ORIGINAL ARTICLE

CONTENTS

Effectiveness of treatment of sexual dysfunction in men with premature ejaculation, injured as a result of hostilities

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ABSTRACT

Aim: To evaluate the effectiveness of selective serotonin reuptake inhibitors (SSRIs) to the treatment of patients with premature ejaculation who have been affected by combat actions.

Materials and Methods: Results of an examination of 50 men injured as a result of hostilities, with sexual dysfunction and complaints of premature ejaculation. Patients were divided into smaller subgroups depending on the selected serotonin reuptake inhibitors, which they received for at least 1.5 months: sertraline (n=14), paroxetine (n=12), citalopram (n=12), venlafaxine (n=12).

Results: After treatment with all serotonin reuptake inhibitors, reactive and personal anxiety symptoms, as assessed by the Spielberger-Hanan scale, were objectively reduced in men. Only treatment with paroxetine and citalopram resulted in a likely reduction in depressive symptoms in men with premature ejaculation, Paroxetine and sertraline appeared to be relatively balanced drugs with moderate efficacy but relatively few side effects. The lack of a «gold standard» among serotonin reuptake inhibitor drugs for the treatment of premature ejaculation on the Ukrainian market necessitates the search for new, more effective drugs with the possibility of flexible use.

Conclusions: The study demonstrates that the neurotransmitter serotonin plays a key role in the modulation of ejaculation, as the use of reuptake inhibitors increases the intravaginal latency to ejaculation. Among the selective serotonin reuptake inhibitors, venlafaxine was found to be the most effective.

KEY WORDS: premature ejaculation, combat trauma, sertraline, paroxetine, citalopram, venlafaxine

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INTRODUCTION

Sexual dysfunction is a stress factor for the patient that negatively affects life quality and relationships, and is closely related to the persistent inability to achieve and maintain an erection sufficient for satisfactory intercourse. This sexual disorder is associated with a state of physical and psychological well-being and has a significant impact on the life quality of both the patients themselves and their partners and family members [1-4].

Male sexual disorders are often not a separate nosological unit, but reflect the manifestations of diseases. In particular, this applies to combatants with combat trauma. Such syndromic disorders can be based on both functional and organic changes, specifically they may be associated with urogenital infections [5, 6]. Among sexual disorders in men, there is a violation of psychological, social and somatic components [1-4].

Since all patients with sexual dysfunction, regardless of nosology, etiological factors, pathogenesis, and clinical manifestations, experience significant psychological problems, it is crucial to thoroughly verify their psychological status. The measurement of these changes has become possible with the introduction of several special questionnaires into medical practice, the main purpose of which is to study quality of life indicators.

Erection is a neurovascular phenomenon under hormonal control, involving arterial dilation, relaxation of trabecular smooth muscle, and activation of the corporal veno-occlusive mechanism [7]. Clinical and laboratory studies of sexual dysfunction in recent years have led to the development of new treatment protocols, including methods of psychosexual therapy, local negative pressure therapy, and new pharmacological drugs [7-11].

Men with sexual dysfunction often complain of premature ejaculation (PE). PE is the inability to control ejaculation for a «sufficient» duration during intercourse [1-4]. For instance, 25-40% of men in the United States suffer from PE [12, 13]. Psychological factors often influence the occurrence of PE. Since men sometimes underestimate the connection between sexual performance and emotional

well-being, PE can be caused by temporary depression or stress. However, medications that slow the rate of arousal are often necessary. At the 24th Annual Congress of the European Association of Urology (2009), serotonin reuptake inhibitors were highlighted as the drug of choice for treating PE. Alongside behavioral therapy, this paper presents our comparative experience with the use of medications from this group. Therefore, for all forms of ejaculatory disorders, a comprehensive psychological examination of patients using objective questionnaire methods is necessary [2, 4, 7]. The development of modern, comprehensive therapy methods will allow for better treatment outcomes.

AIM

To evaluate the effectiveness of selective serotonin reuptake inhibitors (SSRIs) to the treatment of patients with premature ejaculation who have been affected by combat actions.

MATERIALS AND METHODS

The study was based on the results of an examination of 50 men affected by combat actions, who experienced sexual dysfunction and complained of premature ejaculation. Inclusion criteria: neurogenic origin of PE, age between 18 and 52 years and minimum chronicity of PE of 3 months. Exclusion criteria: clinically significant comorbidity: cardiovascular, hepatic, thromboembolic, neurological, oncological or endocrine, history of retroperitoneal surgery or radiotherapy, consumption of medications that affect ejaculation, abuse or dependence on psychoactive substances.

All patients were surveyed using the IIEF-5 scale (International Index of Erectile Function-5) [14, 15], and their sexological and urological histories were collected. A digital rectal examination of the prostate was performed, along with microscopy of the prostate secretion to detect inflammatory processes. Prostate ultrasonography was conducted, and, if indicated, bacteriological culture of the prostate secretion was performed. Screening for TORCH infection antibodies using enzyme-linked immunosorbent assay was carried out, followed by polymerase chain reaction diagnostics for relevant pathogens in the prostate secretion. In doubtful cases, urethroscopy of the prostatic urethra was performed. To determine health-related quality of life, patients were surveyed using the SF-36 questionnaire [4, 7].

Based on etiological principles, a neurogenic origin of PE was confirmed in 50 of the examined patients. These patients primarily complained of PE that persisted with regular sexual activity at a frequency of 2.4±0.3 times per week. They were categorized into this group due to the absence of complaints, history, clinical symptoms, instrumental, and laboratory evidence of prostatitis or chronic pelvic pain syndrome. All patients in this group exhibited pathological fixation on sexual dysfunction, accompanied by an affective component such as anxiety, fear of failure, low mood, intense doubts, leading to the dominance of the sympathetic nervous system during sexual intercourse [2, 16]. The average duration of the disease was 9 ± 0.8 months. The observation of patients lasted from 2 to 6 months.

Thus, this group consisted solely of men with neurogenic (psychogenic) PE, which in all 50 cases (100%) was caused by combat trauma. Considering the complexity of the pathogenesis of premature ejaculation, the treatment for all patients was comprehensive and consisted of two parts: basic therapy and selective serotonin reuptake inhibitors (SSRIs).

The patients were randomly divided into four subgroups depending on the selected SSRIs medication they received for at least 1.5 months. Subgroup 1 (n=14) received sertraline medication at a dosage of 50-100 mg/day. Subgroup 2 (n=12) received paroxetine medication at a dosage of 20-40 mg/day. Subgroup 3 (n=12) received citalopram medication at a dosage of 10-20 mg/day. Subgroup 4 (n=12) received venlafaxine medication at a dosage of 37.5-150 mg/day.

To objectively assess anxiety and depression, patient surveys were conducted using the Spielberger-Hanin and Hamilton scales, respectively [2]. During treatment, criteria for determining erectile dysfunction were taken into account.

To assess the effectiveness of treatment methods for patients with ejaculatory disorders, obtained data were processed using methods of mathematical statistics, employing both parametric and non-parametric methods of multiple comparison. Student's t-test after positive testing of the sample for normality of distribution in it by the Shapiro-Wilk test. When the parameters did not conform to the law of normal distribution of data, nonparametric statistics methods were used with the use of Wilcoxon-Mann-Whitney (U) statistical hypotheses. Differences between experimental groups were considered statistically significant at $P < 0.05$. The mathematical processing of results was conducted using the statistical software package «Statistica for Windows 10.0» and the electronic spreadsheet editor «Excel» from Microsoft.

RESULTS

The study included the treatment of men with neurogenic PE. Men with sexual dysfunction typically have

impaired sexual motivation: instead of focusing on the lovemaking process, patients are oriented towards the possibility of PE, leading to tension and anxiety instead of positive emotions. Considering this, an important component of successful treatment for men was the patient's ability to learn to clearly navigate their sensations and timely apply functional training techniques to prevent triggering the ejaculatory reflex.

Prior to treatment, the mean intravaginal ejaculatory latency time (IELT) in subgroup 1 was 1±0.88 minutes. All 14 patients in this subgroup started therapy with a dose of sertraline 50 mg/day for 45 days, which was generally well tolerated. Common side effects observed during the first few days of medication intake included occasional dizziness, tachycardia, decreased attention, and mild nausea in 5 out of 14 patients (35.7%). In one case (7.1%), severe side effects were observed, including significant deterioration in well-being, paresthesia, tremors, and seizures after the second dose of the medication, leading to its discontinuation. Since we attempted not to draw patients' attention to the possible side effect of erectile dysfunction (ED) after taking SRI to prevent its secondary (iatrogenic) occurrence, only 3 out of 14 patients (21.4%) reported moderate libido decrease and mild ED after treatment.

After 1.5 months, significant subjective improvement with an average increase in IELT to 4±0.63 minutes was reported in 6 out of 14 (42.8%) men; minor improvement with an average increase in IELT to 1±0.22 minutes was reported in 5 out of 14 (35.7%) men; no increase in intercourse duration with an IELT of 0.8±0.35 minutes was reported in 3 out of 14 (21.4%) men.

The last two patients agreed to increase the dose of sertraline to 100 mg/day for the next month. Only 3 (21.4%) men who experienced significant improvement and 3 (21.4%) who noticed some improvement – a total of 42.8% – decided to continue treatment for more than 1.5 months. It should be noted that men were reluctant to agree to long-term treatment with sertraline for more than 45 days, as the effect of the treatment developed too late, mostly after 3-4 weeks of taking the medication. According to some, this was "in vain."

Most patients also had a negative attitude towards being constantly dependent on the medication – the relapse rate of PE from the first days of discontinuation up to six months was 10/14 (71.4%). The observed effectiveness of sertraline over several years of clinical use for PE turned out to be quite low compared to previous studies [4, 12, 17].

Before the treatment initiation, the average duration of sexual intercourse in subgroup 2 was 1±0.06 minutes. All 12 patients in subgroup 2 commenced therapy with a dose of paroxetine 20 mg/day in the afternoon, preferably after work, for 45 days, which was well tolerated. Among the side effects observed during the first few days of medication intake, drowsiness, decreased concentration, dry mouth, and nausea for 1-3 days were most commonly reported in 4/12 (33%) respondents, which typically subsided quickly. Moderate decrease in libido and mild erectile dysfunction were noted in 3/12 (25%) of the men.

After 1.5 months, significant subjective improvement with an average increase in IELT to 2±0.14 minutes was reported in 7/12 (57.1%) of the men; slight improvement with an IELT of 1±0.12 minutes was reported in 3/12 (28.6%); and no increase in sexual intercourse duration with an IELT of 0.8±0.03 minutes was reported by 2/12 (14.3%). The last two patients agreed to increase the dose of paroxetine to 40 mg/day for the next month. Only 4 (35.7%) men who experienced significant improvement and 2 (14.3%) who noted moderate improvement – a total of 50.0% – decided to continue treatment with paroxetine for more than 1.5 months, explaining their reluctance to commit to systematic tablet intake.

Respondents noted different increases in IELT ranging from 1 week to 1 month of paroxetine use. Episodic use of paroxetine did not lead to a significant extension of coitus duration. The relapse of PE from the first days of discontinuation up to six months was observed in 9/12 (75%) cases. Overall, patients were fairly satisfied with paroxetine considering its average effectiveness, moderate cost, and minor side effects compared to other SSRIs.

Before treatment initiation, the average duration of sexual intercourse in subgroup 3 was 1±0.32 minutes. All 12 patients in subgroup 3 started therapy with a dose of citalopram 10 mg/day in the afternoon, preferably after work, for 4 days, followed by a transition to 20 mg for 45 days. It is worth noting that six out of twenty-two patients had previously unsuccessfully used sertraline for several weeks, and another four had tried paroxetine, seeking a more effective medication at a lower cost. Among the side effects observed from the first days of medication intake to two weeks, drowsiness, rapid fatigue, decreased concentration, dry mouth, nausea, anorexia were most commonly reported, significantly affecting 7/12 (58.3%) of the men, prompting two of them to discontinue treatment. One positive aspect of the medication was the rapid increase in IELT within 5-14 days of intake. Therefore, after appropriate consultations and warnings, we prescribed citalopram to physically healthy men who wanted to achieve the effect as quickly as possible, despite the medication's side effects. After 1.5 months, significant subjective improvement with an average increase in IELT to

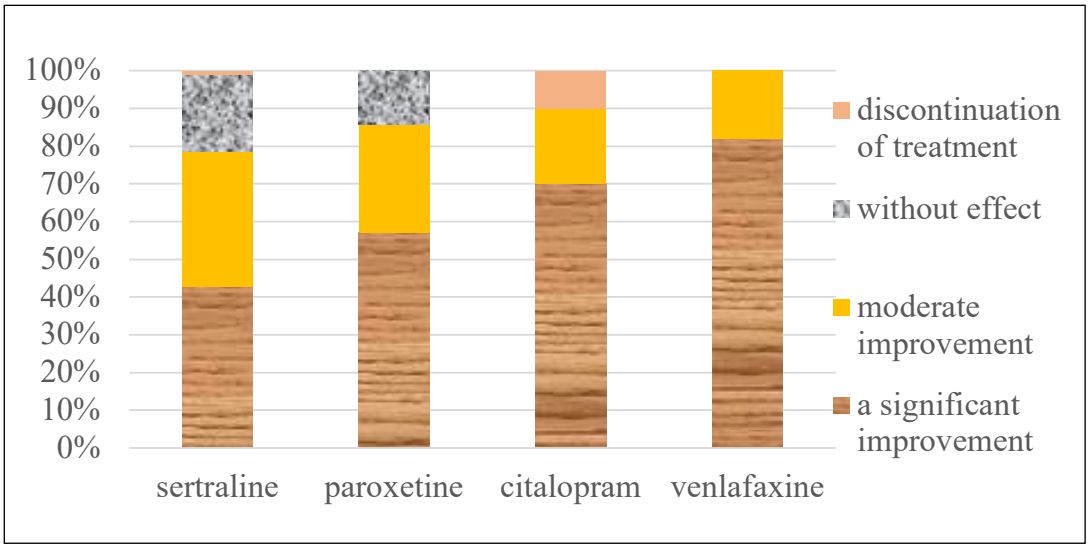

Fig. 1. Comparison of the effectiveness of venlafaxine, citalopram, paroxetine, and sertraline in the treatment of men with neurogenic PE.

3±0.27 minutes was reported in 7/10 (70%) of the men; noticeable improvement with an IELT of 2±0.03 minutes was reported in 2/10 (20%). 1/10 (20%) agreed to continue taking citalopram after 1.5 months. Several patients noted a good effect (increase in IELT) from taking citalopram «on demand» – 2-4 hours before anticipated sexual activity. The relapse of PE from the first days of discontinuation up to six months was observed in 8/10 (80%) cases.

Before treatment initiation, the average duration of sexual intercourse in subgroup 4 was 1±0.4 minutes. All 12 patients in subgroup 4 started therapy with a dose of venlafaxine 37.5 mg in the evening for 2-4 days, followed by a transition to 37.5 mg twice daily to prevent nausea, which was observed with varying degrees of severity in 8/12 (66.7%) of the patients for the first 5 days of intake, but then completely resolved in 11/12 men. One patient refused further use of the medication. In most patients, mild general weakness and fatigue were observed for several days after starting treatment, which was difficult to objectify due to significant subjective sensations. Moderate decrease in libido and mild erectile dysfunction were noted in 4/12 (33%) of the men. A positive aspect was the rapid extension of IELT within 5-7 days of venlafaxine intake, while the negative aspect was that the medication was the most expensive in the segment of SSRIs medications. By 1.5 months of intake, significant subjective improvement with an average increase in IELT to 3±0.45 minutes was reported in 9/11 (81.8%) of the men; two others, unsatisfied with the duration of IELT, switched to a dose of 75 mg twice daily and reported an IELT of 5±0.12 minutes within 2 weeks. Thus, the overall effectiveness of venlafaxine use in patients was practically 100% and depended only on the received dose. However, the relapse of PE after discontinuation of the medication was observed in 9/12 (75%) cases. Some patients noted a good effect (increase in IELT) from taking venlafaxine «on demand» – a few hours before anticipated sexual activity, but these data cannot be reliably objectified. 5/12 (41.7%) agreed to continue taking venlafaxine after 1.5 months.

The absolute majority of patients ultimately found it psychologically challenging to accept medication treatment, which only helps during systematic use and does not provide a lasting effect after discontinuation. Interestingly, there was a notable increase in the overall score of the International Index of Erectile Function (IIEF-5) by 2.7; 3.8; 4.6; and 5.2 after treatment with sertraline, paroxetine, citalopram, and venlafaxine, respectively. Overall, the obtained results indicate the effectiveness of treating PE with SSRIs (Fig. 1).

This once again demonstrates the close interrelation of all components of sexual function, wherein improvement in the ability to control ejaculation also leads to an improvement in the scores of the domains of the IIEF, reflecting overall enhancement of sexual function.

Additionally, after treatment of PE with SSRIs, patients' anxiety levels, as assessed by the Hamilton Anxiety Scale, significantly decreased. This further confirms the close relationship between PE, psychogenic symptoms on a clinical level, and the state of serotoninergic transmission at physiological levels. The most pronounced trend towards reduced anxiety was observed after the use of citalopram and venlafaxine.

After treatment with all SSRIs, men showed a reduction in both reactive and personal anxious symptoms, assessed using the Spielberger-Hanin Scale. However, it is difficult to carry out a comparative analysis of the

Table 1. The effectiveness of treatment for men with PE depending on the type of SSRIs

		subgroup 1 (n=14) sertraline 50 mg/d		subgroup 2 (n=12) paroxetine 20 mg/d
treatment	**before**	**after**	**before**	**after**
Average duration of intercourse (intravaginal ejaculatory latency time (IELT)), min	1±0.88	4±0.63* (42.8% - significant improvement) 1±0.22 (35.7% - slight improvement) 0.8±0.35 (21.4% - no improvement) 4±0.25* (another 14.2% after increasing the dose to 100 mg/d)	1±0.06	2±0.14* (57.1% - significant improvement) 1±0.12 (28.6% - slight improvement) 0.8±0.03 (14.3% - no improvement) 2 (another 14.3% after increasing the dose to 40 mg/d)
Mild side effects, %		35.7		33
Pronounced side effects, %		7.1		-
Decreased libido and mild ED, %		21.4		25
General improvement of sexual performance according to the IIEF-5 scale in all domains, number of points		2.7*		3.8*
Depressive symptomatology according to the Hamilton scale, points	6	5	8	5*
Anxiety symptomatology according to the Spielberger-Hanin scale, reactive/personal, points	28/34	20/9*	28/31	18/12*
Patients who wanted to continue treatment for more than 1.5 months, %		45.6		46.2
Recurrence of PE after withdrawal of the drug, %		71.4		75.0
		subgroup 3 (n=12) citalopram 20 mg/d		**subgroup 4 (n=12) venlafaxine 75 mg/d**
treatment -	**before**	**after**	**before**	**after**
Average duration of intercourse (intravaginal ejaculatory latency time (IELT)), min	1±0.32	3±0.27* (70% - significant improvement) 2±0.03 (20% - slight improvement) (20% - refused treatment due to side effects)	1±0.4	3±0.45* (81.8% - significant improvement) 5±0.12* (another 18.1% after increasing the dose to 150 mg/d) total efficiency 100%
Mild side effects, %		58.3		26.7
Pronounced side effects, %		-		4
Decreased libido and mild ED, %		15.4		33
General improvement of sexual performance according to the IIEF-5 scale in all domains, number of points		4.6*		5.2*
Depressive symptomatology according to the Hamilton scale, points	7	4*	6	5
Anxiety symptomatology according to the Spielberger-Hanin scale, reactive/personal, points	32/33	14/8*	34/31	15/9*
Patients who wanted to continue treatment for more than 1.5 months, %		10		41.7
Recurrence of PE after withdrawal of the drug, %		80		76

* the difference with the indicator before treatment is significant, $P<0.05$.

effectiveness of different medications because the subgroups included men with very different self-assessments of anxiety. Some patients denied it, while others noted pronounced anxiety, most likely associated with sexual disorders.

Only treatment with paroxetine and citalopram led to a probable reduction in depressive symptoms in men with PE. However, this was more dependent on the even distribution of patient groups, many of whom, despite having PE, denied any depression. Men with PE always hope for «complete cure» which is rarely possible at the current stage of development in sexology, psychiatry, and pharmacology, unfortunately. This underscores the necessity to search for new, more effective treatment methods.

The effectiveness of PE treatment by SSRIs in patients of all age groups, expressed in terms of increased duration of sexual intercourse (IELT), presence and severity of side effects, as well as recurrence of PE, is given in Table 1.

Thus, the results of the study indicate a significant prevalence of neurogenic (psychogenic) PE among men affected by combat actions. The study demonstrates that the neurotransmitter serotonin plays a key role in the modulation of ejaculation, as the use of its reuptake inhibitors contributes to an increase in IELT. Among the SSRIs, venlafaxine proved to be the most effective during its use. Specifically, significant improvement was observed in 81.8% of patients. Its intake was not associated with significant side effects. However, after the treatment ended, most patients experienced a recurrence of PE.

Citalopram proved to be sufficiently effective. A significant improvement was observed in 70% of patienrs. However, its use was accompanied by pronounced side effects (58.3%). Paroxetine and sertraline were found to be relatively balanced medications with moderate effectiveness but relatively few side effects.

The most effective general improvement of sexual performance according to the IIEF-5 scale in all domains was observed in patients taking citalopram and venlafaxine (number of points – 4.6 and 5.2 respectivelly). A decrease in anxiety according to the Spielberger-Hanin scale was the most expressed in patients taking citalopram and venlafaxine.

The absence of a «gold standard» among SSRIs for the treatment of PE in the Ukrainian market highlights the need to search for new, more effective medications with flexible application options.

DISCUSSION

The use of antidepressants – selective serotonin reuptake inhibitors leads to an increase in the time to ejaculation [17, 18]. In the USA, the most commonly prescribed antidepressants for treating premature ejaculation include Prozac, Zoloft, Celexa, Effexor, and Lexapro. Some clinical studies from previous years have indicated significant effectiveness of paroxetine [2, 3]. Clomipramine may be helpful in severe cases of premature ejaculation associated with serious nervous system disorders. It has also been reported to improve the quality of erections in some patients [2]. Clinicians also often recommend the use of condoms with local anesthetics or non-aerosol topical anesthetic sprays for patients with PE [19].

It is known about the success of intramuscular injections of magnesium sulfate solution, as it is believed that PE is associated with magnesium deficiency [18, 19]. Authors from South Korea [20, 21] applied the method of functional visualization LORETA (low-resolution electromagnetic tomography of the brain) to 14 patients and found that the SSRIs sertraline contributes to increased electrical activity mainly in the frontal, limbic, and temporal lobes of the left hemisphere of the brain, which may be associated with the therapeutic effect of SSRIs in premature ejaculation. Scientists from Italy reported that 77.8% of patients with lifelong PE decided to continue daily use of paroxetine after 3 months of successful application, while 30.8% discontinued due to unsatisfactory effectiveness [4, 18].

A multicenter study involving 491 heterosexual couples over 6 months in 5 countries utilized the stopwatch method to measure IELT [5]. It was found that IELT ranged from 30 seconds to 44 minutes, with an average of 5.4 minutes. Additionally, depending on the country, it ranged from 3.7 minutes in Turkey to 7.6 minutes in the United Kingdom. In over 14% of men, the average IELT was less than 200 seconds, while in 26% it was longer than 600 seconds. The 0.5 and 2.5 percentiles were calculated to be 0.9 and 1.3 minutes, respectively.

The Premature Ejaculation Perceptions and Attitudes (PEPA) study revealed that PE occurs even more frequently in men worldwide than ED, comprising 20-30% of populations and practically remaining unchanged with age [6]. PE not only affects men's sexual health but also negatively impacts the psychosocial health of their partners. In our previous studies it was shown that in the psychological domain, the most pronounced changes in men injured as a result of hostilities are recorded in such components as mental health, vital activity and social functioning [22].

The treatment of PE "on-demand" by using new short-acting representatives of SSRIs, such as dapoxetine, is considered promising. Dapoxetine affects the lateral paraganglionic cell nucleus in the brainstem, with a decrease in blood serum concentration to 5% of the peak level within 24 hours after intake [16, 23, 24].

Currently, dapoxetine is the only clinically approved drug in the world for the treatment of PE, as indicated in the instructions for use. The drug has been tested on 6000 men in 5 randomized, placebo-controlled phase III clinical trials, as well as in a 9-month open-label safety study [16, 24, 25]. The drug was found to be effective for all three components of PE: time to ejaculation, ejaculatory control, and reduction of negative interpersonal relationships. After 12 weeks of dapoxetine use, the average IELT in men tripled compared to the baseline level and continued to increase up to 24 weeks [25-28].

Due to the polyetiological nature of PE, involving not only the anatomical and physiological aspects of pathogenesis but also socio-psychological factors, and considering the paired nature of sexual function, certain difficulties arise in finding effective comprehensive treatment methods for PE at the current stage of medical development.

CONCLUSIONS

1. Among the selective serotonin reuptake inhibitors (SSRIs), venlafaxine was found to be the most effective. Its use was not associated with significant side effects. However, after the treatment ended, most patients experienced a recurrence of premature ejaculation.
2. Citalopram proved to be sufficiently effective, but its use was accompanied by pronounced side effects.
3. Paroxetine and sertraline were relatively balanced medications with moderate effectiveness and relatively few side effects.
4. The absence of a «gold standard» among SSRIs for the treatment of premature ejaculation in the Ukrainian market highlights the need to search for new, more effective medications with flexible application options.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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