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Flibanserin - a challenging drug in the treatment of hypoactive sexual desire disorder

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Abstract

Hypoactive sexual desire disorder (HSDD) is a condition characterized primarily by the decrease of sexual desire, affecting the quality of life. HSDD seems to be the most common sexual dysfunction in women. Therefore it should not be ignored, but treated. Recently the first drug for the treatment of HSDD, flibanserin, has been approved by FDA. Flibanserin is an agonist at 5-hydroxytryptamine (5HT1A) receptors and antagonist at 5HT2A receptors, acting also on dopamine receptors. It has been approved for premenopausal women but with certain restrictions. It was originally developed as an antidepressant drug, but studies have not supported its safety and efficacy. Its effect in HSDD was observed serendipitously. Studies conducted in North America and Europe have highlighted that flibanserin increases the number of satisfying sexual events and sexual desire, reducing the distress among premenopausal women.
Keywords: *HSDD, sexual desire, flibanserin*

Introduction

HSDD is characterized by a persistent or recurrent deficiency or absence of the sexual fantasy and/or sexual desire which lead to the development of personal distress or interpersonal problems and is not the consequence of a medical disorder or the effect of a drug[(1)].

HSDD is much more common than it was previously believed, affecting 7-16% of adult women in Europe and similar percentages were reported in America and Australia. In most cases, the onset occurs in adulthood, the manifestations are intermittent or continuous and the disease may affect both pre and postmenopausal women[(2)]. We must take into account the significant impact of HSDD on the quality of life. Studies have shown that it has an impact similar to that encountered in women with diabetes or chronic back pain. The diagnosis of HSDD is based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). These criteria have recently been revised with the appearance of 5th edition of DSM[(3)].

Regarding the HSDD management, until recently there was no FDA approved treatment. Many therapies have been suggested, including the administration of estrogen or testosterone. Studies have targeted women with HSDD in which low levels of these hormones were identified. Studies in both pre and postmenopausal women regarding the transdermal administration of testosterone through patches were conducted with satisfactory results[(1)]. The first drug to treat HSDD, flibanserin a postsynaptic 5HT1A receptor agonist and 5HT2A receptor antagonist was recently approved by FDA.

Sexual desire - a complex concept

The concept of sexual desire is difficult to explain. It is defined as the motivation to be involved in a sexual activity. It should be known that sexual desire is strongly influenced by both sex hormones and neurotransmitters[(4)]. Studies have shown that low levels of estrogens or androgens interfere with sexual desire in women[(5)]. Testosterone seems to be one of the main hormones which play an important role in sexual activity, a low level being associated with the reduction of sexual desire and pleasure[(2)].

The main neurotransmitters which play an excitatory role in the sexual desire are dopamine, noradrenalin, oxytocin and serotonin (through 5 hydroxytryptamine (5HT1A receptors). Serotonin (through 5HT2A receptors), gamma amino butyric acid and prolactin have an inhibitory effect[(6)]. The mechanism of the occurrence of HSDD is still unknown, but it seems that there is an imbalance between inhibitory and stimulating neurotransmitters[(7)].

Dopamine is one of the major neurotransmitters involved in sexual desire and sexual activity. Thus, it has been observed that the patients who received a dopamine agonist medication undergo an increase in sexual desire.

The effect is achieved by acting on dopamine neuronal circuits in the mesolimbic system and hypothalamus. The therapies based on the enhancement of dopamine action were not approved because big doses lead to addiction and small doses are not efficient[(8)]. Noradrenalin is an important neurotransmitter involved in sexual arousal.

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The effects of these two mediators may be lowered by the increase of serotonin release. Serotonin is the main inhibitory neurotransmitter.

Serotonin stimulates uterine contractions, affecting the orgasm and reduces the sexual function by decreasing the noradrenalin effect and inhibiting nitric oxyde synthetase. The action on 5HT2 receptors leads to the orgasm inhibition[1].

A long way to approval

At first, the research was focused on the antidepressant properties of flibanserin in order to obtain a new antidepressant drug. It was initially developed by Boehringer Ingelheim, but the efficacy and safety studies failed[3]. The role of flibanserin on sexual desire was observed accidentally[7].

In 2009, Ingelheim proposed flibanserin to FDA for approval in the treatment of HSDD. They conducted Phase 3 double-blind, placebo-controlled trials, in North America and Europe, including premenopausal women, with HSDD. The dose of flibanserin administered was 100 mg per day, at bedtime.

In 2010 its approval was rejected, as there were insufficient data to support its effectiveness and safety. Three years later, Sprout Pharmaceuticals bought flibanserin from Ingelheim and proposed it to FDA for approval, after further studies. Again the studies were not convincing, given both the side effects on the nervous system (especially somnolence) and the high interaction with alcohol, resulting in hypotension and syncope. Subsequently the studies were continued and Sprout resent flibansein for evaluation in 2014. Then on 4 June 2015 flibanserin was approved with certain restrictions[9,10].

Many studies were conducted to evaluate the efficacy and safety of flibanserin. The most significant were DAISY, VIOLET, BEGONIA and ORCHID trials.

The VIOLET study conducted in North America consisted of the administration of flibanserin 50 mg to 295 women, flibanserin 100 mg to 290 women and 295 received placebo. All subjects included in the study were premenopausal women.

The drug was administered once daily at bedtime for 24 weeks. At the end of the study both the increase of satisfying sexual events and sexual desire (measured using the Female Sexual Function Index) and the decrease of distress related to the low sexual desire (female sexual distress scale-revised Item 13) have been observed.

The changes in sexual desire were also monitored using an electronic diary but the results were not statistically significant[11,12]. Regarding the side effects, 14% of the women who received flibanserin discontinued the treatment, in comparison with the placebo group where the rate was 5%[13].

Another study, performed in North America that demonstrated the efficacy of flibanserin for the treatment of HSDD was the BEGONIA, which involved 542 premenopausal women with HSDD who received flibanserin 100 mg once daily and 545 women with the same characteristics receiving placebo. The study lasted 24 weeks the same as the VIOLET study[14]. The results were similar to those obtained in previous studies.

The European Phase 3 study, the ORCHID trial included 634 premenopausal women, who received the same dose of 100 mg of flibanserin. An increase in sexual desire was recorded; it was measured using an electronic diary. In addition there was a decline in the distress level associated with sexual dysfunction and low sexual desire, evaluated using FSDS-R and FSD-R item 13 scores[13].

Adverse effects were similar to those in other studies. A percentage of 16% of women discontinued the treatment because of its side effects[15].

A single study was conducted on postmenopausal women. The study known as SNOWDROP used the same dose of 100 mg per day, administered at bedtime, the same parameters as in the previous studies involving premenopausal women were monitored. Satisfying sexual events increased by one per month. Adverse events occurred in 6-9.9% of the subjects, compared to 1.5-4.8% in the placebo group[16,17]. Further studies are needed prior to the aprroval of the treatmernt for this group.

However clinical studies have revealed a modest increase in sexual desire due to flibanserin[18]. There was an increase of 0.3 to 0.4 points (on a 1.2 to 6 point scale) in sexual desire in the last 4 weeks of treatment. Similar results were observed with regard to the reduction of distress. Although results were statistically significant, the clinical benefits observed were not convincing[19]. Some authors have received flibanserin enthusiastically, but others regard its efficacy with skepticism.

Understanding the mechanism of action of flibanserin

Flibanserin has an affinity for 5HT receptors. It exhibits an agonist effect binding to 5HT1A receptors and an antagonist effect binding to 5HT2A receptors. Flibanserin also binds to other serotonin receptors, 5HT2B, 5HT2C and to dopamine D4 receptors but it has a lower affinity for them, behaving as an antagonist. The drug displays the most potent effect on 5HT1A receptors. In a study conducted on rats, receiving flibanserin, it was noticed that 5HT1A receptors were occupied in a proportion of 80%, 5HT2A 70% and 5HT2C 10%[7]. It was shown that 5HT1A receptors are inhibitory and 5HT2A receptors are excitatory. Moreover, 5HT1A receptors are involved in the improvement of mood and reduction of anxiety, while 5HT2A receptors lower sexual desire[20].

Flibanserin binds specifically to pyramidal neurons in prefrontal cortex resulting in an increased release of norepinephrine and epinephrine at this level. Furthermore, it decreases the release of serotonin in prefrontal cortex, accumbens nucleus and hypothalamus[21]. It was hypothesized that changes of neuronal activity in the prefrontal cortex are involved in the occurrence

of HSDD. In the presence of an increased excitatory stimulation in the prefrontal cortex the release of noradrenaline, dopamine and serotonin may be altered.

In order to understand the mechanism of action of flibanserin we should recall some notions of anatomy. Pyramidal neurons in prefrontal cortex are connected to three nuclei located in the brainstem (dorsal raphe nucleus, ventral tegmental area and locus ceruleus). The dorsal raphe nucleus displays an inhibitory effect, being modulated by serotonin, the dopaminergic ventral tegmental area is involved in reward circuits and the noradrenergic locus ceruleus is related to sexual arousal[22].

The action on 5HT2C receptors has an inhibitory effect on the release of dopamine and noradrenalin in the frontal cortex, but flibanserin exhibits a modest effect on these receptors. With regard to D4 receptors, *in vitro* studies have shown that flibanserin behaves as an antagonist, but at high doses it may become agonist. The antagonist effect does not influence extracellular noradrenaline and serotonin. In this setting flibanserin presumably mediates serotonin, dopamine and noradrenalin concentrations stimulating 5HT1A receptors and inhibiting 5HT2A receptors[23].

A study which evaluated the action of antidepressants on 5HT7 enteric receptors revealed that flibanserin has no affinity for those receptors[24].

Persons with a diminished sexual desire underwent neuro-imaging investigations and abnormalities were observed in the prefrontal cortex, where it was shown that flibanserin acts. Moreover it is thought that flibanserin has a selective effect on 5HT1A and 5HT2A receptors in the cortex. It seems that flibanserin has a selective effect on pyramidal neurons which have an excitatory effect on the brainstem 5HT neurons and it also has a selective effect on pyramidal neurons with an inhibitory action on brainstem dopamine and noradrenaline neurons. This selectivity is not yet understood but it was also observed in other antipsychotic drugs[4]. This targeted effect on the cortex makes flibanserin different from other 5HT1A agonists.

This selectivity was also revealed by measuring levels of Fos immunoreactivity, which reflects the neuronal activity, in rats receiving flibanserin. According to some studies acute administration of flibanserin results in the increase of Fos protein in nucleus accumbens and arcuate hypothalamic nucleus. In chronic administration, elevated levels of Fos protein were recorded in the medial preoptic area and arcuate nucleus of the hypothalamus, ventral tegmental area, locus coeruleus, and lateral paragigantocellular nucleus[25].

At doses below 1 mg/kg, flibanserin acts as an inhibitor of the neuronal firing rate in the CA3 region of hippocampus and dorsal raphe. At doses between 1 and 10 mg/kg, flibanserin acts in the cortex, on 5HT1A and D4 receptors. At doses above 10 mg/kg it acts in the hipocampus and dorsal raphe. Studies have shown that flibanserin produces antidepressant, antipsychotic and anxiolytic effects. Sedation occurs at doses higher than 32 mg/kg[21].

It should be noted that flibanserin acts rapidly on serotonin receptors but the therapeutic effect in HSDD installs more slowly, after a few weeks[26]. If a result is not achieved after 8 weeks of therapy, the treatment should be discontinued[27].

Flibanserin is rapidly absorbed after oral administration, it binds to proteins in a proportion of 98% and its major metabolic pathway is in the liver under the action of cytochrome P450. Its half-life is about 10 hours[28].The main side effects described in studies were somnolence, nausea, dizziness. It has been noticed that flibanserin leads to a lower blood pressure and syncope. The risk of occurrence of adverse events is increased by alcohol consumption during treatment. In terms of drug interactions, the association with certain contraceptives and antifungal medication should be avoided. In addition it should not be administered to women with various liver diseases[29].

Can flibanserin be used in other disorders than HSDD?

Agonists of 5HT1A are used as antidepressant drugs. Their disadvantage is the long period from the first administration to achieve a satisfactory therapeutic effect. It was presumed that this delay was due to the fact that they initially act on 5HT1A somatodendritic autoreceptors. Thus flibanserin was assessed from the perspective of a possible antidepressant medication. Studies have shown that the administration of flibanserin has the effect of desensitizing somatodendritic autoreceptors 5HT1A, allowing the resumption of normal activity of 5HT neurons in a shorter period of time compared to the rest of antidepressant drugs[30,31]. However the lack of results that support its efficacy and safety resulted in no approval of flibanserin in the treatment of depression.

A possible anxiolytic effect of flibanserin was highlighted. Given that the treatment with benzodiazepines is encumbered by many adverse reactions, various studies were performed in order to find new therapeutic options in the treatment of the anxiety. For this reason buspirone was introduced, which is a non-benzodiazepine anxiolytic, which acts on the 5HT1A receptors. It has the great disadvantage of obtaining the desired effect slowly, after several weeks of treatment. In this context, it was observed in studies performed on rats, that flibanserin has an anxiolytic effect. It acts fast and unlike other anxiolytics it presents no side effects on the locomotive system, but further studies are needed[32].

Conclusions

Flibanserin, a controversial drug, whose mechanism is not fully understood, is the first ever drug approved by FDA for the HSDD treatment.

Flibanserin is a non-hormonal molecule, acting in the brain, whose main effect is the modulation of sexual desire. HSDD is a condition with a significant impact

on the patient's quality of life and the introduction of a drug for treatment was a necessity. Patients who will benefit from this treatment should be carefully selected in order to avoid the occurrence of side effects. The long way to approval, its questionable efficacy and its side effects make flibanserin a disputed drug. ■

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