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Retrospective evaluation of the efficacy of daily paroxetine/tadalafil combination in patients with premature ejaculation and erectile dysfunction

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Abstract. – OBJECTIVE: Premature ejaculation (PE) and erectile dysfunction (ED) are sexual dysfunction diseases affecting males. The phosphodiesterase type 5 (PDE5) inhibitors such as tadalafil are used to treat ED whereas selective serotonin reuptake inhibitors (SSRIs) are preferred for PE. Most of the patients with ED also suffer from PE simultaneously. The combined drug therapies are commonly preferred as they favor elevated intra-vaginal ejaculation latency time (IELT) scores and improved sexual function. The study aimed to evaluate the efficacy and safety of daily paroxetine and tadalafil combination therapy in patients with PE and ED.

PATIENTS AND METHODS: A total of 81 PE patients with ED were enrolled in the study. Patients were treated with daily paroxetine 20 mg and tadalafil 5 mg for 4 weeks. Pre- and post-treatment IELT, premature ejaculation profile (PEP), and International Index of Erectile Function-Erectile Function (IIEF-EF) scores of the patients were analyzed.

RESULTS: The mean IELT and PEP index scores, and mean IIEF-EF values improved after combination therapy ($p<0.001$ for each). When lifelong and acquired PE+ED patients were compared, significant improvements were observed in IELT, PEP, and IIEF-EF scores in both groups ($p<0.001$).

CONCLUSIONS: Even though the treatment methods are different, combined therapies to treat simultaneous PE and ED presence are effective compared to monotherapies. However, there is still no definitive treatment that can cure all subtypes of PE or ED.

Key Words:
Premature ejaculation, Erectile dysfunction, Tadalafil, Paroxetine.

Introduction

Premature ejaculation (PE) is a widespread sexual dysfunction in men that affects not only sexual relationships between partners but also the emotional and psychological life of patients[1]. The prevalence may range between 20% and 30% regardless of ethnicity and age[2]. Until the last decade, the definitions of PE in the literature were unclear since they were not evidence-based but mainly expert-opinion-driven descriptions. The International Society for Sexual Medicine (ISSM) published a guideline in 2007 which refers to three criteria to define PE: the intravaginal ejaculation latency time (IELT), loss of control over ejaculation, and presence of distress between the partners[3]. In 2013, the ISSM guideline was revised and the new definition of PE was defined as "a male sexual dysfunction characterized by (i) ejaculation that always or nearly always occurs before or within about 1 minute of vaginal penetration from the first sexual experience (lifelong PE) or a clinically significant and bothersome reduction in latency time, often to about 3 minutes or less (acquired PE); (ii) the inability to delay ejaculation on all or nearly all vaginal penetrations; and (iii) negative personal consequences, such as distress, bother, frustration, and/or the avoidance of sexual intimacy[4]".

Lifelong (LL)-PE is the condition at which the ejaculation length is <1 min in almost all vaginal penetration thus probably originating from an abnormal physiology or pathology[5]. Acquired(A)-PE defines a condition at which the ejaculation length is reduced to 3 min or less even though the past ejaculation lengths were within the normal ranges[6]. The other two subclasses (variable and subjective) of PE seem to be conditional since the variable PE is irregular, unexpected early ejaculation which can be assumed as an ejaculation time variation; whereas subjective PE is self-perceived early ejaculation even in the presence of normal IELT[7,8]. A well-established questionnaire developed by Symonds et al[9] in 2007 is

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used as the premature ejaculation diagnostic tool (PEDT) used in the assessment of PE.

The loss of feeling control over the entire reflex of ejaculation owing to lack of enough synaptic levels of serotonin is the main problem favoring PE, which can be solved by the ejaculation-delaying effects of selective serotonin reuptake inhibitors (SSRIs), among them, paroxetine is the most prevalent off-label drugs used on-demand or daily in clinical practice[10-13].

Erectile dysfunction (ED) is the consistent or recurrent inability to attain enough erection for satisfactory sexual intercourse[14]. According to Male Aging Study (MMAS), 52% of men ranging from 40-70 years old suffer from ED, and over 320 million men are estimated to be ED affected by 2025 globally[15,16].

The severity of ED is classified as no ED, mild-moderate, moderate, and severe ED according to the five-item International Index of Erectile Function (IIEF-5) questionnaire scores[17]. A sedentary lifestyle, obesity, alcohol, and tobacco seem to be the main risk factors[18-20]. Even though aging is reported to be an independent risk factor for developing ED, Feldman et al[15] concluded that only two-thirds of 70 years old men have erectile difficulties.

The physiological erectile function is maintained by elevated levels of cyclic guanosine monophosphate (cGMP). The phosphodiesterase type 5 (PDE5) regulates normal Nitric oxide-cGMP levels. In the presence of ED, however, using a PDE5 inhibitory (PDE5i) enzyme leads to cGMP accumulation in the corpus cavernosum of the penis and finally results in corporal blood flow, vasodilation, and erection[21]. The first PDE5 inhibitors emerged in 1998 as sildenafil followed by the approval of vardenafil and tadalafil by the Food and Drug Administration (FDA) in 2003, and avanafil use has been initiated in 2012[22]. Among them, tadalafil is the most preferred drug to treat ED due to its advantage over the other PDE5 inhibitors. Tadalafil use is not affected by diet and it attains its effective plasma concentration 30 minutes after administration and the efficacy is maintained for up to 36 hours[23,24].

According to recent studies[25,26], half of the men with PE also suffer from ED[25]. If a patient with PE tries to control his ejaculation, he will probably reduce his level of excitation resulting in ED. On the contrary, if a patient with ED tries to attain a penile erection, he will probably increase his excitation level, resulting in PE, which seems to be a vicious circle[26].

In the present study, we aimed to evaluate the efficacy and safety of daily SSRI-paroxetine and PDE5i-tadalafil combination therapy in patients with PE and ED.

Patients and Methods

Files of 81 patients (18-65 years) who applied to Istanbul Prof. Dr. Cemil Tascioglu City Hospital Urology-Andrology Outpatient Clinic between January 2017 and October 2018 with complaints of Erectile Dysfunction (ED) and Premature Ejaculation (PE) were evaluated retrospectively. The study was approved by the clinical research ethics committee of Istanbul Prof. Dr. Cemil Tascioglu City Hospital (Decision Number: 989). Patients with a PEDT score >11 for PE and IIEF-EF score <21 for ED, who received daily Tadalafil 5 mg (PDE5 inhibitor) and Paroxetine 20 mg (SSRI) treatment for 1 month, and with pre-and post-treatment IELT duration and PEDT[27], Premature ejaculation profile (PEP)[28] and IIEF-EF[17] questionnaires were enrolled in the study. The detailed medical and sexual history of the patients will be obtained from the patient files. The obtained pre- and post-treatment parameters will be evaluated and compared retrospectively, and the effect of the treatment on the improvement in the investigated parameters will be analyzed. IELT was recorded as estimated according to the patients' own statements.

Patients <18 or >65 years of age, who did not receive regular treatments, and with missing PEP, IELT, and IIEF-EF forms, patients with a history of surgery, anatomical disorder or neurological condition, trauma, or infection related to the development of symptoms of PE, those with genital anomalies other than penile curvature that will not prevent sexual intercourse, those who developed PE or ED due to drug withdrawal or drug use, those whose spouses have problems with any sexual intercourse, those with a history of prostatitis, thyroid hormone disorders, allergy to SSRI and phosphodiesterase inhibitor drugs, suicide attempt, severe psychiatric illness, epilepsy, myocardial infarction, life-threatening arrhythmias, stroke, heart failure, unstable angina, or hypotension in the past 6 months, those who are not suitable for sexual intercourse due to existing health problems, those who continue to use nitrates, vasodilators alpha-blockers, itraconazole, ketoconazole, saquinavir, ritonavir, nefazodone, telithromycin, atazanavir, nelfinavir, erythromycin, cimetidine, antiplatiagulant, fluconazole clarithromycin, amprenavir, fosamprenavir, verapamil, aprepitant, antiplatiazem users of dapoxetine, any other PDE5i or SSRI, alcohol and stimulant drugs,

monoamine oxidase inhibitor, selective-norepinephrine reuptake inhibitor, thioridazine, tricyclic antidepressant, atypical antipsychotic drugs and serotonergic drug/herbal product, or who quit within the last 14 days, those who are likely to receive drug therapy that may affect the pharmacokinetic/pharmacodynamic properties of study drugs during the study and those whose resting Systolic/Diastolic blood pressure <90/50 mmHg and <170/100 mmHg were excluded from the study.

Statistical Analysis

SPSS 22.0 software (IBM Corp., Armonk, NY, USA) program was used for statistical analysis of the study. Paired sample *t*-test and Wilcoxon test will be used to measure pre- and post-treatment values. Significant *p*-value was determined as <0.05.

Results

Of the patients, 52 had lifelong PE and 29 had acquired PE. The mean age of the patients was 37.25±11.44 years. At the end of the four-week treatment period, the patients' mean IELT had increased significantly (pre-treatment: 29.67±22.88 sec and post-treatment:108.65±48.91 sec, $p<0.001$) (Table I).

The mean PEP scores were 0.98±0.79 for pre-treatment and 2.14±1.09 for post-treatment ($p<0.001$). The mean IIEF-EF scores were 12.27±5.01 for pre-treatment and 23.11±4.47 for post-treatment ($p<0.001$). 7 patients (10.52%) were observed to have non-serious adverse events such as weakness in 4 and headache in 3. Of these, 3 discontinued the treatment (Table II).

When life-long and acquired PE patients with ED were compared, significant improvements were observed in IELT, PEP, and IIEF-EF scores in both groups ($p<0.001$ for each), and similar improvement scores were observed between the two groups after treatment ($p>0.05$).

Discussion

All recommendations suggest that any pharmaceutical or psychological ED treatment must be preceded by or coupled with lifestyle modifications and risk factor reduction[21]. Smoking cessation, keeping an appropriate body weight, regular exercise, and care for these disorders may help to avoid the development of ED[29-32]. Besides, aging has the potential to result in a PE phenotype, since around 68% of males at

Table I. Demographic characteristics.

		Mean	SD	Min	Max	n	%
Age		37.25	11.44	19	47		
BMI		24.12	10.45	18.90	38.42		
PE Type	Lifelong					52	64.2
	Acquired					29	35.8
PEDT		14.03	4.30	11	20		

BMI: Body Mass Index; PE: Premature ejaculation; PEDT: Premature ejaculation diagnostic tool.

Table II. Comparison between pretreatment and posttreatment values.

	Pre-treatment	Post-treatment	p
IELT (sec)	29.67±22.88	108.65±48.91	<0.001
PEP (Index)	0.98±0.79	2.14±1.09	<0.001
IIEF-EF	12.27±5.01	23.11±4.47	<0.001
For LPE Patients			
IELT (sec)	27.03±18.62	106.40±51.63	<0.001
PEP (Index)	0.96±0.74	2.09±1.03	<0.001
IIEF-EF	12.01±5.67	23.81±5.02	<0.001
For APE Patients			
IELT (sec)	32.65±25.55	110.21±60.07	<0.001
PEP (Index)	1.01±0.98	2.18±1.01	<0.001
IIEF-EF	12.50±5.90	22.95±5.11	<0.001

IELT: Intravaginal ejaculation latency time; PEP: Premature ejaculation profile; LPE: lifelong premature ejaculation; APE: Acquired premature ejaculation; IIEF-EF: International Index of Erectile Function-Erectile Function.

the age of 70 reported having ED, representing that ED is age-dependent[24].

Four PDE5 inhibitors, including sildenafil, tadalafil, vardenafil, and avanafil, are among the approved drugs to treat ED. PDE5 inhibitors favor the accumulation of cGMP in the penile cavernosa resulting in erection hardness and elevated duration[33]. By directly enhancing erection function, as well as indirectly enhancing spontaneity and decreasing attention to time, PDE5 inhibitors might enhance a patient's sexual confidence[34]. Even though they have a higher risk of adverse events than a placebo, they are typically well tolerated for the treatment of ED[35]. Pharmacokinetic characteristics include the duration of responsivity and onset of four FDA-approved PDE5 inhibitors, including sildenafil, vardenafil, avanafil, and tadalafil differ from each other. The choice of PDE5 inhibitor depends not only on these pharmacokinetic properties but also on tolerability, cost, and other pharmacokinetic properties, including speed of onset and duration of responsivity[21].

The most recommended PDE5i, Tadalafil, has distinct pharmacokinetic properties, including a delayed onset and a prolonged impact lasting approximately 36 hours providing a diverse range of options for sexual intercourse[36].

SSRIs, behavioral approaches, tricyclic antidepressants, topical anesthetics, and alpha-adrenergic receptor antagonists can all be used to treat PE. Paroxetine, an SSRI which has no FDA approval, has the benefit of improving IELT scores with tolerable side effects compared to placebo and other SSRIs[2]. Compared to the overall male population, patients with erectile dysfunction are more likely to also experience premature ejaculation[33]. Thus, PDE5 inhibitors have also been used to treat PE in clinical investigations as combination therapy although there are conflicting reports in the literature.

The present study aimed to evaluate the efficacy and safety of daily paroxetine 20 mg (an SSRI) and tadalafil 5 mg (a PDE5 inhibitor) combination therapy in patients complaining of PE and ED. According to our findings, at the end of the four-week treatment period, significant improvements were observed in the mean IELT and PEP index scores, and mean IIEF-EF values. Several researchers[37-39] have reported combined therapy results. Polat et al[37], for example, compared the efficiency of paroxetine alone or combined with tadalafil to treat PE, whereas Tuken et al[38] compared the dapoxetine/sildenafil combination. They have concluded that combination therapy has provided a better outcome in terms of ejaculatory latency time[37] and PEP and IIEF-EF scores[38]. Moudi and Kasaeeyan[39] in 2016, confirmed these results with similar findings.

In several randomized control trials[40,41], the efficiency of combined or monotherapy was explored. Paroxetine was superior to the sertraline-another type of SSRI- concerning sexual satisfaction and IELT scores. In another randomized controlled study of PE, Shao and Li[42] reported that although the tolerable side effects were higher in combined paroxetine and behavior therapy than in paroxetine alone therapy, the IELT scores were high in combined therapy. Accordingly, a small-scale study by Salonia et al[43] concluded that IELT scores and intercourse satisfaction were significantly greater in patients treated by combination therapy of sildenafil and paroxetine than in the patients treated by paroxetine alone.

Limitations

Even though the results were interesting, our study has some limitations. First, we could not compare tadalafil-alone or paroxetine-alone-treated patients due to their retrospective nature. Second, the sample size is not enough to conclude the overall efficiency of combined therapy. Third, the subtypes of PE may affect the statistical significance due to their nature of origin. The longer IELT in patients with acquired PE and the inclusion of all PE patients in the study without distinguishing between APE and LPE play a role in this statistical difference. Larger population size, multicenter, randomized, double-blind, placebo-controlled trials are necessary to clarify the effectiveness of combination therapy in the treatment of PE with ED.

Conclusions

Daily paroxetine/tadalafil combination therapy significantly improves IELT scores and self-reported assessment measures in PE patients with ED. The treatment drugs may differ individually, but it is clear that if combined, improving and/or restoring sexual function and psychological outcomes in most men will be more favorable.

Conflict of Interest

The authors declare no conflicts of interest.

Ethics Approval

The study was approved by the clinical research Ethics Committee of Istanbul Prof. Dr. Cemil Tascioglu City Hospital (Approval Number: 989).

Informed Consent
Not applicable due to the retrospective nature of the study.

Data Availability
Data may be provided on a reasonable request to the corresponding author.

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Authors' Contributions
BO: study concept, writing, hypotesis; OC: patient collection, writing; BE: patient collection, data collection; MGC: analysis and interpretation of data, critical revision.

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