10. The premenstrual syndrome: An overview

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Abstract. Premenstrual Syndrome (PMS) involves a high proportion of the feminine population of fertile age. Mode of treatment is based predominantly on a plausible etiopathogenetic hypothesis according to which hormonal changes are correlated with ovulative and serotonergic alteration. A number of studies have demonstrated the effectiveness of SSRIs in the treatment of PMS.

The aim of the present article is to verify the efficacy and safety of low dosage sertralin administered continuously to a group of patients affected by PMS.

Seven female patients, each affected by PMS according to the diagnostic criteria of DSM IV, were treated with 50 mg per day of sertralin continuously over six menstrual cycles. Evaluation of the outcome indicators of the pilot study was carried out by means of a scale for the symptoms of PMS, composed of 10 items, which was self-administered both pre- and post-therapy.

From the analysis of the outcome indicators of the scale employed, each of the symptoms of PMS evaluated (tension and breast swelling, headache, exaggerated hunger, irritability, tiredness, difficulties in sleeping, difficulties in concentration, acne

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and increase in weight) showed a substantial reduction in all of the patients treated. Furthermore sertralin was well tolerated to the extent that none of the patients was obliged to retire from the study as a consequence of adverse reaction to the drug administered.

The results of this trial indicate that continuous low dosage sertralin is efficacious and well tolerated in the treatment of PMS.

Introduction

Premenstrual Syndrome (PMS) is a clinical entity characterized by symptoms like emotional, physical and behavioral that have a cyclical pattern, variable intensity and which are closely related to the post-ovulatory menstrual cycle then resolved by the arrival of menstruation (1).

It is estimated that the percentage of women of childbearing age so seriously afflicted by this disorder varied from 2% to 10%, while the percentage of women who report milder symptoms varied, depending on the studies, from 30% to 80% (1).

More than 50% of women have a history of PMS. Various studies have found that every woman has an increase of over 30% of negative symptoms about 7 days before menstruation that interfere with the habits of every day. The graphs (Figure 1.1) shows three examples of women with PMS (2).

Diagnosis

The term MRMD Menstrual cycle-related mood disorders (disorders related to mood during the menstrual cycle) is used to emphasize the affective symptoms in disorders of the cycle that is more commonly known premenstrual syndrome.

Despite numerous attempts to frame nosographic PMS, disputes were not easily overcome and, in 1983, has formed an american study group to define uniformly the temporal criteria and clinical of mental disorders associated with it.

In 1988, PMS was included by the American Psychiatric Association in DSM-III-R and renamed "Late luteal phase dysphoric disorder" (LLPDD). Currently, the same study group has further amended the name of LLPDD that in the DSM-IV, is defined as "premenstrual dysphoric disorder (PMDD) and is included as an example of depressive disorders, between disease that requiring further study. The latest version, compared to the previous one, have been added, including the symptoms, "the subjective feeling of being out of control" and, among the diagnostic criteria, the existence of a symptom-free period that corresponds to the week after menstruation. Today,
Figure 1.1. Evolution of depressive symptoms in 3 women with PMS.
even if the diagnosis of PMDD has been included in the DSM-IV, however, we refer again to the general criteria of PMS. The DMS IV provides that for a diagnosis of PMDD, there must be at least five symptoms one of which must be of psychic order between mental depression, intense anxiety, emotional lability, irritability and loss of interest in usual activities.

The symptoms must occur during the week preceding the onset of menstruation and start to fall a few days after the onset of menstruation itself. The duration of such disorders may therefore vary from a few days up to two weeks. The symptoms then cease with the onset of the menstrual cycle or shortly after, to give way to a completely symptom-free interval (70.71).

More rarely, some women have these symptoms but for several days around ovulation: thus some women who have short cycles, may be without cycle to cycle for a week.

These disorders are therefore closely related to the menstrual cycle and, according to this criteria, the diagnosis can be made when the symptoms reported retrospectively by the woman returns in most cycles regularly for several years and is confirmed by prospective ratings for at least two symptomatic cycles. Warner and Bancroft (1990) found that such confirms was only in 20-50% of women who reported severe problems due to PMS. The diagnosis of PMDD requires, also, that the disorder is not the exacerbation of a pre-existing psychiatric illness as major depression, dysthymia or panic disorder, nor may be due to a medical condition or gynecological (endometriosis, fibroids, menopause, or endocrine abnormalities) below (44).

According to the DMS IV five of the symptoms listed below must be present during the final week of the luteal phase and a few days after the beginning of the follicular phase (71).

1. depressed mood
2. intense anxiety
3. affective lability
4. irritability
5. loss of interest in usual activities
6. difficulty concentrating
7. lethargy
8. change in appetite
9. sleep disorders
10. feeling of being out of control
11. physical symptoms
Framework and the clinical course of premenstrual syndrome

Although PMS is mentioned in the DMS IV, are not well defined diagnostic criteria dominating the physical symptoms, whereas in PMDD, the criteria for definition are essential as physical and as psychic ones (fig. 2.1).

The premenstrual molimen, that is the set of minor physical and psychological changes before menstruation in ovulatory cycles, is so frequent that it can be considered a very common event in a large population of women of childbearing age (from 30 to 80% depending on the studies).

But there is a subgroup of women reporting an intense and disabling symptoms in the days before menstruation.

The percentage of these women ranges from 20 to 10% (1).

The main symptoms attributed to PMS are of a psychological, physical, algie and behavioral: depressed mood, anxiety, impaired concentration, emotional lability, irritability, headache, constipation, abdominal and breast tenderness, changes in appetite, changes body weight and water retention, acne and neurodermatitis. Less frequently encountered are, however, alterations of thyroid hormones, anemia, migraine, diabetes mellitus, asthma, epilepsy, allergy, irritable bowel and autoimmune syndrome, neurodegenerative disorders characterized by aggressive behavior auto and bait directed as criminal acts and suicide (10). About the risk of suicide from

Box 1. DSM-IV diagnostic criteria for PMDD (2).

- 1-year duration of symptoms which are present for the majority of cycles (occur during luteal phase, remit during follicular phase).
- Five of the following symptoms (with at least one symptom marked with an asterisk) must occur during the week before menses and remit within days of menses.
  - Irritability*
  - Affective lability*
  - (sudden mood swings)
  - Decrease interest in activities
  - Difficulty concentrating
  - Lack of energy
  - Change in appetite, e.g., food craving
  - Seriously interferes with work, social activities, relationship
  - Not an exacerbation of a prior disorder
  - Confirmed by prospective daily ratings during at least two consecutive symptomatic cycles

Box 2. ACOG diagnostic criteria for PMS (3).

- Patient reports >1 of the following effective and somatic symptoms during the 5 days before menses in each of three prior menstrual cycles:
  - Affective
    - Depression
    - Angry outbursts
    - Irritability
    - Anxiety
    - Confusion
    - Social withdrawal
  - Somatic
    - Breast tenderness
    - Abdominal bloating
    - Headache
    - Swelling of extremities
  - Symptoms relieved within 4 days of menses onset without recurrence until at least cycle day 13
  - Symptoms present in absence of any pharmacologic therapy, hormone ingestion, or drug or alcohol abuse
  - Symptoms occur reproducibly during two cycles of prospective recording
  - Patient suffers from identifiable dysfunction in social or economic performance

ACOG. American College of Obstetrics and Gynecology
PMS: Premenstrual syndrome

Figure 2.1. Diagnostic criteria for PMS and PMDD.
a 2004 study, it is found through retrospective diagnosis that such is more common in the late luteal phase, also appears that PMDD may not be associated with the act of suicide (50). Delusions and hallucinations have been reported in the late luteal phase of the menstrual cycle, but are very rare. Woman also have as dysmenorrhea (painful menstruation), as premenstrual dysphoric disorder, require more easily the treatment, compared to those who have one of these conditions, but most are carriers of a condition and not the other (2). The perception of such physical and psychological changes can lead women to a difficulty in interpersonal relationships with family and isolation from social relationships, to an inability to derive pleasure from leisure activities, to absenteeism from work, to refuse to take important decisions, delegating them to others. In these cases, mental illness is similar to that seen in patients with major depression, which implies the need to set up a personalized and effective treatment. In addition woman with PMS have a higher risk of developing a depressive episode (27). The symptoms appears to be, however, varies greatly from woman to woman, and, in some, only one symptom may predominate also of considerable intensity, there may be other different symptoms and minor (11). In addition to these findings negative symptoms, there are descriptions of positive physical and psychological changes reported by women in the premenstrual phase (54).

These modifications relate to an increase of the energy and mood, in the sense hyperthymic slightly, an increase of the sexual desire and greater creativity. In a study published in February 2006 by Accort and Allen were analyzed EEG results, and it was shown that the frontal asymmetry encephalography plays an important role in depression as well as in other diseases related psycho to an emotions (54). In one study, women who reported low symptoms of PMDD showed a good activity on the left lobe compared to women with premenstrual dysphoric symptoms high. Since some studies have also found that alexithymia is associated with strong PMDD. Women with PMDD also show a low opinion and dissatisfaction with their physical appearance than women with PMDD are not suffering from alexithymia (55).

The exacerbation of premenstrual symptoms is commonly found in women already suffering from a psychiatric disorder of major affective or dysthymic, in women with panic disorder, in those with obsessive-compulsive disorder, eating disorders and in alcoholism. In these cases one can't speak, of a "stress disorder premenstrual primary applicant", but of a secondary form of disorder it self. The PMS may begin at any age after the first menstruation, but the average age recognized in several studies is of 26 years. With time, probably due of the continuous fluctuations in hormones, the symptoms tend to worsen and last for a period of time gradually
increased. Women who report with less frequent disturbances from PMS are in fact those who were less exposed to these fluctuations by a greater number of pregnancies or taking of oral contraceptives. Hysterectomy without removal of the ovaries does not alleviate premenstrual symptoms more pronounced, the appearance of which can be documented by changes in urinary excretion of sex steroids. There are no specific laboratory tests to diagnose the disorder. However, in several limited preliminary studies some findings of laboratory (eg. Pattern of secretion of serotonin and melatonin, the sleep ECG findings) were abnormal in groups of women with this disorder compared with control subjects (53).

In women of childbearing age menstruation indicates is the culmination that the renewal of a very complex monthly rhythm neuroendocrine which has as its ultimate goal the release of an ovule and preparing the uterine environment to accept and permit the establishment of a pregnancy. The menstrual cycle is divided into two parts (Figure 3.1): the follicular phase and luteal phase. The follicular phase, which corresponds to the first half of the cycle and begins with the menstrual cycle is characterized by the maturation of several ovarian follicles under the influence of follicle-stimulating hormone and luteinizing hormone. From this group of follicles, only one emerges at follicular half-phase, as dominant. Theca cells of the outer and inner part of the granulosa of these follicles multiply and for the effect of LH, synthesize and release increasing amounts of estrogen. These types are to inhibit the release of FSH, with regression of follicles smaller and less mature, and produce local stimulation of follicle maturation. Estrogen secretion reaches its peak before of the middle of the cycle and the granulosa cells begin to produce progesterone. These changes stimulate the brief peak of LH and FSH that precedes and causes ovulation. When the follicle bursts, the ovule is released into the abdominal cavity near the uterine tube.

Following these events, the cavity of the follicle exploded fills with blood, theca cells luteinized and granulosa proliferate and replace the blood forming the corpus luteum. The cells of this structure produce estrogen and progesterone for the remainder of the cycle or for a longer time if the pregnancy begins. If pregnancy does not occur, the corpus luteum undergoes regression and stop hormone production, eventually becoming a corpus albicans. Most of the hormonal events that occur during the ovarian cycle can be explained on the basis of negative feedback regulation. The endometrium has gone to meet proliferation during the follicular phase and has developed its glandular structure during the luteal phase, falls apart during menstruation (72.69).
Etiopathogenesis

Sociocultural factors

It is generally accepted now that the PMS is caused by a combination of several factors, socio-cultural, psychological and biological processes that, acting in synergy, determine the clinical picture. As already mentioned in the introduction, beliefs, attitudes towards cultural and religious roots of menstruation, they still amount, in most women, a negative predisposition to this stage of the reproductive cycle.

In a survey how the menstruation are perceived by the woman herself, it was shown that they are still considered a negative event during which the female accused physical and psychological symptoms, of which the entity is often overestimated. The PMS, also, happens as we have seen happen in menopause: the maternal experience of this reproductive cycle has a decisive influence on the attitude that will have her daughter. Thus, if a mother has lived in a traumatic way and embarrassed their menarche and did not prepared adequately their daughter, or has contributed to satisfy the shame
and the limitations of behavior which often are associated, the same daughter will be more inclined to put in act in the same negative attitudes.

No less important is for women, the role of his partner into confirm the rejection of menstruations treating her as a disease (1).

**Psychological factors**

In many studies, researchers have attempted to draw a specific psychological profile of women suffering from PMS reaching, at times, conflicting results. Some, in fact, have found a discomfort more pronounced in who do not accept the traditional female role, while others report that this symptom is higher in women more traditionals and conservatives. Generally, women with PMS are however more doubtful, more apprehensive and emotionally unstable, with low self-esteem, little self-confidence and a strong need for confirmation from others.

According to a 1989 study, if you can isolate a specific group of women who meet the criteria of DSM for the PMS, those which require help and treatment for disorders attributed to PMS, are at high risk for one or more concurrent psychiatric disorders and should be evaluated carefully. The PMS is very often associated with the presence of concurrent stressors, and this is in support of a predominantly psychological genesis of the disorder. However, some authors compared a group of women with PMS with a control group, not found that the first negative feelings attributed to specific biological events nor that had, to these events, particular attitudes.

This discovery confirms the existence of a specific disorder of the luteal phase, which develops on a free base from psychiatric illness and is contrary to the sociocultural and psychological theories set out above (1).

**Biological factors**

The theories that have sought to explain the biological origin of psycho¬physical disorders being of PMS are varied and, probably, this syndrome does not present a unique etiopathogenetic mechanism. Among the most credible hypothesis there is those that it attaches importance to gonadal steroids, estradiol and progesterone, which oscillations regulate the menstrual cycle (Figure 4.1). Also Frank (1931) attributed the disturbances in the premenstrual phase, an excess of estrogen and, on the basis of this theory, he treated the women with PMS with ovariectomy or with the application of radiation on female gonads in order to reduce the amount of their secretion.

However, the second half of the menstrual cycle is characterized by a decline in the level of sex hormones, so this theory can not be confirmed.
In one study (Wolkowitz and Rothschild) of 15 patients with PMS and 15 controls, FSH and LH products due to release of GnRH were in similar concentrations (Figure 5.1). Some studies don't show differences in secretion, others, show an increase of the frequency and a reduction in amplitude of the secretion. In summary there isn't however a substantial evidence that the PMS is related to abnormal blood levels of steroids and gonadotropins. Nevertheless, the clinic emphasizes a close correlation between symptoms and phases of the reproductive cycle and is now credited with the action of estrogen and progesterone on mood: the first improve it in preovulatory phase and the second has a sedative and slightly depressogena action. This correlation may provide a delayed effect of steroids on the sexual parts, centers hypothalamic neurotransmitters (78). These, in fact, modulate reproductive hormones and could induce the symptoms of premenstrual syndrome or even affect on the control centers of mood and of behavior. Menstrual cyclicity of ovarian hormones is more characteristic for psychological symptoms rather than somatic. Other hypotheses on endocrine dysfunctions cover a deficit of progesterone in the late luteal phase, an altered ratio estrogen / progesterone or an alteration of its metabolism. The lower levels of progesterone found in some women with PMS, reflect an altered function of the corpus luteum that occurs because of its lack of development.
An inadequate secretion of progesterone in the luteal phase, due to defects of secretion, metabolism, excretion and interaction with other substances (some prostaglandins promote the luteolysis and therefore reduce the secretion of progesterone), was associated with a level of pain threshold more low in some women, the same ones that benefit from therapy with progestin.

It was discovered that some hormones produced by the brain, neurosteroids, progesterone derivatives, would be responsible for change in mood, anxiety, depression, headaches and bloating, in seven, ten days before the flow. They are substances found in high concentrations in childbearing age, and virtually absent in menopause. They act on the same cellular receptors of anxiety, of sedation and sleep. So involved in emotional control, in modulating sleep and reactive anxiety (24). The physiological decrease of progesterone during the luteal phase creates the complex of premenstrual disorders depending of the entity of the decrease and depending of the predisposition of the subject (within three years should be available a patch that can make up for these shortcomings and thus eliminate the problem). They produce smaller quantities of allopregnenolone that amplifies the function of GABA receptors in the brain and has anxiolytic effects. But the production of pregnenolone, which has an opposite effect on the brain can be increased.

It was also noted that alcohol would play a modulatory action with neurohormones. The woman then tends to resort to the use of alcohol own in function of this modulating action for these disorders, would control the alterations of the cycle of drinking more. According to a recent publication of the Journal of NeuroSciences alcohol stimulates the brain production of these steroids that are active on the anxiety receptor. In June 2004, on Psychoneuroendocrinology has published a study about alcohol abuse in

![Figure 5.1. Levels of FSH and LH in patients with PMS.](image)
relation to affective disorder and PMDD (79). This study was conducted evaluating the effects of intravenous infusion of alcohol and evaluating the SEV (saccadic eye velocity). The results showed that there is some correlation between the use of alcohol and PMDD in particular during the late luteal phase (79). Altered renin-angiotensin-aldosterone axis, with an excess of the latter and greater reabsorption of sodium, and then water retention, was implicated in symptoms of PMS, considering the fact that many women complain about own water retention and swelling as a major disturbance. The mood changes could be due to the influence that of this hormonal axis has on brain neurotransmitters. It is also considered the influence of prolactin, whose levels are higher in women with PMS, as etiopathogenetic factor in this disorder. This hormone, in addition to a direct action on the breast, out of which many women complain about problems in the course of PMS, it also acts on the ovaries, causing an alteration of the corpus luteum resulting in deficiency of progesterone (78).

According to the hypothesis that attributes the PMS central action of neuropeptides, women with PMS have abnormal secretion and hypersensitivity to beta-endorphins, which have a stimulatory effect on prolactin and inhibition on gonadotropins, and the peptides alpha-MSH, dependent on the cyclic secretion of ovarian steroids during the luteal phase of the cycle. In these women the secretion of beta-endorphins, lower, would act in the luteal phase, on the modulation of mood, on behavior and on neurotransmitter interactions in hypothalamic pituitary axis. Other etiopathogenic factors of biological order given for the PMS, are the reduced availability of vitamin B6 and a deficiency of prostaglandins: the first is an important cofactor in the metabolic transformation of amino acids and is involved in the decarboxylation of 5-hydroxytryptophan to 5-hydroxytryptamine and dopamine, the second acts causing vasodilatation and water retention during the menstrual cycle (69).

In addition to social, psychological and biological factor assumed a role for several neurotransmitters and particularly for the serotonergic system, involved in pain perception, in depression, in food and in taking aggressive behavior. Numerous data show differences in sex in various serotonergic parameters: changes appear more pronounced in females to the point where it is believed that the serotonergic system is more flexible in women but this feature would pay in terms of increased vulnerability to disorders related to dysfunction of this neurotransmitter, such as depression.

Research in vitro on platelets (which have different biochemical and pharmacological similarities with the pre-synaptic terminals containing serotonin) to evaluate cycle-related changes of serotonin, have shown an
influence on the inhibitory effect of sex steroids on these with a reduction in reuptake of serotonin and its low blood levels.

Most of the studies found a decrease in serotonin reuptake limited to the luteal phase, according to some authors because of a reduced number of membrane transporters for serotonin or alteration of transmembrane ion gradient. Moreover, since that the changes in the reuptake of serotonin by platelets are contemporary to the symptomatology, may be that are causally related to it. It was also seen that the administration of serotonin agonists induces an elevation of mood, however, the administration of substances that decrease the activity of serotonin, cause irritability and social disintegration, symptoms that we find in PMS. These same changes are found in other psychiatric patients, in depressed and manic depressive, something that justifies even more the correlation serotonin-symptomatology in PMS (78).

It was also studied the influence of dopamine and norepinephrine, and we have seen how, in the cerebrospinal fluid, the levels of the metabolite MetossiDrossiFeniGlicole (MHPG) are significantly higher in the luteal phase of patients with PMS compared with healthy controls, suggesting a role of noradrenergic system in this syndrome. The PMDD also appears to have some correlation with the change in heart rate. The reduction in heart rate indicates a reduction of parasympathetic tone involved in depression and anxiety disorders. The aim of a study published in 2004 Psychoendocrinology was that to estimate the frequency in women with PMDD. From this study came out that PMDD may be associated with a reduction of vagal tone since, during the follicular phase in women with PMDD, were manifested changes in heart rate. A role is not well defined could be attributed also Gamma-aminobutyric Acid (GABA), whose levels are lower, particularly in the luteal phase in women with PMS.

Undoubtedly, among the women with PMS, you may find the alteration of one or more neurotransmitter or hormonal systems mentioned above, but it remains to be determined whether these are primary or secondary to the PMS itself. It is also not clear whether the theories outlined above are significant for the genesis of the most severe form of PMS, and which ones are relevant to the understanding of the changes of mood. The biological differences include the increase of hormone stimulating the thyroid after thyrotropin-releasing hormone release, which decreases slowly, decreases the secretion of melatonin and magnesium in the blood, decreases growth hormone and cortisol in response to tryptophan and increases the cortisol response to corticotropin-releasing infusion. During the luteal phase in the blood reduces the beta endorphins and reduces the reuptake of serotonin (57). It was made a study (Wolkowitz and Rothschild) which 7 days after the release of LH, at the women with PMS are administered placebo or mifepristone, a
progesterone-receptor blocker that causes a rapid reduction in plasma progesterone and early of menstruation within 48-72 hours. The patients also received or human chorionic gonadotropin (HCG) or placebo. Women that receiving mifepristone and hCG were cycles 48-74 hours, but during luteal phase the normal progesterone levels were maintained by the effect on the ovaries of hCG, a second cycle took place about 9 days later with an involution of the corpus luteum. The hCG preserved luteal phase despite the induction of menstruation given by mifepristone. Alternatively, patients who received mifepristone and placebo came in the follicular phase after that the mifepristone induced menstruation. The results showed that women with PMS felt the typical premenstrual mood after that the mifepristone had definite the menstrual, in time when the endocrine profile was that of the early follicular phase (Figure 6.1) (78).

**Genetic factors**

Although haven’t been identified specific genes responsible for PMDD seems that genetic factors play an important role: 70% of women whose mothers were themselves suffering from PMS have PMS compared to 37% of women who have PMS, but whose mothers were not affected. According to a study made on twins, is present with 93% in monozygotic and 44% in heterozygotes. The genetic influences are derived phenotypically from neuroreceptors and neurotransmitters and seem to play an important role in the etiology (1). In March 2005, was published a study by Damberg, Westberg et all in which they analyzed the expression of the transcription factor AP-2beta in neuronal cells. This study showed that this protein may be important for the functional characteristics of neurons to regulate the expression of target genes. The study however showed that AP-2beta genotype is a risk factor for PMDD (59).

**Relationship between PMS and affective disorders**

The attention that psychiatrists have turned in recent years to the PMS is justified by the prevalence in this syndrome, of mood disorders, sometimes so severe and debilitating in terms of emotional, of cognitive and of performance to be similar to those reported by patients suffering from depression, for which pharmacologic treatment is essential. The very fact that the symptoms most often reported to be mainly psychological order, in particular affective (depression, dysphoria, irritability, anxiety), did favor the existence of a correlation between PMS and specific psychiatric disorders.
Figure 6.1. Performance of premenstrual symptoms following administration of mifepristone.

Table 1. Aetiological of PMS and PMDD and pharmacological strategies

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<thead>
<tr>
<th>Aetiological factor</th>
<th>Relevant treatment</th>
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<tr>
<td><strong>1. Neurotransmission disorders:</strong></td>
<td>SSRIs, especially intermittent-luteal</td>
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<td>Serotonergic deficiency and dysfunction:</td>
<td>• GnRH agonists</td>
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<tr>
<td>• lower luteal phase of whole blood serotonin</td>
<td>• Continuous oestrogen</td>
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<td>• decreased platelet uptake of serotonin</td>
<td>• Oral contraceptive pills</td>
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<td>• blunted response to 5-HT</td>
<td>• Danzol</td>
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<tr>
<td>GABA dysregulation</td>
<td>• Benzodiazepines</td>
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<th><strong>2. Gonadal hormone dysfunction</strong></th>
<th>Ovulation suppression</th>
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<tr>
<td>A. PMS are not reported the premenarchal and</td>
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<tr>
<td>postmenopause period</td>
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<td>B. Symptoms are absent during:</td>
<td></td>
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<tr>
<td>• anovulatory cycles</td>
<td></td>
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<td>• menopause</td>
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Figure 7.1. Etiology and pharmacological strategies for PMS and PMDD.

Although the DSM-IV highlights the possibility of a diagnosis of PMDD only when there are other underlying psychiatric disorders, many women who require treatment for severe premenstrual disorders, or have an underlying psychiatric disorder is not diagnosed, or are already being treated
for a other disorders of this type. The women who complains premenstrual disorders, and that they seek help, it must be carefully evaluated in order to distinguish those who have severe changes in mood and behavior in the luteal phase by those that has instead in act one or more mental disorders such that require a complete diagnostic evaluation and a proper therapy. PMDD is distinguished from other psychiatric disorders by specific symptoms. There must be an interval of duration of 7-10 days max during the menstrual cycle in which the woman feel physically and mentally well.

If the woman is anxious and depressed during the entire month, even if her condition worsens during the menstrual period, is likely to have another type of problem (eg major depression) and not the PMDD (1.66). Although PMS and PMDD are often used interchangeably to denote the set of symptoms that characterize the premenstrual period, a distinction should be made, (over that chronological in fact the PMDD term was coined after), taking into account the fact that for PMDD includes: premenstrual disforic disorder while for PMS the syndrome. In fact in 1987 the third edition of DMS, the reference text for psychiatric diagnoses, the American Psychiatric Association has included the so-called "end of the luteal phase dysphoric disorder", which became the fourth edition of "premenstrual dysphoric disorder" as "depressive disorder not yet specified", corresponding to a most serious form of the common PMS. The premenstrual dysphoric disorder can be distinguished from the more common "PMS" for the performance of their symptoms, their degree of severity, and resulting disability.

The premenstrual dysphoria is therefore a more severe form of premenstrual syndrome, and in contrast to PMS is characterized by mood swings. The most common symptom is irritability and in fact many women often exhibit depression, anxiety and irritability (67).

Meir Steiner, Department of Psychiatry and Behavioural Neurosciences and Obstetrics and Gynecology at McMaster University in Hamilton, Canada, points out how the mood and emotion are part parcel of premenstrual syndrome, which now has a real dignity nosological: "It is no longer considered only a mental disorder of the woman or an invention of male doctors to discriminate again the opposite sex" (67).

The American Psychiatric Association Task Force, in the fourth edition of the Diagnostic and Statistical Manual of Mental Disorder (DSM-IV) has in fact included the dysphoria that characterizes the syndrome premenstrual between depressive disorders. The symptoms that characterize the premenstrual dysphoria, may overlap with another disorder, such a Major Depressive Disorder, of Panic or Dysthymia, or a Personality Disorder (71). The presence of
a cyclical trend should be confirmed by at least 2 consecutive months of record comparative of daily symptoms.

The daily records of symptoms must be made by the woman herself, or can be made by someone who lives with her. It is important that these diaries are kept on a daily basis, rather than being put together retrospectively by heart (41, 42).

Several studies have evaluated the relationship between mood disorders and PMS but the results, by adopting different diagnostic criteria, often based on retrospective assessment of PMS, are not always unique.

Among the investigations that have used uniform criteria, four found a prevalence of "premenstrual depression" in about 65% of women with depressive disorder, a value significantly higher than that found in controls or in women with other psychiatric illness. If it is a frequently encountered clinical worsening of premenstrual symptoms in women with major depression, it may seem that those with both disorders have a worsening of depressive symptoms in the premenstrual phase.

In fact we have seen that in some women, PMS disorders persist despite the use of an effective treatment that leads to resolution of depressive symptoms (62). This supports the combination of two separate disorders rather than a worsening of a depressive episode already in progress (60).

Further confirmation for this theory comes from biochemical studies on circadian variation of endogenous secretion of cortisol, a hormone that is an index of endogenous depression.

The comparison between women with PMS, women belonging to an asymptomatic control group and women with major depression, it appears that daily cortisol secretion is comparable between the first two groups, while the third reaches the highest peaks and, characteristically, not go through a dormant period between 18.00 and 24.00 hours.

Patients with PMS have in the luteal phase, on the basis of psychometric assessment carried out, a level of tension, anger, confusion and loss of energy comparable to that reported by depressed patients. The degree of depression of the first is high in same phase of the cycle, and significantly higher than the control group, however, is always less than what is found in cases of major depression.

The PMS and major depression are therefore two distinct clinical entities based on biochemical measurements made. In fact, the PMS is intermittent, cyclical and closely linked to the phases of the menstrual cycle, disappears during pregnancy and after menopause, but may recur after hormone replacement therapy. Then associated with physical clearly symptoms, but characteristic, such as breast pain and bloating. The functionality of the hypothalamic-pituitary-adrenal is normal, contrary to what is observed in
patients with major depression. The response to selective serotonin reuptake inhibitors, also is a snap, even in the first cycle of treatment or within days, while in patients with other mood disorders, the response to these drugs has not before 8 to 12 weeks (66).

Also, PMDD appears to be more than one thing in common with SAD (seasonal affective disorder) from different perspectives: symptoms, epidemiology, pathophysiology and therapy.

Seasonal Affective Disorder (Seasonal Affective Disorder - SAD) is a depressive recurrence in winter, accompanied by autonomic manifestations "atypical", such as increased appetite, the desire for carbohydrates (carbohydrate craving) and weight gain, hypersomnia, and lethargy. The disturbance clearly prefers the female (the male / female ratio ranges from 1:2 to 1:40). The average age of onset is between 20 and 30 years. So the similarities with Premenstrual Dysphoric Disorder (Premenstrual dysphoric Disorder - PMDD) is characterized by a cyclic recurrence of depressive symptoms "atypical". The observed frequency of this occurrence is, by definition, approximately monthly; were, however, described the circadian rhythm and approximately annual circulation of some symptoms of PMDD (carbohydrate craving), which may show an increase in intensity in the evenings and during winter months.

Similarly, patients with SAD may experience premenstrual exacerbation of symptoms.

Also, many observations of neuroendocrinology nature argue for an alteration of serotonergic function in PMDD, for which SSRIs are, in fact, the drug of choice.

These drugs appear to act at the interface between neurohormonal and neurotransmitter control mood and other mental functions, restoring in patients with PMDD the sensitivity (which is supposed to be reduced) sedative action of benzodiazepines and the so-called steroid neuroactive, such as pregnenolone, potent allosteric modulators of GABAergic receptor. The relationship between the concentrations of several neurosteroids is also shifted, from antidepressant treatment, in favor of those compounds with the potentiating action the function on neuronal excitability, mediated by this receptor (23). The changes in certain brain receptors can cause anxiety attacks during the menstrual cycle. It reveals a study published in the journal Nature Neuroscience. This discovery may lead to new treatments for premenstrual syndrome and other disorders of the central nervous system associated with the menstrual cycle.

"Our results are also applicable to post-partum depression and mood swings during pregnancy, and may explain how stress hormones can influence brain activity," explained Istvan Mody, professor of neurology at
the Reed Neurological Research Center at the David Geffen School of Medicine of the University of California at Los Angeles and leader of the research team. "Through our research may be identified new therapeutic targets to treat premenstrual syndrome and catamenial epilepsy, a form of epilepsy that in women are much worse during certain phases of the menstrual cycle, or any other disease caused by imbalances in the levels of steroid hormones". By studying the menstrual cycle of the rats, the researchers found that a specific subclass of receptors in the brain, GABA A receptors located in the cerebral region of the hippocampus, suffered changes during the cycle.

These changes took place in an area of the brain which were active neurosteroids derived from progesterone, and results inevitably associated with an alteration of the behavior of nerve cells, which had as resulted in an increased susceptibility of animals studied for anxiety attacks.

"This may reveal how nerve cells respond to stimuli in the human brain during the menstrual cycle" (67). A study conducted in September 2005 by Smith, Ruderman, Frye, Homanics, Yuan was analyzed on 3 alpha-OH-5 alpha (beta) pregnan 20 one (THP), a positive modulator of GABA A receptor that is responsible for anti-anxiety effect. There are conditions that increase levels of PMDD in the THP, levels associated with low mood serene. Following research carried out by injecting THP in rats it was shown that this modulator could serve as a model to cause in rodents PMDD (57).

The neurosteroids play an important role in the interaction between alcohol and GABA A receptors for the symptoms of PMDD. Some studies were focused on the changes brought by alcohol about concentration in the blood of allopregnenolone. (63) During the late luteal phase, regardless of the diagnosis of PMS, the low dose of alcohol gave as consequently a reduction of peripheral levels of allopregnenolone (58). The foto-therapy, first-line treatment of seasonal affective disorder, which is found the process of enhancing the neurotransmitter serotonin, has proved effective in PMDD, although not unequivocal evidence for the presence, in the latter disorder, alteration of circadian rhythms similar to that suggested by the SAD (51).

Another type of syndrome is related to menstruation (PERI-MS).

According to a study by Angst, Cellaro et all. published in 2001 by Acta Psychiatric Scandinavica, the frequency of PMS is quite high 80-90%, while that of PERI-MS is generally low 4.9-3.2%.

The characteristics of this syndrome are usually irritability, nervousness, and tension and more than half of women with this syndrome reported anxiety and depression. In addition there is also a part of these women that manifests the syndrome without change in mood, and the data suggest that
there may be a distinction between two subtypes of PERI MS based on the presence or absence of mood swings (38).

Some studies have also employed to evaluate the characteristics common to PMDD and PD (Panic Disorder).

According to a study by K. Vickers, R.J. Nally, published in 2004 by Clinical Psychology, patients with PD have hypersensitivity to the marked suffocation, in women with PMDD, the hypersensitivity is exacerbated by premenstrual hormonal changes, probably caused by an increase in carbon dioxide during this period (53).

In 1993, Klein used the change in the levels of progesterone during the menstrual cycle to explain the panic in women with PMDD.

Progesterone is a respiratory stimulant and reduces carbon dioxide levels in the blood in men.

The levels of progesterone increase during the early luteal phase of the cycle.

About three days at the beginning of each month, the progesterone is reduced and there is an increase in carbon dioxide and according to Klein the probability of a panic attack (53).

The fundamental problem with this statement were the effects of exogenous progesterone on the panic, the relationship between endogenous progesterone and panic, and the correlation between the reduction of progesterone and anxiety.

If higher levels of progesterone reduces the risk of panic attacks, then for this problem would be used the pre-administration of progesterone. An experimental study hasn’t however supported this prediction.

In fact in 2001 Le Melledo, Jhangri, et all given to women suffering from PD for 3 days medroxyprogesterone acetate with an injection as a pre-treatment and however panic attacks weren’t reduced.

The two main metabolites of progesterone, pregnenolone and allopregnenolone are neurosteroids and are positive modulators of GABAergic system that intensifies the inhibition of GABA-mediated and produces anxiolytic, anticonvulsant and anesthetic effect. Researchers have examined whether low levels of allopregnanolone characterize patients with PD and PMDD.

In opposition to this hypothesis, patients with PD had high levels of allopregnenolone and pregnenolone in plasma, whereas, in women with PMDD were significantly lower levels (53).

Since there was no difference in the cardinal symptoms and in psychopharmacological response, Landen and Eriksson concluded that PMDD could not be classified neither as an anxiety disorder nor a variant of depression. Few studies have addressed the role of the traumatic event and
post-traumatic stress disorder as a risk factor for PMDD. According to this study, both disorders are risk factors for the development of PMDD, although the mechanisms are still unknown (61).

Conversely, the menstrual cycle may be associated with an improvement episodic of a psychiatric illness coexisting.

Figure 8.1 illustrates the evolution of dysphoric symptoms in a woman who had initially PMS and whose diagnosis was confirmed.

After the onset of menstrual irregularities, the woman has experienced a chronic dysphoria accompanied by intervals with no symptoms during the post-menstrual and menstrual phase of cycle (78).

The menstrual phase of cycle may affect the symptoms of a psychiatric disorder.

Some studies have not identified the menstrual cycle as related to an exacerbation of symptoms of panic or anxiety in patients with panic disorder (fig 8.1).

![Figure 8.1. Evolution of states of mind in a woman with PMS.](image)

**Therapeutic aspect**

**General considerations**

The etiopathogenetic multifactorial of PMS, due to the interaction of biochemical, psychological and socio-cultural factors, has preferred a different therapeutic approach that takes into account all these aspects. According to the Italian section of Psychiatry, after the diagnosis of PMS made with a careful and daily assessment of symptoms, the physician should consider the following strategies to individualize the therapy for PMS:
• "validate the subjective experience of each patient";
• "understand the factors contributing to the presence of premenstrual symptoms";
• "understand the psychological and social consequences of a long-term PMS";
• "teach how to control self-managed PMS";
• "sensitize the patient to doesn’t minimize the impact of PMS";
• "prescribe medicines that reduce or resolve the symptoms";
• "support the patient in recovering the damage that the PMS may have caused her and its interpersonal relationships".

In reference to this last point, may be useful meetings with family, to explain the situation and promote an attitude of greater tolerance towards the patient. The record and the daily evaluation of symptoms alone can already give women a sense of control over the PMS, since, in this way, they learn to recognize problems and feelings which before they felt overwhelmed. When you realize that the cause of their malaise is hormonal and aren’t mentally ill, often realize that they can deal with PMS.

Besides this, a simple behaviors remedial action may relieve mild symptoms: play a regular exercise: often sporting activity can be useful because it allows you to download stress and causes the release of endorphins, which bring a feeling of well being, it is also important get enough sleep, reduce stress and observe a balanced diet.

The latter should be rich in carbohydrates and low in fat and protein must be organized into small meals a day, should exclude caffeine that, increasing tension and nervousness, the symptoms worsened and, finally, it must drastically reduce salt intake, especially for those women who complain about water retention, bloating, breast pain and headaches (69).

**Nutritional supplements**

Many nutritional supplements have proven effective in the treatment of PMS. In an analysis comparing patients treated with these supplements in PMS, with a control group that used placebo demonstrated the efficacy of the vitamin $B_6$. Research has shown that the vitamin $B_6$ at dose of 100 mg pro die is effective in patients with premenstrual symptoms and depression.

In another study involving 466 patients, was evaluated the effectiveness of calcium carbonate. It has been shown that calcium supplements with doses of 1.200 and 1.600 mg for day reduced PMS symptoms in 48% of patients. In addition, vitamin E, an antioxidant that seems to relieve the physical
symptoms. Also the tryptophan, serotonin substrate seems to be beneficial (tab1.1).

A study published in February 2006 made by Khine, Rosenstein, Niemelä et all it takes to analyze the magnesium deficiency and therapeutic efficacy of magnesium in PMS and PMDD.

There were no evidence of magnesium deficiency in women with PMDD compared with control subjects. Moreover, the placebo has not proved superior to placebo in mitigating the mood in women with PMDD (1,56).

**Table 1.1.** Non-pharmacological treatment for PMDD.

<table>
<thead>
<tr>
<th><strong>Lifestyle</strong></th>
<th><strong>Non-pharmacological treatment</strong></th>
</tr>
</thead>
</table>

**Nutritional Supplements**

<table>
<thead>
<tr>
<th>Vitamin B6, 100 mg for day</th>
<th>Calcium carbonate 1200,1600 mg for day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin E, 600mg for day</td>
<td>Magnesium, 500 mg for day</td>
</tr>
<tr>
<td></td>
<td>Tryptophan, 6 g for day</td>
</tr>
</tbody>
</table>

*PMDD = premenstrual dysphoric disorder; PMS = premenstrual syndrome.*

For women whose symptoms persist after these non-pharmacological remedies or for those who are leaving a more severe clinical picture must be put in place drug treatment strategies (1).

**Antidepressants and anxiolytics**

From the older tricyclic antidepressants (TCA), administered several times a day, with heavy side effects (cardiovascular problems, drowsiness, nausea, loss of libido. ...) have given way to recent SSRI (selective serotonin reuptake inhibitors). One tablet a day can increase the availability of serotonin (77).
As part of the therapy can also be used as alprazolam, anxiolytic belonging to the class of benzodiazepines. Since it was shown that this drug causes drug addiction is considered a second choice, and used only in cases of therapeutic failure of SSRIs. Its use is limited to the luteal phase and the dose is of 0.375 to 1.5 mg for day. By using non-continuous can be reduced dependence, this mode should be used only in patients who do not have to shoulder the use of drugs of abuse (14).

Other drugs with selective action on serotonin, which can be used are: nefazodone, antagonist of reuptake and the 5HT2 receptors; fenfluramine, the serotonin agonist; venlafaxine, an inhibitor of serotonin and norepinephrine reuptake; and buspirone, serotonin receptor agonist.

**Hormone therapy**

In the course of mental illness hormonal therapies can be used alone or where the extent of the pathology required it with the drugs associated. The rationale for these therapies comes from the observation that some hormones act as modulators in the brain function of the main neurotransmitters, whose alterations are antiormoniche which may be involved in the pathogenesis of these diseases (discussed in detail in biological etiopathogenesis). Were used as modulators of secretion of neurotransmitters and their receptors sensitivity treatment with antiestrogens.

The androgen danazol is used in the treatment of endometriosis and hereditary angioedema and is sometimes used to treat PMDD. The typical dosage is 100 mg 2 times a day. With treatment you can reduce the symptoms but you may experience side effects such as masculinization and this limits its use.

GnRH agonists, leuproide and goserelin may be used in intermittent therapy to prevent the paradoxical effect of antagonism that occurs at high doses for desensitization of the receptor. To its side effects and high cost, GnRH agonists and danazol are considered the last choice.

Birth control pills also inhibit ovulation and haven’t significant effects in the treatment of PMDD. Ocps (oral contraceptive pills) could worsen dysphoria in some women who do not suffer from PMDD (Tab.2.1). Studies on the effectiveness of progesterone have shown limited benefits but we have seen that this is certainly superior to placebo.

Currently gonadotrophic ovarian hormones have a limited use in the treatment of PMDD and no drug among these was approved by the FDA because these drugs are responsible for determining the decrease in concentrations of estrogen to levels similar to those seen in menopause and are associated with this effect side as hot flushes, vaginal dryness and increased risk of osteoporosis (1).
The premenstrual syndrome: An overview

Table 2.1. Hormone therapy for PMDD.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Doses</th>
<th>Recommendations for use</th>
<th>Reviews</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leuprolide depot</td>
<td>3.75 mg IM per month</td>
<td>six cycles</td>
<td>It can produce symptoms of menopause</td>
</tr>
<tr>
<td>Leuprolide depot surcharge of ovarian hormones</td>
<td>3.75 mg IM per month with estrogen and progesterone</td>
<td>six cycles</td>
<td>It causes less symptoms of menopause. The symptoms of PMDD may return to using this combination less effective</td>
</tr>
<tr>
<td>Gosereelin with estrogen</td>
<td>3.6 mg sc every 28 days with estrogen</td>
<td>six cycles</td>
<td></td>
</tr>
<tr>
<td>Danazol</td>
<td>100 mg 2 times a day</td>
<td>six cycles</td>
<td>It can induce masculinization</td>
</tr>
</tbody>
</table>

Treatment based on the etiopathogenesis

Bromocriptine (500 mg per day) reduces the levels of prolactin; mefenamic acid (250-500 mg several times a day) is an inhibitor of prostaglandin synthesis; verapamil also think the acting on the release of neurotransmitters through an action on calcium channels (1).

Symptomatic therapy

It is anti-inflammatory drugs non-steroidal like ibuprofen or naproxen to relieve pain and headaches; spironolactone (4 mg 4 times daily) is used when dietary measures are not sufficient to reduce the swelling due to fluid retention. They are also used drugs, which highlight the correlation of the syndrome to bipolar affective disorder, including lithium salts, valproic acid, clonidine and naltrexone (1).

Phototherapy

Interestingly, the use of phototherapy, which plays a therapeutic role in the autumn-winter depression. The action of phototherapy is expressed on
the behavioral component (hyperphagia, hypersomnia), but also on emotional and affective disorder.

Phototherapy is generally used in those patients who may not tolerate antidepressants or who may experience adverse effects. The effect of phototherapy seems to be of serotonin.

In this regard, studies have been conducted, including one published in 2005 by the American Journal of Obstetrics and Gynecology, where it was noted the role of phototherapy in PMDD (51).

**SEROTONIN IN THE PREMENSTRUAL DYSPHORIC DISORDER**

![Figure 1.2. Serotonin.](image)

**The serotonin**

Serotonin (Fig.1.2) continues to pose a conundrum for researchers and clinicians.

Despite always been involved in numerous processes psychobiological, was never proposed a specific theory about his role. Even the most recent evidence on the distribution of serotonergic terminals in each region of the CNS, the mode of release of 5HT that does not follow the general rules of synaptic physiology and the existence of a wide variety of pre and postsynaptic receptors on which the 5-HT acts not showed a specific action of 5HT.

The hypothesis of a relationship between serotonin and psychic functions dates back to the '60s.

Brodie and Shore in 1957 suggested to consider the serotonin and catecholamines such as the autonomic nervous system of the brain, as capable of exerting opposite actions on affective states. The vast literature in the following years on serotonergic transmission and its implication in psychiatric disorders documents there cognition of the importance of serotonin in the psychiatric field.
The extensive and widespread distribution of serotonergic terminals in the cortex and structures Libyan explains how serotonin contributes to the regulation of many physiological functions, such as mood, anxiety, thought, attention, impulsivity and aggression and biological, such as appetite, sleep, circadian rhythms, pain, neuroendocrine functions and brain development, which are altered in many psychiatric disorders and neuropsychiatric (74).

**Anatomy**

The bodies of serotonergic neurons are located in the midline of the brainstem at the level of the bulb, pons and midbrain, where they are concentrated particularly in the raphe nuclei.

The serotonergic neurons of the raphe nucleus are the largest and most complex system of efferent brain.

However, the innervation is not considered to be ubiquitous and not specific. The distribution of serotonergic innervation may be varied within the same region, some areas may receive a dense innervation and surrounding the fibers scattered.

According to the name proposed by Olszewski and Baxter (1954) serotonergic neurons can be divided into two groups, the rostral includes nucleus of the upper middle, the dorsal raphe nucleus, the sopralemniscale nucleus and the nucleus dorsomedial hypothalamic and the tail that includes the raphe obscurus nucleus, the nucleus raphe pale, the nucleus raphe magnus of the nucleus raphe and the ventricular-paragiganto cellular lateral reticular nucleus (73).

**Synthesis and catabolism of serotonin**

The precursor of serotonin is tryptophan, which is supplied from the diet and transported into the neuron through the carrier of neutral amino acids. The tryptophan hydroxylase catalyzes the hydroxylation reaction of tryptophan to 5-hydroxytryptophan (Fig.2.2).

This enzyme is the limiting factor of the serotonin pathway and its activity is positively modulated by stimulation of serotonergic neurons.

The tryptophan hydroxylase requires molecular oxygen and a pteridine cofactor for its activity, is localized exclusively in serotonergic neurons and probably is not saturated by substrate concentrations in the brain.

The 5-hydroxytryptophan can be used as a drug to increase the concentration of serotonin than tryptophan has a higher efficiency than isn't used in other metabolic processes or protein synthesis.
Figure 2.2. Summary of serotonin.

The 5-hydroxytryptophan is decarboxylated to 5-hydroxytryptamine by an aromatic amino acid decarboxylase.

Serotonin is synthesized and stored in vesicles and released when the neuron fires. The main catabolic reaction is by MAO-A.

Serotonin, which is not metabolized, is quickly re-uptake in the cytoplasm of serotonergic neurons via a membrane carrier, and then stored in vesicles or degraded.

It may also be substrate of MAO-B, having a lower affinity for the serotonin-MAO-A, switch on when the neurotransmitter concentrations are high, equal to 10−3 M.

Serotonin remained into the cytoplasm is released the same carrier that serves for the re-uptake, but in this case it works in reverse (73). (fig.3.2)
The serotonin carrier is part of the family of plasma membrane carrier, Na+-dependent.

It is the site of action is the old generation of antidepressants such as tricyclics imipramine and amitriptyline, which the latest selective serotonin reuptake inhibitors. The sites for the uptake of serotonin have been localized to the amygdala, thalamus, hippocampus, hypothalamus, black substance, locus coeruleus and raphe nuclei (Figure 4.2).

As for the norepinephrine carrier, the destruction of serotonergic neurons with neurotoxins causes a reduction of the sites marked by antidepressants in the projection areas, given consistent with the localization of presynaptic carrier (73).
In addition to locating the neuronal, the serotonin carrier is present in platelets, placenta, lung, endothelium, and mast cells. The serotonin carrier has been cloned from rat brain, is a polypeptide of 630 amino acids, 68 kD, which has sequence homology of 50% with the human norepinephrine carrier.

With the techniques of in situ hybridization, mRNA specific for the serotonin carrier was found in the brainstem, lung, spleen, intestine and adrenal gland. With other molecular methods has also been highlighted in the telencephalon.

It was shown that the serotonin carrier may be regulated in acute and in chronic by protein kinase C and dall'AMPc. The kinase protein inhibits it in pulmonary endothelial cells and platelets while active in leukemic cell lines. Increased levels of AMPc reduce the activity of the carrier.

The sites labelled by 3H-imipramine in platelets of healthy subjects decreased after chronic treatment with clomipramine, increase after treatment with amitriptyline and remain unchanged after treatment with imipramine.

**Figure 4.2.** Serotonin receptors.
Treatment with specific antagonists, serotonin reuptake inhibitors, decreases the content of specific mRNA for the carrier in rat brain. The binding of 3H-imipramine on platelets has been proposed as a diagnostic marker in depression (73).

**Serotonergic receptors**

The discovery of serotonin as a neurotransmitter back to the '50s. In 1957 Gaddum and Picarelli have shown in the suburbs the existence of two types of serotonin receptors on which it acts, the type D and type F, in 1979 identified two populations of serotonin receptors in the brain of rats, which were called 5HT1 and 5HT2.

Subsequent pharmacological studies have highlighted the heterogeneity of 5HT1A receptors, which have been grouped in the class called 5HT1-like and the existence of a third serotonin receptor called 5HT3.

The classification criteria were based on the affinity of ligands specific to each type of serotonergic receptor, an approach that initially there was evidence of good but not without limitations later.

The 5HT2 receptors and the 5HT3 receptors seem to correspond to the 5-HT-D and 5-HT-M, identified in the periphery. They are currently approved 7 types of serotonin receptors and each type may belong to different subtypes distinguishable from each other by point of view molecular and pharmacological, at least 15 subpopulations have been cloned.

The nomenclature used today, while taking account of new molecular data, it is based on the pharmacology classification of Peroutka and Snyder 1979.

The strength of the original classification based drug has been demonstrated by the data of molecular biology, because the receptors are classified as 5HT1A, 5HT1B, 5HT1C, 5HT1D, 5HT1E 5HT1F and share high sequence homology with each other, with shares 30-50% identical and much less when compared to the 5HT2 receptors (tab.1.2). All have a high affinity for serotonin and inhibit adenylyl cyclase.

An exception is the 5HT1C receptor that has 78% homology with the 5HT2 and how 5HT2 it stimulates phosphoinositide hydrolysis. It is therefore a member of the 5HT2 class even though it was originally classified as a 5HT1 for its high affinity for serotonin. The 5HT2 receptors were called 5HT2A and 5HT1C 5HT2C.

On the basis of physiological and pharmacological properties has been identified another class of serotonin receptors, the 5HT4. They were then cloned three other types of serotonin receptors, called 5HT5, 5HT6 and
5HT7, that do not meet the criteria of molecular and pharmacologists no other type of serotonin receptor.

With the techniques of molecular biology have identified two types of serotonin receptors, those coupled to G proteins and those associated with an ion channel.

The compounds tricyclic antidepressants or neuroleptics, which bind the receptor 5HT2a (73).

**Serotonergic receptors**

**Serotonergic system and psychiatric disorders**

Since 1948, when serotonin was isolated and identified, there has been an exponential growth of information on the biochemical, physiological and behavioral effects.

The use of several serotonergic agents in a variety of clinical conditions indicate that serotonin is involved in many functions and behaviors. Although changes were observed in many disorders of the serotonergic system, has not yet been identified serotonergic disorder with clear and defined genetic, anatomical and biochemical.

The search initially focused on the route of synthesis and catabolism of serotonin and the discovery of new drugs that interact with these processes. The demonstration of the efficacy of MAOIs in the treatment of depression and psychostimulant effects of LSD have suggested that serotonin might play a role in the pathogenesis of depression and schizophrenia.

The use of precursors, or agonists and antagonists serotonin showed the impairment of the serotonergic system in various clinical conditions.

The direct demonstration of the serotonin function at the central level is still difficult.

Alteration of serotonergic transmission seems to be involved in many psychiatric disorders, mood and anxiety disorders, particularly obsessive-compulsive disorder, schizophrenia, eating disorders and in disorders of impulse control.

However, the observed changes, because the serotonin system is a complex modulatory and its interdependence with other neurotransmitter systems, may be secondary to an alteration in another primary system.

The impetus to study the relationship between serotonin and depression is derived from data on receptor function after chronic treatment with antidepressants.
### Table 1.2. Classification of receptors.

<table>
<thead>
<tr>
<th>RECEPTOR SUBTYPE</th>
<th>DISTRIBUTION</th>
<th>MECHANISM POST-RECEPTOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>5HT1a</td>
<td>Raphe nuclei, hippocampus</td>
<td>↓ cAMP potassium channels</td>
</tr>
<tr>
<td>5HT1b</td>
<td>Substantia nigra, globus pallidus, basalganglia</td>
<td>↓ cAMP</td>
</tr>
<tr>
<td>5HT1d</td>
<td>Brain</td>
<td>↓ cAMP</td>
</tr>
<tr>
<td>5HT1e</td>
<td>Cortex, putamen</td>
<td>↓ cAMP</td>
</tr>
<tr>
<td>5HT1f</td>
<td>Cortex, hippocampus</td>
<td>↓ cAMP</td>
</tr>
<tr>
<td>5HT2a</td>
<td>Platelets, smooth muscle, cerebral cortex</td>
<td>↑IP3</td>
</tr>
<tr>
<td>5HT2b</td>
<td>Gastric fundus</td>
<td>↑IP3</td>
</tr>
<tr>
<td>5HT2c</td>
<td>Choroid plexus, hippocampus, substantianigra</td>
<td>↑IP3</td>
</tr>
<tr>
<td>5HT3</td>
<td>Sensory innervation and enteric</td>
<td>The receptor is an ion channel sodium/potassium</td>
</tr>
<tr>
<td>5HT4</td>
<td>Snc and myenteric neurons, smooth muscle</td>
<td>↓ cAMP</td>
</tr>
<tr>
<td>5HT5</td>
<td>Brain</td>
<td>Unknown</td>
</tr>
<tr>
<td>5HT6,7</td>
<td>Brain</td>
<td>↓ cAMP</td>
</tr>
</tbody>
</table>
The most important changes observed after treatment with tricyclics and MAOIs are a reduction in the number of 5HT2 receptors and increased sensitivity of serotonergic receptors, as judged by electrophysiological studies.

After treatment with selective serotonin reuptake inhibitors, with the techniques of binding was shown a down-regulation of 5HT1 receptors and 5HT2 receptors, with electrophysiological studies an increased sensitivity of serotonergic receptors of the same.

Desensitization of presynaptic serotonergic receptors causes disinhibition of serotonergic transmission.

Electrophysiological studies show enhancement of the sensitivity of postsynaptic 5HT1A receptors and, therefore, of serotonergic transmission.

Recent studies have focused on the mechanisms of uptake, in particular on the serotonin carrier, have shown that treatment with drugs blocking the reuptake of serotonin reduces the content of specific mRNA in the raphe nuclei. There are also experimental evidences that indicate a dysfunction of the serotonergic system in depression (25).

Researchers at Duke University Medical Center have determined for the first time the role of an enzyme in rats that specifically controls the production of serotonin in the brain.

Different versions of this enzyme (TPH2) can have large effects on brain levels of the chemical messenger, which has been associated with numerous physiological and behavioural functions, including mood, emotion, sleep and appetite.

The study, described in an article published recently in the journal "Science", has important implications for the understanding of some psychiatric disorders and their treatment.

"For the first time - said the biologist Marc Caron, Howard Hughes Medical Institute researcher and lead author of the study - we have identified a natural genetic difference that controls the brain's production of serotonin." The discovery provides new clues for understanding the role of the enzyme and the gene that codes for it, in animal behavior and psychiatric disorders in humans.

Low levels of serotonin have been associated with disturbances such as depression, anxiety, post-traumatic stress and attention deficit hyperactivity disorder.

Scientists at Johns Hopkins and the National Cancer Institute have discovered a "missing link" a brain chemical whose levels rise and fall quickly in response to stress, fear and mood swings – and consequently affects new neural circuits.
"What we have discovered a connection between what happens to a person daily, and the way his brain responds, in terms of emotional, long-term," explains neuropathologist Vassilis E. Koliatsos of Johns Hopkins Institute. News of the discovery was published on the issue of 21 December 1999 of Proceedings of the National Academy of Sciences.

Serotonin is a molecule closely related to depression. Neuroscientists also know for some time that serotonin plays an active role in other psychiatric disorders: impulsive behavior, aggression, eating disorders, schizophrenia. More generally pertaining of serotonin to the major highways of the brain, which regulate the traffic devoted to mood, sleep and appetite.

In a congress held in Rome in June 1999 by Professor Paolo Curatolo University of Rome Tor Vergata, were presented the first results of research conducted using functional neuroimaging and no longer, as in the past, roughly anatomy. D. C. Chugani from Detroit has shown, using PET with labelled tryptophan, a characteristic profile in the development of brain synthesis serotonin. In normal subjects there is a decrease with age is higher in children under five, the age at which he begins to decrease to move quickly to levels that are less than half of adults and children. Despite the huge number of data showing a deficit of serotonergic presynaptic activity and alteration of postsynaptic receptors at central level, in particular an increased responsiveness of the desensitization of 5HT1A and 5HT2, you still can not determine whether the altered activity serotonin is directly related to the pathogenesis of depression or is a factor of vulnerability. To propose a pathogenetic model valid for the various depressive disorders must consider the interactions between subsystems serotonergic and between the serotonin and other neurotransmitter systems together with the complexity of the depressive symptoms.

The frequent comorbidity and overlap in symptoms observed in those psychiatric disorders, which is documented dysfunction of the serotonergic system, suggest that altered serotonergic transmission correlate with a particular psychobiological function rather than a specific diagnosis. An analysis of the literature indicates that serotonin reuptake inhibitors are effective only in 50-60% of patients and the results of both biochemical studies, aimed at measuring blood and liquoral markers of serotonergic transmission, and those of stimulation drug are controversial.

With regard to pharmacological challenge studies suggest a hypersensitivity of the serotonergic system with regard to the behavioral aspect and a hyposensitivity with regard to neuroendocrine responses, in particular prolactin. The hypothesis of hypersensitivity is also based on the
action of serotonin uptake inhibitors, which cause, after chronic treatment, a down-regulation of serotonergic receptors (76).

**Serotonin and premenstrual dysphoric disorder**

Numerous studies have shown that the neurotransmitter involved in premenstrual disorders is serotonin. It is involved in the phenomena of irritability in the onset of depressive features, in altering appetite and other neuro-behavioral disorders. To test these hypotheses have been numerous animal experiments that confirm that aggression is between the effects of serotonin deficiency in the CNS of rodents.

Although depressed mood and carbohydrate craving are characterized by adjustment serotonin.

The involvement of serotonin in premenstrual dysphoric adjustment problem is also demonstrated by the fact that drugs that facilitate serotonergic neurotransmission reduce aggressive behavior. Unequivocally positive results were obtained with drug treatments performed with the so-called SSRIs (selective serotonin reuptake inhibitors).

**Selective inhibitor of serotonin reuptake**

**Structural-chemical aspects**

The selective serotonin reuptake inhibitors (SSRIs) represent a group of molecules with antidepressant activity with high affinity for serotonin carriers, and with much lower affinity for norepinephrine and dopamine carriers, and for adrenergic, histaminergic, muscarinic, serotonin and dopamine receptors.

The first specific inhibitor of serotonin in therapy introduced in the early 80' was the zimelidina that, whilst there have been effective in the treatment of depression, caused significant side effects in some individuals so as to be withdrawn from the market. Currently in Italy are commercially available compound 5 (Figure1.3):

- fluoxetine: a fenilpropilamina straight chain;
- fluvoxamine: consists of a single benzene ring type with two side chains;
- paroxetine: phenylpiperidine compound;
- sertraline: naphthylamine compound structure;
- citalopram: ftalenico bicyclic derivative, a racemic mixture whose use has recently been replaced dall'enantiomero active escitalopram.
The different chemical structure results in unique characteristics in terms of pharmacokinetic and pharmacodynamic properties, in turn, can lead to differences in the clinical profile of action of the different SSRIs (76).

**Mechanism of Action**

The serotonergic neurotransmitter system is the main target of SSRIs neurobiology. These compounds are able to block the serotonin carriers with a different potency and selectivity.

The blocking of carriers takes place immediately after their administration, but, like other medications to antidepressant activity, should be administered for prolonged periods of time before bringing in significant improvements in clinical status of depressed patients.

The latency of onset of the clinical effect suggests the presence of neurobiological adaptive mechanisms responsible for clinical action of SSRIs.
Studies in animal models have shown that acute administration of SSRIs reduces the firing activity of serotonergic neurons after prolonged treatment and that it has the complete recovery of this activity. A process of desensitization of 5-HT1A autoreceptor somatodendritic present on serotonergic neurons, could be the explanation for this phenomenon.

These autoreceptors, via inhibition of serotonergic neurons, have a duty to "regulate" the release of serotonin in the target areas (cortex, hippocampus, etc.) and it is likely that the immediate effect of administration of an SSRI, namely the increase of serotonin in the synaptic space following the expected blocking reuptake, is eliminated, or at least reduced by the reduction of discharge of serotonergic neurons. In fact, it was demonstrated that acute administration of SSRIs leads to an increase in extracellular concentrations of serotonin in the cell body of neurons in the raphe, but not at the level of the projection areas of serotonergic neurons (frontal cortex, striatum).

After prolonged treatment with an SSRI is observed a significant increase in extracellular concentrations of serotonin also at the terminal, probably due to the desensitization of 5-HT1A autoreceptor somatodendritic..

This hypothesis could explain the latency of clinical response as the time required for desensitization of autoreceptors, and therefore to increased levels of serotonin in terminal areas, reflects the need to onset of antidepressant (down regulation).

At the synaptic level after chronic treatment with SSRIs, serotonin interacts with specific membrane receptors. With the exception of 5-HT3 receptor, which is permeable to several ion-channel, all serotonin receptors are G protein-coupled.

Their activation results in stimulation or inhibition of various intracellular signal transduction cascades that lead to various biological responses. Although it is not clear whether the clinical response is the immediate consequence of activation of certain serotonin receptors are also required if synaptic mechanisms in adaptive mode, has been well documented that treatment with SSRIs can alter the intracellular mechanisms. SSRIs can increase the activity of some protein kinases and some of their substrates involved in the regulation of the release of certain neurotransmitters.

The changes induced by them on protein phosphorylation processes result in short-term modulators of neuronal function (release and synthesis of neurotransmitters, receptor sensitivity), while the processes leading to modification of gene expression modulators of neuronal function in the long term (synthesis of enzymes and receptors).

While considering the serotonin system as the main target of SSRIs, in considering their mechanism of action is necessary to bear in mind that this system regulates and is in turn regulated by other neurotransmitter systems (noradrenergic, dopaminergic, GABAergic) (Fig.2.3) (75).
Pharmacokinetics

Absorption

Administered orally, all SSRIs are well absorbed. In general, their use may be made either before or after meals, because the presence of food does not affect their absorption and thus bioavailability.
If you're using sertraline or fluoxetine, it's still recommended in take during or immediately after meals because their plasma concentration seems to be increased. The only compound currently available for parenteral use is citalopram (76).

**Distribution**

SSRIs are fat-soluble molecules and have a high volume of distribution, being present, as well as in the central nervous system, also in many other tissues. The plasma protein binding varies from drug to drug in a range between 50 and 99%.

Fluvoxamine and citalopram are the SSRIs that bind to a lesser extent to plasma proteins.

The binding capacity must be taken into account if they are co-administered drugs with higher affinity to plasma proteins (eg., Acetylsalicylic acid), which, by displacing the binding site SSRIs, may increase its concentration in plasma, which could result in an increase in side effects (77).

**Metabolism and cytochrome P450**

The metabolism occurs primarily in the liver. SSRIs are indeed catabolized by microsomal enzyme complex isoenzymes of cytochrome P450 (CYP) localized in the endoplasmic reticulum of hepatocytes, but also, albeit to a lesser extent, in the central nervous system.

Among the various isoenzymes involved in the oxidative metabolism of endogenous substances and drugs, it seems that at least CYP1A2, CYP2D6, CYP2C19 and CYP3A3/4 are implicated in that of SSRIs. Some isozymes are also encoded by polymorphic genes that express that is a considerable variability of expression.

This implies the existence of subjects who metabolize the substances in a long time (slow metabolizers) or quickly (rapid metabolizers). The SSRIs differ considerably in their ability to inhibit certain CYP450 enzymes in vitro. This can lead to important interactions with other medications to antidepressant activity that is otherwise. In setting up a therapeutic strategy must take into account the possible side effects (onset or increase in side effects, increase or decrease the plasma concentrations of drugs associated), but also the ability to leverage in positive terms, that is clinically useful, these interactions. In fact, reducing the metabolism of a drug can enhance the action.
The half-life SSRIs, after single doses in healthy subjects, it is within the range of between 15 and 48 hours. After repeated administration, these values are significantly modified because these drugs, with the exception of sertraline and citalopram, are able to inhibit their own metabolism.

Fluoxetine is the only SSRI that gives rise to a metabolite, norfluoxetine, strongly active on serotonin reuptake and a half-life of approximately 15 days.

Paroxetine, sertraline, and citalopram produce metabolites that have no clinical relevance; fluvoxamine gives only inactive metabolites. Fluoxetine, fluvoxamine and paroxetine should be used with caution, i.e., at doses below those used in clinical practice, in all patients presenting with liver dysfunction because they have variations in their metabolism and their pharmacokinetics. (77)

**Elimination**

SSRIs are excreted in the urine and only a small part in the stool.

It should be noted that even in subjects with renal dysfunction and in the elderly SSRI can be used at full dosage, with the exception of paroxetine for which you can see increases in plasma levels up to 150% (77).

**Drug interactions**

Fluvoxamine, even at low doses, predominantly by inhibiting the isoenzyme A2 leads to increased plasma levels of molecules such as propranolol, warfarin, theophylline, carbamazepine and tricyclic antidepressants, fluoxetine and paroxetine, most of the inhibitory '2D6 isoenzyme, are greatly reduced when used in doses associated with a tricyclic antidepressant, and when associated with AEDs have a lower plasma level.

Sertraline has less potential for inhibition of cytochrome P450 and, consequently, less potential for pharmacokinetic interactions give, there is little knowledge about the possible drug interactions with other drugs of citalopram.

**Side effects, toxicity and withdrawal syndromes**

SSRIs are well tolerated and safe compared to other antidepressants. Nausea, found in approximately 20% of cases treated is one of the reasons for stopping treatment with SSRIs.

In this regard it is important to emphasize that there is an effect "dose dependent" for which, starting treatment with low doses and increasing it gradually, the incidence of the symptom is reduced considerably.
It is also possible occurrence of diarrhea, dry mouth and decreased appetite, and these symptoms tend to disappear with continued treatment. In patients with gastritis or ulcer prior should be recommended gastroprotective therapy. In case of occurrence of migraine and/or sexual dysfunction (decreased libido, impotence, delayed ejaculation, anorgasmia and dysmenorrhea) increased gradually in increasing or a slight reduction in the dosage of the drug may be useful. Anxiety, agitation, nervousness are the most common side effects during treatment with fluoxetine and paroxetine, and sedation and asthenia with fluvoxamine and sertraline. Insomnia can often be "corrected" by changing the time of taking the drug. It has also been reported, although in rare cases, the appearance of extrapyramidal effects (tremor, akathisia, dystonic reactions). (45)

Rare event, but to consider is the possible occurrence of serotonin syndrome, serotonin hyper toxic condition, which most common cause is the effect of the interaction between serotonergic agents (SSRIs, tricyclics) and MAOIs. The optimal strategy to prevent it is obviously to avoid the use of combinations of drugs with serotonergic activity. Treatment of serotonin syndrome involves the suspension of serotonin, the restoration of vital signs, hydration, benzodiazepine therapy to reduce muscle stiffness and, in severe cases, the use of serotonin receptor antagonists such as methysergide.

Recent studies have reported the possible occurrence of withdrawal syndromes after discontinuation of treatment with SSRIs.

This syndrome is characterized by the appearance of symptoms not previously experienced as part of the disease (sweating, numbness, visual disturbances, drowsiness, anxiety, irritability, insomnia, nightmares, headache, nausea) and can be lysed by reintroducing the antidepressant treatment.

The SSRI discontinuation syndrome appears on average after 3 days of discontinuing treatment and, if not re-administered the drug, lasts for about 15 days. The risk of occurrence of withdrawal syndrome is greater when the treatment with SSRIs is more than 2 months.

It is therefore appropriate to gradually reduce the dosage of SSRIs over a few weeks before the administration permanently discontinued (77).

**Therapeutic indications**

Major depression  
Obsessive  
Bulimia and anorexia nervosa  
Panic attacks  
Social phobia  
Pain associated with diabetic neuropathy  
Premenstrual syndrome
SSRIs and PMS

Most of the studies about the effectiveness of antidepressants in PMDD is in clinical trials with the SSRIs sertraline and fluoxetine in particular (25).

Other drugs that have shown their efficacy in random studies, double-blind studies or case-control studies are paroxetine, citalopram: they too SSRIs, SNRIs the (serotonin and norepinephrine reuptake inhibitor), venlafaxine and tricyclic antidepressant clomipramine. SSRIs are becoming the treatment of choice for severe premenstrual syndrome, although, for now, have been officially approved for this indication only in Great Britain, United States, New Zealand, Portugal and Austria (2004) (3,47,34,35) (fig.3.3).

Numerous studies with a double-blind, randomized, confirm that SSRIs reduce substantially the mental disorders, but also physical ones, improving the quality of life of women who suffer from it (Lancet, Paul Dimmock).

The efficiency thanks to low doses should not even deal with major side effects, mostly limited to insomnia, fatigue and gastrointestinal disturbances manageable. In addition, the long-term use does not seem to be an obstacle, given the numerous studies demonstrating the safety of these drugs in long-term treatment and low cost (39,40).

Still provisional and limited data indicate a possible optimal activity at doses lower than those used for initial therapy of depression, with the appearance of clinical benefit in a short time (1-2 days), significantly lower than those necessary for the appearance of effects in the case of depression or anxiety disorders (3-4 weeks) (47).

If a woman does not show improvement after 3 menstrual cycles of treatment you can try another SSRI, and in the same way if you experience adverse side effects too (48, 49). The administration of these drugs is also possible in different ways: treatment with a daily intake for the only period in which symptoms occur (called intermittent mode of administration), a consistent daily treatment for the duration of the cycle (continuous administration), treatment with two different doses to start connecting to menstruation and ovulation (semi-intermittent mode) (Wikander et al 1998, cited above, by Grady-Weliky, 2003) (5,6).

The effectiveness of non-continuous cycles would indicate a temporary increase in serotonin concentrations in the luteal phase of the menstrual cycle, suggesting the possibility that menstrual disorders may actually be cured with a dose intermittent cycles of selective reuptake inhibitors serotonin, which would not only save money, but also a lower risk of side effects and therefore a better tolerability (28).

Because it can be difficult to locate the precise moment in which ovulation occurs, for this final type of treatment you rule by calculating
the expected two weeks before the start of menstruation (the more regular the cycle is the more plausible is the precision mode of treatment).

Also as regards the duration of treatment, many trials have lasted longer than 3 months and 6 months.

SSRIs do not affect at all the hormonal and its variations during the menstrual cycle will interfere with the sexual sphere. Several randomized, blind, placebo-controlled, based on different diagnostic criteria and outcome measures have established the efficacy and tolerability of fluoxetine in the treatment of PMDD.

Positive responses have also been reported in controlled studies and not with sertraline, paroxetine, and fluvoxamine.

In a study by Eriksson and co-workers in 1995 was made a direct comparison between one of the members of the class of SSRIs better performing treatment, paroxetine, and maprotiline, a selective inhibitor of noradrenaline, and was first demonstrated significant efficacy of the two in significantly reducing the symptoms of premenstrual disorder, while the other drug had no different results than those achieved with placebo (7).

In a 2004 study by Cohen and colleagues set out to evaluate the efficacy of daily treatment with paroxetine during the menstrual cycle in tablets of 12.5 mg / day or 25mg/day vs. placebo.

This study evaluated the efficacy of paroxetine in both doses compared to placebo: in fact there was a reduction of symptoms of PMDD by 50% to 71% in patients using 25 mg tablets and 67% of patients using tablets from 12.5 mg.

Paroxetine is also effective in reducing the physical symptoms associated with PMDD as well as reducing irritability, tension and emotional lability.

Citalopram in doses from 10 mg-30 day use only during the luteal phase of the cycle is more effective than continuous treatment.

Sertraline and fluoxetine are the only SSRI approved by the FDA in the treatment of PMDD.

Sertraline in doses of 50 and 150 mg daily is superior to placebo when used during the entire menstrual cycle or used only in the luteal phase. Many studies have also reported the probable mechanism by which fluoxetine is effective in PMDD.

One hypothesis is that there may be an increased sensitivity to progesterone, possibly caused by a deficiency of serotonin. In fact, the allopregnenolone, a metabolite of progesterone was found to be neuroactive modulator of the GABA receptors that alter the central stress response. In support of this hypothesis, the effectiveness of other SSRIs in the treatment of PMDD (29).

The use of SSRIs in the treatment of PMDD may be problematic for a low compliance as there some side effects like sexual dysfunction,
anorgasmia. (31) A promising new treatment suggests that just take 20 mg of fluoxetine for two weeks before your period to achieve the same result. (30) the same procedure was effective with sertraline. (16)

There is also the possibility of using controlled-release fluoxetine long-acting 90 mg once a week. Stone and colleagues in 91'proved the efficacy of fluoxetine versus placebo in 20 women.

In women who had given fluoxetine adverse events that were manifested were fatigue, decreased appetite, insomnia and decreased libido. In women who had received placebo instead were manifested headaches, insomnia, apathy, anxiety, nausea and increased appetite. However, all patients using fluoxetine did not abandon the study.

In the broader clinical trial, of Steiner and colleagues, 313 women with late luteal phase dysphoric disorder in DSM-III-R, received 20mg of fluoxetine daily, 60 mg of fluoxetine or placebo for 6 cycles, after a washout period with placebo for two cycles.

Hundred and eighty women completed the study. Both doses of fluoxetine were superior to placebo from the first menstrual cycle and for all 6 cycles.

A greater number of patients treated with 60 mg of fluoxetine compared to those treated with 20 mg or placebo discontinued therapy because of side effects. Moreover, a higher number of patients treated with placebo discontinued treatment due to lack of response, compared to those treated with a dose of fluoxetine and the other.

So Steiner and colleagues showed that the use of fluoxetine to treat PMDD to 20 mg was well tolerated. In a follow-up study of 34 women, fluoxetine was superior to bupropion and placebo in the treatment of PMDD. (52) This dysphoric disorder often begins during adolescence.

In the study by Thomas J. Silber et all 2004, published in 2005 in the Journal of Adolescent health have reported 3 cases of adolescents suffering from PMDD and treated with fluoxetine for 2 years.

The more interesting case is that of ZW, a seventeen year old African-American although that had always been in good health, for a period of 2 years has not attended school.

The patients in these 2 years she had felt tortured by menstrual disorders, irritability and outbursts of aggression for which they later regretted. A house had been nicknamed as "Ms. Jekyll and Ms. Hide" because of his mood swings during the menstrual cycle.

The girl was initially treated with diet, exercise program and a hormonal contraceptive, but since there had been no improvement, he began treatment with fluoxetine 20 mg.
After this treatment does not absented himself to school, also did not take place any weight gain. For two years there have been no symptoms. Later moved to a dose of fluoxetine once a week long duration of action. (26,46,32)

It remains to determine the impact of antidepressants on girls under 18 years and especially on women taking oral contraceptives (which are still hormones).

In fact, many women during their reproductive age are using oral contraceptives and a major clinical trial has evaluated the impact of the use of oral contraceptives and use of antidepressants in women with PMS / PMDD.

Freeman and colleagues compared the use with non-use of oral contraceptives during the three-month double-blind treatment with sertraline, desipramine or placebo. From this trial no significant differences emerged between the use and non-use, oral contraceptives are therefore no influence of antidepressants used during the PMDD (22).

![Figure 3.3](image.png)

**Figure 3.3.** Antidepressants versus placebo for premenstrual syndrome. In the meta-analysis conducted in Great Britain negative values indicate a reduction in noise.

In addition to SSRIs, venlafaxine has been proven to PMDD. In a study of 164 patients to 4 cycles of treatment of continuous administration of venlafaxine to 50-200 mg / day was found to be more effective than placebo as regards mental and physical symptoms of PMDD.

The improvements with venlafaxine were quick and with a 80% reduction in premenstrual symptoms. 60% of subjects in the group that had
used venlafaxine have responded to treatment whereas the placebo group only 35% (21,33).

**Dose**

20-40 mg fluoxetine* (Prozac-Fluoxeren)  
100-200 mg fluvoxamine (Fevarin-Maverin)  
20-40 mg paroxetine (Seroxat-Sereupin)  
50-100 mg sertraline (Zoloft-tätig)  
20-40 mg citalopram (Elopram-Seropram)  
5-10 mg escitalopram (Entact) (65)

The active ingredient in Prozac, fluoxetine*, a drug that has revolutionized the treatment of depression for a dose of 20 mg daily, from March 1, 2004 is being marketed in the U.S. with a new formulation of 90 mg can be taken just once a week indicated in the treatment of premenstrual dysphoria (3).

In this class of drugs in the treatment of premenstrual dysphoric disorder is gaining one of these drugs: sertraline, the active ingredient Zoloft and Tativ.

**Sertraline**

Sertraline is a selective serotonin reuptake inhibitor can be administered orally. It has a molecular weight of 342.7. Chemically it is (1S-cis)-4 (3,4-chlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naftalenammina hydrochloride and its empirical formulation is C17H17NCl2 • HCl. (Fig1.4) is a white crystalline powder soluble in water and isopropyl alcohol and less in ethanol.

![Figure 1.4. Chemical structure of sertraline.](image-url)
Pharmacodynamics

The mechanism of action of sertraline is inhibiting uptake of serotonin in the CNS. Clinical studies show that together with paroxetine is the most potent inhibitor of the reuptake of serotonin in vitro is 36 times more potent than fluoxetine and 205 times more potent than amitriptilina.

Studies on anesthetized rats have demonstrated that sertraline increases serotonin transmission to 14 times more potent than fluoxetine, the ID50 (inhibitory dose intravenous average) of the drug is 86 µg/kg (fluoxetine for 1175 µg/kg). The effect on the reuptake of serotonin is low, contrary to what is potent on dopamine resulting in a third of that of d-amphetamine. You may also have an indirect effect as a dopamine agonist, since it is similar to the human dopamine transporter. In vitro studies have shown that sertraline has no significant affinity for adrenergic receptors (alpha 1, alpha 2, beta), cholinergic, GABA, dopaminergic, histaminergic, serotonergic and benzodiazepine receptors. It is the SSRI with the lowest risk for anticholinergic effects such as constipation and tachycardia (76).

Pharmacokinetics

The half-life of the drug is less than 26 hours, the half-life allows for once daily orally. Concomitant food intake does not change the pharmacokinetics, but it enhances the bioavailability to 28% compared to the bioavailability on an empty stomach. It is therefore preferable to recommending the intake of the drug during meals (higher peak plasma concentration).

The pharmacokinetic profile is similar whether sertraline is taken in the morning and evening, it does not show variations in its efficacy and tolerability.

Metabolism is by demethylation with the formation of the main metabolite, des-methyl sertraline, inactive. Below this is metabolized to alpha-hydroxyketones and then conjugated and excreted in the urine or bile.

The in vitro desmethyl sertraline has less than 5% of the drug sertraline. Also shows no clinical activity in vivo: in a study of anesthetized rats the metabolite has no effect on the disposal by the cells of the dorsal raphe as opposed to the unchanged drug. After oral administration, sertraline is slowly absorbed with speed not dependent on the dosage.

The peak plasma concentration is reached after 7 hours, approximately, at doses ranging between 50 and 200 mg.

The peak plasma concentration is proportional to dose. The concentration of steady state is reached but after about 7 days once daily.

Pharmacokinetics in the elderly is unchanged, are not reported accumulation. There is therefore no need to adjust dosages.
A double-blind study shows that sertraline in the elderly compared to fluoxetine has a faster onset of the clinical effect in two weeks. Plasma levels are proportional to dose.

In patients with renal dysfunction the drug's pharmacokinetic profile has not changed so you do not need a dose adjustment, and careful monitoring is recommended. The dosage should instead be reduced in patients with liver dysfunction: time to breakdown and the average life of the drug tend to increase significantly in patients with mild disease (76).

**Dosing**

Sertraline should be taken once daily. According to the results of a series of studies, the optimal dose of sertraline is 50 mg daily.

This dosage is recommended in the treatment of depressive disorders, but there are indications that demonstrate the efficacy of this dose in patients with obsessive compulsive disorder and panic disorder.

The daily dose for all indications may be increased to a maximum of 200 mg per day (76).

**Overdose**

Cases of overdose taking sertraline occurred only at doses greater than 13.5 grams. The use of excessive doses of sertraline in combination with other drugs and/or alcohol was sometimes fatal, symptoms of overdose include serotonin-mediated side effects such as drowsiness, gastrointestinal disturbances, tachycardia, tremor, agitation and dizziness. Less frequently reported were also episodes of coma.

There are no specific antidotes to sertraline (76).

**Inhibition of cytochrome P 450**

The formation of the demethylated metabolite is probably effected by isoenzyme to 3 to 3 / 4. The drug has weak inhibitory activity on isoenzyme 2 D 6; in the literature there are few studies of changes in the metabolism of tricyclic drugs, desipramine and imipramine, substrates of the same isoenzyme, induced by sertraline.

The drug is inhibitor of 3 A, even in this case is low power. This inhibitory effect could result in increased plasma levels of carbamazepine, if the drugs are administered simultaneously, the drug is not, however, can inhibit the metabolism of carbamazepine or alprazolam (another substrate of 3A) even at the maximum dose of 200 mg.
As for the 1A2 isoenzyme, the inhibitory effect is minimal, therefore, there are no interactions with warfarin. In healthy volunteers receiving warfarin but was instead reported an increase in prothrombin time due to the inhibition of 8% isoenzyme 2C9/10, was also reported an increase of 18% of plasma concentrations of tolbutamide. The fallout of these clinical effects is still considered to be insignificant (76).

**Indications and clinical use**

Major depressive disorder
Obsessive Compulsive Disorder
Panic attacks
Post Traumatic Stress Disorder
Premenstrual dysphoric disorder
Social Disorder (especially in the elderly)

**Contraindications**

It’s generally contraindicated in pregnancy and lactation.

The concomitant use of sertraline and monoamine oxidase inhibitors drugs is contraindicated. The use of this drug should be avoided in patients with unstable epilepsy (76).

**Interactions**

Some cases of severe reactions occurred in patients in whom sertraline was administered concomitantly with monoamine oxidase inhibitors (MAOIs). In some patients have manifested the features of neuroleptic malignant syndrome (serotonin syndrome) whose symptoms include hyperthermia, muscle rigidity, myoclonus, autonomic nervous system dysfunction with the possibility of rapid fluctuations of vital signs, altered mental status such as confusion, irritability and extreme agitation progressing to delirium and coma.

Therefore, sertraline should not be used in combination with an MAOI or within 14 days of discontinuing an MAOI.

The co-administration of sertraline with other drugs that enhance serotonergic neurotransmission (5-HT receptor agonists) should be avoided because of potential pharmacokinetic interactions.

It should be administered with caution in patients taking concomitant use of anticoagulant drugs that affect platelet aggregation. (76)
Addiction and dependency

In human studies and animal studies, sertraline has been shown to induce some dependence potential.

In any case, as with any CNS active drug, physicians should carefully evaluate the patient with regard to any history of drug abuse, and follow these patients and see if you develop signs of misuse or abuse of sertraline (76).

Side effects

It is generally well tolerated. The most common side effects are headache, nausea, diarrhea, insomnia, fatigue. Ejaculatory disorders may also occur. Are rare tremor, paresthesia, weight loss and disorders of psychiatry (76).

Sertraline and premenstrual dysphoric disorder

Sertraline: Drug of choice?

According to a study by Endicott, McLaughlin et al.. published on J. Clin. Psychiatry in 2003, making a comparison between the various SSRIs, sertraline is the drug of first choice in the treatment of PMDD.

There are many factors that influence in making a drug of first choice: the patient's symptoms, the proven effectiveness of the drug in treating the symptoms, tolerability and experience of the physician with the drug. The cost is considered important in the choice of treatment: often choose a drug with the lowest cost without considering the total cost of care about the possible side effects.

The results of this study demonstrated that sertraline can be considered the drug that allows for lower spending in the treatment of PMDD.

Treatment with this drug is in fact the one with the lowest cost during the first 6 months of starting treatment. In general the cost of the treatment of PMDD appears to be $ 165 for the six months of treatment for patients using sertraline instead of spending was $ 126 and this was significantly less than the cost of treatment with paroxetine $ 217.

As for fluoxetine and citalopram but the difference was not significant because the costs were respectively $ 160 and $ 158.Even in the total expenditure the cost of sertraline was the lowest compared to the $ 1649 cost of paroxetine and fluoxetine ($ 1828 and $ 1892). (19)

In 96 'Freeman and Rickels in one study evaluated the efficacy of sertraline and desipramine, tricyclic antidepressant agonist norepinephrine.
The assay was performed on 32 women. The study found that sertraline and desipramine are both effective in the treatment of PMS / PMDD, but sertraline is better tolerated. In fact, in 27% of patients taking desipramine were manifested: insomnia, nausea, dry mouth. The side effects reported by patients using sertraline were instead included nausea, insomnia, headaches, and were generally temporary. Only 4 people who went more than 2 months the trial of sertraline resulted in loss of libido.

So that both sertraline and desipramine are effective in reducing depressive symptoms of PMDD although sertraline is generally better tolerated than desipramine, which in addition to having a higher side effect profile has also cost more. (15) Further studies were carried out by Freeman and colleagues in the same 99 'and Halbreich and L. Kahn published in 2003 that led to the same trial with the same results of the previous study.

The subjects taking sertraline at doses between 50-150 mg / day, and desipramine at the same dose or placebo for 3 cycles of treatment. There was an improvement in symptoms reported by the Daily Symptom Report Scale of 65% for sertraline, 36% for desipramine and 29% for placebo (20).

In September 97, the study of Dr. Yonkers and colleagues tested the efficacy of sertraline to fluoxetine in PMDD as an alternative.

The advantage of sertraline is that you can use a lower starting dose. The half-life of sertraline also being lower is definitely an advantage, it is preferable to use drugs with short half-life to those with longer half-life because they are more easily eliminated. Fluoxetine and its metabolite have a half-life of 4 days, respectively, and 4-16 days.

Sertraline has a half-life instead of about 24 hours and desmethylsertraline of 3-5 days. The rapid plasma clearance is also a benefit in women who wish to become pregnant and those whose pregnancy is unexpected.

In addition, sertraline at a dose of 50 mg has weak inhibitory activity on isoenzyme 2 D 6 and this reduces the risk of adverse events caused by drug interactions and toxicity (12).

About tolerability during the clinical trial we have seen that the strongest effects occurring only 8% of patients using sertraline compared to 2% of the patients who received placebo; occur the nausea, insomnia, diarrhea, fatigue and decreased libido.

Only nausea, diarrhea, and decreased libido were significantly higher for sertraline compared with placebo.

It was finally shown that sertraline has neither sedative and addictive, and addiction (36).
Mode of treatment: Continuous or intermittent?

Treatment with sertraline in premenstrual dysphoric disorder begins with a dose of 50 mg every day of the menstrual cycle or only in the luteal phase. It was not yet established a relationship between dose and effect.

Patients who do not respond to a dose of 50 mg/day may increase the dose to 150 mg daily throughout the cycle or during the luteal phase of the cycle, however, starting with a dose of 50 mg/day for at least three days beginning of each luteal phase.

The efficacy of sertraline in long-term treatment for more than three menstrual cycles has not been established yet fully in clinical trials.

Since the symptoms of PMDD in some women get worse until the beginning of menopause, it is important to have a treatment during the fertile period. Of course you can have dose adjustments or changing the mode using intermittent or continuous with the lower dose by checking periodically.

According to a study conducted by Uriel Halbreich, Jordan and Smaller published in September 1997, about the efficacy of sertraline in the treatment of PMDD performed on 15 women were assessed differences in continuous and intermittent treatment with sertraline at a dose of 100 mg daily.

This study showed that patients respond well to continuous treatment, but respond equally well when the treatment is limited to the luteal phase.

However, intermittent treatment has the benefit of being less expensive and also reduces what are the side effects (8).

Later in 2002 another study was published Halbreich et all in which it was shown that sertraline is certainly more effective than placebo and well tolerated in the treatment of PMDD when used for intermittent doses during the luteal phase of the menstrual cycle.

Sertraline has no advantage over placebo in improving physical symptoms of PMS but it is much more effective in reducing premenstrual disturbances in thinking and level of vegetation such as increased appetite, increased sleepiness and apathy.

The study also shows that following treatment with sertraline showed a rapid improvement in symptoms of PMDD using a lower dose (50-100 mg) than that used in previous studies that used continuous doses that reached 150 mg.

The patients tolerate the treatment very well intermittently, with only a few patients withdrew from the study due to adverse events.

Treatment with intermittent doses of sertraline was effective not only in alleviating the sufferings of PMDD, but also the quality of life (9).
In 2004, Freeman et al. compared the efficacy and compliance by the patient of continued treatment and intermittent treatment in the use of SSRIs, especially sertraline.

This study was conducted by the University of Pennsylvania from 1998 to 2002. The criteria were: age from 18 to 45 years, regular menstrual cycles of 22-35 days, and patients whose urine test indicated the possibility of ovulation.

They were also selected patients with persistent premenstrual symptoms for a minimum of six months, which affected negatively the work, family, life and social activities.

The rating scale used was the Daily Symptom Rating Form that includes symptoms such as depression, guilt, anxiety, tension, irritability, loss of interest, difficulty concentrating, etc. ...

This study revealed that there are significant differences between the two dosing regimens. Although side effects did not differ between the two groups that make use of sertraline in two different ways, although minor adverse events are reported in the assay in a continuous loop after 3 months of treatment.

However, the intermittent dosing offers less exposure to the drug which is an important factor to consider in the balance sheet risk -benefit.

The conclusion of this study is that the choice between the two modes is based on the patient and their individual experiences about the side effects (13).

Another study on the dosage form is performed by Pearlstein and colleagues in 2004, published in the Journal of Affective Disorder.

According to this study can be associated with a therapy dose intermittent doses or continuous depending on length and type of symptoms suffered by women with PMDD.

We analyzed the various subtypes of women: women who experience initially in a moderate and then more strongly until the symptoms more than two weeks before each menstrual period, may receive benefits from a full course of treatment, so even a and not just a pretreatment dose premenstrual phase, a larger subset of women whose symptoms persist for days after the start of each menstrual period, could benefit from a more efficient continuous treatment (37).

In 2005 was published in the Journal of Affective Disorders another study by Yonker, Pearlstein about the dosage of sertraline, the study set out to assess premenstrual symptoms, which were extended during the follicular phase were a dequately treated by lutein izing hormone assay, and if the sudden stop was associated with a withdrawal syndrome by drugs often reported after long-term treatment with some SSRIs.
The premenstrual syndrome: An overview

The third patient persistence of symptoms in the early days of the follicular phase has raised questions about the potential effectiveness of using a dosing during the luteal phase.

According to this study there is a sustained improvement in symptoms even in the first three days of the follicular phase, despite the discontinuation of sertraline on the first day of the cycle (37).

One study (Rosenbaum et all, 1998, Judge et all, 2002, Michelson et all, 2000) has also shown that there is a big improvement over the first three days of the follicular phase with the use of continuous therapy with either sertraline than with intermittent therapy.

It is likely that the interruption of the symptoms resulting from treatment with ovulation or at least started very early in the luteal phase leads to extend the benefits even after stopping the drug.

The other important issue addressed in this study is its sudden interruption of treatment.

The results were encouraging: there is no evidence of drug withdrawal syndrome. For the evaluation we used the criterion of 9 items of the DRSP about the withdrawal symptoms during 3-5 days.

This research, however, were not considered entirely reliable because, studied the effects include chills, diarrhea, nausea and dizziness, which are not mentioned in the DRSP as symptoms of withdrawal syndrome.

On the other hand, not all items of the DRSP seem to have credibility. From this study, as in all previous studies show that the optimal treatment is the dose in the luteal phase in relation to the individual needs of each woman.

Variations in treatment may include the continued administration of the pill for a period of time during the follicular phase, or for a longer interval in the early follicular phase, a daily dosage for women who have had only one week or less absence of symptoms.

The women whose profile is highly variable PMDD may benefit from a regime continuously.

You still need to do more research about treatments to understand how to identify dosing strategies for women with PMDD and to better understand the differences in the mechanism of action(depression) that SSRIs such as sertraline achieve effectiveness rapidly in PMDD (48, 17, 18).

**Treatment of premenstrual syndrome with continuous low dosage sertraline**

The aim of this section, was to evaluate the efficacy of sertraline in a group of patients with PMDD according to the DMS IV diagnostic criteria as described in previous chapters.
This clinical study took place at the outpatient clinic of the 'Mental Health Unit of District 44 (Chiaia, San Fernando, Posillipo) ASL Napoli 1.

They were followed every 7 women suffering from PMDD mean age 27 years, between 21 and 30.

The inclusion criteria of the trial provide a regular ovulatory menstrual cycle (26-35 days), good general health assessed by history medical, with physical examination and blood chemistry tests and regular weight (BMI between 20 and 25).

Exclusion criteria included evidence of major psychiatric disorders, any type of medical treatment and hormonal (birth control, non-conventional treatment such as homeopathy, herbal medicine) and pregnancy.

All patients followed a treatment with sertraline 50 mg continuously. The observational trials had a duration of 6 cycles with periodic medical checks monthly.

The evaluation of the outcome indicators of the trial was made possible through the administration of a self-assessment test.

This test consists of 10 items on the assessment of basic symptoms for the diagnosis of PMDD.

This scale of symptoms has allowed an assessment of the percentage difference before and after treatment with sertraline.

None of the patients emerged from the study for evidence of side effects.

The test was carried out as follows:

<table>
<thead>
<tr>
<th>Name:</th>
<th>City:</th>
<th>Birth:</th>
<th>Email:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Anno</td>
<td></td>
</tr>
</tbody>
</table>

0 Absence of symptoms
1 Symptoms of mild
2 Symptoms of moderate
3 Symptoms of severe

1) Bloating and breast tension or less associated with feeling of heaviness in the legs, swelling of the face, hands and abdomen

0 1
2 3
<table>
<thead>
<tr>
<th></th>
<th>2) Headache with or without nausea, vomiting, dizziness and tinnitus, visual disturbance</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3) Excessive hunger directed mainly to carbohydrates, including chocolate, bread and pizza</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4) Irritability, mood swings or less associated with palpitations, Feeling of lump in throat, tremors, chest pains, stomach cramps and abdominal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5) Profuse fatigue associated with sense of distaste, lack of motivation, sleepiness, tendency to isolation and the weeping</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6) Difficulty falling asleep or frequent waking at night or early morning awakening</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7) Forgetfulness, confusion, difficulty concentrating</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8) Constipation or diarrhea associated with or without abdominal cramps and bloating</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9) Furunculosis of the face, or cold sores</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10) Difficulty in following a diet, weight gain</td>
<td></td>
</tr>
</tbody>
</table>

Privacy Policy

I agree  |  disagree  |
Results
Rating percentage

Tables 1.5 and 2.5 show the frequencies with which a symptom has occurred with a certain size before and after therapy.

0 No symptoms
1 Symptoms of mild
2 Symptoms of moderate
3 Symptoms of severe

Table 1.5. Frequencies percentages prior to administration of sertraline.

<table>
<thead>
<tr>
<th>Symptoms/entities</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast swelling and Tension</td>
<td>_</td>
<td>_</td>
<td>57%</td>
<td>43%</td>
</tr>
<tr>
<td>Headache</td>
<td>_</td>
<td>28%</td>
<td>57%</td>
<td>14%</td>
</tr>
<tr>
<td>Excessive hunger</td>
<td>_</td>
<td>_</td>
<td>28%</td>
<td>72%</td>
</tr>
<tr>
<td>Irritability</td>
<td>_</td>
<td>_</td>
<td>57%</td>
<td>43%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>_</td>
<td>43%</td>
<td>43%</td>
<td>14%</td>
</tr>
<tr>
<td>Difficulty falling asleep</td>
<td>14%</td>
<td>86%</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Forgetfulness</td>
<td>_</td>
<td>57%</td>
<td>43%</td>
<td>_</td>
</tr>
<tr>
<td>Constipation</td>
<td>_</td>
<td>57%</td>
<td>43%</td>
<td>_</td>
</tr>
<tr>
<td>Furunculosis</td>
<td>85%</td>
<td>15%</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Increase Weight</td>
<td>_</td>
<td>_</td>
<td>43%</td>
<td>57%</td>
</tr>
</tbody>
</table>

Table 2.5. Frequencies rates after administration of sertraline.

<table>
<thead>
<tr>
<th>Symptoms/entities</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
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<td>28%</td>
<td>_</td>
</tr>
<tr>
<td>Headache</td>
<td>14%</td>
<td>72%</td>
<td>14%</td>
<td>_</td>
</tr>
<tr>
<td>Excessive hunger</td>
<td>_</td>
<td>43%</td>
<td>57%</td>
<td>_</td>
</tr>
<tr>
<td>Irritability</td>
<td>_</td>
<td>72%</td>
<td>28%</td>
<td>_</td>
</tr>
<tr>
<td>Fatigue</td>
<td>_</td>
<td>100%</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Difficulty falling asleep</td>
<td>14%</td>
<td>86%</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Forgetfulness</td>
<td>43%</td>
<td>57%</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Constipation</td>
<td>14%</td>
<td>58%</td>
<td>28%</td>
<td>_</td>
</tr>
<tr>
<td>Furunculosis</td>
<td>85%</td>
<td>15%</td>
<td>_</td>
<td>_</td>
</tr>
<tr>
<td>Increase Weight</td>
<td>_</td>
<td>57%</td>
<td>43%</td>
<td>_</td>
</tr>
</tbody>
</table>
The premenstrual syndrome: An overview

The analysis of the percentage tables, it appears that the swelling and the tension on the breast patients showed an incidence of 57% in the entity 2 and 43% in the entity 3.

After treatment with the drug in question, there has been a regression of the disorder: in fact, the symptoms disappeared completely in the entity 3 but the entity 1 surfacing in 72% of patients, while symptoms of entities 2 have been reduced to 28% of the subjects in question.

As for the headache, the patient samples analyzed in 28% of cases showed symptoms of 1 entities, in 57% of cases symptoms of 2 entities and 14% of the cases of 3 entities. Even for this item, after the administration of sertraline was noted the total absence of symptoms of entities 3 and even 28% did not experience any discomfort while only 72% of entitâl symptoms.
With regard to excessive hunger, where 72% of patients had symptoms of magnitude 3 and 28% of 2 entities, have completely disappeared disorders 3 entities, in 43% of cases have symptoms of magnitude 1 and 57% of cases symptoms of magnitude 2.
Similarly for the irritability has completely undone the component level 3, which was 43%, 43% surfacing a component of magnitude 1, while 57% of cases continues to feel discomfort level of 2.
With regard to fatigue for which 14% of cases have symptoms of magnitude 3 and 43% symptoms of magnitude 1 and 2, respectively, showed a concentration of 100% in disorders of entities 1.

Were not seen, however, changes with regard to difficulty falling asleep.

Positive notes are also recorded as regards the amnesia for which 57% of cases reported disturbances of entity 1 and 43% of entities 2: after administration of the drug in question 43% did not feel any discomfort and 57% noise only 1 entity.
As for the constipation for which respectively 57% and 43% of patients had experienced problems of entity 1 and 2, after treatment with sertraline was noted that 14% of cases does not feel any discomfort, inconvenience only 58% of entity 1 and only 28% of entity 2.
Remained unchanged figure for furunculosis, while the weight gain that appeared respectively for 43% and 57% noise level of 2 and 3, showed a regression to disorder of magnitude 1 and 2 respectively by 57% and 43%.
Overall score the extent of symptoms before and after treatment

An analysis of tests of individual patients and by adding the individual scores of the various items you have seen a marked overall improvement and therefore a reduction in symptoms (Tab.3.5).

Table 3.5. Overall score the extent of symptoms.

<table>
<thead>
<tr>
<th>PATIENTS</th>
<th>RESULTS BEFORE TREATMENT</th>
<th>RESULTS AFTER TREATMENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) S.B.</td>
<td>20</td>
<td>13</td>
</tr>
<tr>
<td>2) I.P.</td>
<td>18</td>
<td>12</td>
</tr>
<tr>
<td>3) M.D.</td>
<td>17</td>
<td>10</td>
</tr>
<tr>
<td>4) S.C.</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>5) E.I.</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>6) C.F.</td>
<td>16</td>
<td>7</td>
</tr>
<tr>
<td>7) A.D.</td>
<td>16</td>
<td>10</td>
</tr>
</tbody>
</table>

| AVERAGE SCORE | 17,57 | 10,14 |

![Bar chart showing average score before and after treatment](image)
From the self-assessment tests, for each patient showed the following results:

**Before treatment**

**Patient 1 S.B. Naples 26/02/1976**

- Breast swelling and tension
- Headache
- Excessive hunger
- Irritability
- Fatigue
- Difficulty falling asleep
- Forgetfulness
- Costipation
- Furunculosis
- Weight gain

**Patient 3 M.D. Naples 03/08/1977**

- Breast swelling and tension
- Headache
- Excessive hunger
- Irritability
- Fatigue
- Difficulty falling asleep
- Forgetfulness
- Costipation
- Furunculosis
- Weight gain

**Patient 4 S.C. Naples 19/09/1983**

- Breast swelling and tension
- Headache
- Excessive hunger
- Irritability
- Fatigue
- Difficulty falling asleep
- Forgetfulness
- Costipation
- Furunculosis
- Weight gain
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**Patient 5 E.I. Naples 04/04/1985**

- Breast swelling and tension
- Headache
- Excessive hunger
- Irritability
- Fatigue
- Difficulty falling asleep
- Forgetfulness
- Costipation
- Furunculosis
- Weight gain

**Patient 6 C.F. Naples 10/11/1975**

- Breast swelling and tension
- Headache
- Excessive hunger
- Irritability
- Fatigue
- Difficulty falling asleep
- Forgetfulness
- Costipation
- Furunculosis
- Weight gain

**Patient 7 A.D. Naples 08/02/1980**

- Breast swelling and tension
- Headache
- Excessive hunger
- Irritability
- Fatigue
- Difficulty falling asleep
- Forgetfulness
- Costipation
- Furunculosis
- Weight gain
After treatment

Patient 1

Patient 2

Patient 3
Conclusions

The results highlighted in this study showed a good clinical efficacy of the treatment of symptoms of PMDD treatment with sertraline at a dose of 50 mg continuously for 6 months.

Evaluation of the results of the self-assessment tests, the outcomes for the individual items showed a reduction in all 10 symptoms observed.

On average, after treatment in the form of the disorder warned type 3 (severe) were completely reversed with a reduction of 24%; forms of type 2 (medium size) have declined an average of 17% for mild symptoms, there was an increase of 35% and for type 0 (no symptoms) there was an increase of 7%.

By calculating the frequency percentages of the total 10 items are obtained:
• SYMPTOMS OF TYPE 3 (severe ') before therapy 24% / 0 after treatment with a reduction of 24%

• SYMPTOMS OF TYPE 2 (moderate ') before therapy 37% / 20% after treatment with a reduction of 17%

• SYMPTOMS OF TYPE 1 (mild ') before therapy 28% / 63% after treatment with an increase of 35%

• No symptoms before therapy 10% / 17% after treatment with an increase of 7%

As shown in clinical practice and reported in international literature on sertraline did not result in depressive disorders specific adverse events, even during the observation period of our study.

Sertraline has shown a high tolerance so that none of our patients left the trial for evidence of side effects.

The assessment of the results we observed that the psychological symptoms (irritability, excessive hunger, profuse fatigue, difficulty sleeping, forgetfulness) showed a greater reduction in the percentage of physical symptoms (bloating and breast tension, headache, constipation, furunculosis, weight gain).

We believe this finding is related to the ability of sertraline on the pharmacodynamics of the neurotransmitters serotonin pathways that govern many neuropsychological functions involved.

A further consideration is the type pharmacoeconomic.

The patients reported that they observed during the treatment period showed a marked reduction in the use of drugs in an attempt to control the symptoms of PMDD, such as: anti-inflammatory drugs, NSAIDs, diuretics, beta blockers, anti-anxiety drugs and hormones.

Of course our study as an observational clinical study has limitations in relation to the large number of patients not followed and the inability to compare them with a control group.

It is the intention of the authors to expand this preliminary stage in the near future by comparing the continuous therapy with intermittent therapy of SSRI.

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