ EMT against LMT; $p = 0.0001$ LMT against EPM).

In 2014, Avar NP et al. [20] performed a study whose objective was to investigate psychiatric problems related to the menopause, stress and experiences in accordance with the psychological conditions related to the menopause as a developmental crisis. This mixed method study, using the triangulation approach, was carried out on 300 women in the menopause. The results showed that the majority of psychosomatic listed disorders experienced by women present: sexual problems 101 (33.7%), hypertension 39 (13%) and constipation 30 (10%); 2.9% had also experienced hypochondrias disorder.

In 2014, Xianglan Wang [21] aimed to investigate fractional anisotropy (FA) in the white matter of the entire brain in perimenopausal women with Subsyndromal depression (SSD) using diffusion tensor imaging (DTI). Of the 48 women of between 45 and 55 years old, when compared to healthy controls, those with SSD exhibit significantly lower FA values for the left insula. Meanwhile, higher values of FA were observed in the left ventral lateral thalamus and left and right brainstem in the midbrain ($r = 0.453$, $p = 0.026$).

Randomized clinical trials

In 2005, Lund TD [22] carried out a study with young Sprague Dawley male and female rats, obtained from Charles Rivers Laboratories (Wilmington, MA), which were gonadectomised (removal of gamete producing organs). In order to determine whether anxiolytic actions of estrogen could be mediated by estrogen receptor (ER) beta, behaviours related to anxiety were examined after treatment with ER subtype-selective agonists n = 8 animals per treatment group. There was a significant difference ($P < 0.05$) in comparison with the control treatment. The results of the study support the hypothesis that the dichotomous action of estrogen in the regulation of mood and behaviours related to anxiety is mediated by the opposing and distinct roles of ER alpha and ER beta.

Studd [23], in 2008, studied the diagnosis and treatment of pre-menstrual depression (PMT), postnatal depression and depression occurring in the climacteric period, in order to emphasize the chronic nature of the problem and the best forms of diagnosing and relieving this anguish. Although the efficacy of estradiol in the treatment of PMT was demonstrated in clinical trials with placebo, its value has not been explored by psychiatrists anywhere in the world. The benefit of this therapy in cases of severe PMT is probably due to the inhibition of ovulation, but it is also probable that it is a central tonic mental effect.

Postnatal depression is another example of depression caused by fluctuations in sexual hormones. There was an improvement in 12 of the 23 patients after one week and 19 of the 23 patients after two weeks. This study demonstrated a rapid response to estradiol in this profoundly hypo-estrogenic group of women. Further placebo controlled studies are necessary, together with information on bleeding patterns, in order to support or refute the original article of the authors [24].

In 2013, Daendeea S [25] developed a study whose objective was to examine the effects of estrogen deprivation time on anxiety related behaviour and on expressions of the subunit gene of the GABAA receptor in ovariectomized rats. The GABAA receptor was of special interest, since it was shown that it is influenced by estrogens. The Elevated T-Maze (ETM) results demonstrated that the OVX rats were more anxious than the estrogen replacement rats, confirming the anxiolytic effect of estrogen.

In 2013, Craig MC [26], obtained mixed results from various studies on estrogen therapy, which were unable to demonstrate superiority over a placebo in menopausal women with depression [27,28]. However, these included long term studies of post-menopausal women and the benefits of estrogen therapy were found to be limited to women in the perimenopause. This is proved by a pilot study of 4 weeks on 22 menopausal women with depression, who related an improvement in mood in 6/10 of those in perimenopause, but in only 2/12 women in post-menopause, with (100 mg / day) 17b-estradiol therapy [29-31].

A recent RCT reported that although Selective serotonin re-uptake inhibitors (SSRIs) significantly improve the symptoms of PMDD [32]. Ten sessions of cognitive behavioural therapy (CBT) were associated with an even better result in one year of follow up [33]. However, the study needs to be replicated as the size of the sample was small and the rate of abandonment was high.

Discussion

According to the available literature the results highlight that the relationship between alterations of mood and the menstrual cycle has been recognised for many years. More recently the use of high doses of estrogen has been explored with some success [34]. A diagnosis of depression related to the hormone and based on the history of the patient is made at the time at which the problem is most accentuated, which is when there is hormonal fluctuation, as in the pre-menstrual phase, in the post natal period and in the years preceding the menopause. Antidepressant medication is not generally very successful, although it is often the treatment of choice of medical professionals in general, possibly as a result of the possible side effects resulting from the administration of high doses of estrogen [34].

The steroid hormone of ovarian estrogen may be involved in anxiety disturbances [5,10,35,36]. Defects in serotoninergic transmission, including the serotonin transporter function (SERT),have been implicated in depression, anxiety disorders and some aspects of schizophrenia [34]. The sexual steroid hormone estrogen is known for modulating the functional activity of SERT, upwards or downwards, so that it regulates the density of the SERT connection, this being significantly lower in the hippocampus of OVX rats (ovariectomized) than in the controls [37,38]. Hormone replacement therapy can alleviate the physical and psychological symptoms associated with the menopause. However, the beginning of estrogen replacement has also been associated with the development of panic attacks [39,40].

Case-control studies show that the incapacity to suppress fear responses in safe conditions may be a biomarker for PTSD. The low level of estrogen in women with normal cycle is associated with deficits in the extinction of fear [41-43]. Studies show that women are protected against psychotic illnesses when their levels of estrogen are high, which is an emphatic result of our revision. This hypothesis is supported by various preliminary studies on the therapeutic effects of estrogen therapy on schizophrenia. However, a meta-analysis of four randomized clinical trials (n = 108) published up to 2003 concluded that, in general, estrogen therapy did not have a significantly beneficial effect as sole treatment or as an adjuvant therapy [44,45]. Sensory motor gating (an automatic process in which the brain adjusts to stimulation) is interrupted in patients with schizophrenia and other mental illnesses. The effect of a reduction in estrogen may produce a more profound view of the possible beneficial effects of estrogen as support in these treatments [38,46,47].

Research on the estrogen receptor genes ESR1 and ESR2 indicates that they may contribute to genetic susceptibility to OCD [48-51]. This was the first study to examine the role of estrogen receptor genes in predisposition to OCD [50,51]. The ESR1 gene may contribute to genetic susceptibility to certain OCD subphenotypes; specifically, these findings may influence the development of contamination/cleaning obsessions and compulsions [41]. Affective disorders, such as pre-menstrual syndrome, postnatal and post-menopausal depression and depression, are the most common mental disorders associated with low serum levels (i.e., in the blood) of estrogens [52-57].

Furthermore, estrogen is hypothesized as having a protective role in schizophrenia and in Alzheimer's [58]. Therefore, this study represents a useful tool for the analysis of possible therapies for the treatment of disturbances related to phases of the menstrual cycle and menopause in women [58-61]. Studies have shown that periods of depression often correlate with hormonal fluctuations in women with bipolar disorder or major depression [62-65].

Many women with long term depression improve considerably when their periods finish. Depression in the perimenopause, without doubt, would be related to pre-menstrual depression, since it worsens with age as a result of a fall in the levels of estrogen [65]. Finally, postnatal depression is another example of depression caused by fluctuations in sexual hormones, whereby hormonal treatment directly improves mood. This was shown in high doses [65], and in other psycho-endocrinal studies of depression in the climacteric period [66] and postnatal depression [24] that demonstrate the benefit of transdermal estrogen in high doses for these conditions.

As a limitation of the present study, the results suggest that there is a difference between sexes in the genetic pattern contributes to susceptibility to the development of these illnesses. It also suggests that the differences in the binding of the estrogen receptor may contribute to the risk of developing bipolar disorder in women. There is a necessity for further research examining the influence of hormonal status on fear inhibiting processes.

Conclusion

Estrogen alterations interfere in anxiety and mood, especially in people with greater vulnerability to the same disorders, especially during postpartum and menopausal periods when endogenous estradiol levels are low. According to the present study, as it is a female sexual hormone, there is a greater prevalence of mood and anxiety disorders which are twice as common in women as in men. Thus, this demonstrates the effective influence of this hormone on female behaviour and emotions.

It was observed that women with OCD, PTSD, schizophrenia, PMDD, perimenopause and menopause, when in periods of hormonal oscillation, experience a greater incidence of the respective symptoms. As an example, we have the evidence that the rates of prevalence of depression are twice as high in women as in men. There is a necessity to take female hormonal variations into account in regard to the efficacy of psychiatric medication prescribed for regulating the intensity and frequency of moods and anxiety, precisely because of the interference of estrogen in such disorders in women.

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