On-demand Modafinil Improves Ejaculation Time and Patient-reported Outcomes in Men With Lifelong Premature Ejaculation

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OBJECTIVE To evaluate the effects of modafinil on the intravaginal ejaculatory latency time (IELT) and patient-reported outcomes in patients with lifelong premature ejaculation (PE).

PATIENTS AND METHODS Treatment-naïve lifelong PE patients were included in this proof-of-concept study. Self-estimated IELTs of the patients were recorded and the Premature Ejaculation Profile (PEP) questionnaire was administered before the initiation of on-demand modafinil 100 mg treatment. At the end of 1 month of treatment, self-estimated IELTs were recorded again, along with posttreatment PEP outcomes.

RESULTS Overall, 55 lifelong PE patients with a mean age of 35.07 ± 7.80 (range: 22-58) years were enrolled. Modafinil treatment modestly increased the mean IELT at the end of 1 month (24.82 ± 16.10 seconds vs 49.82 ± 31.46 seconds, $P = .0001$). Moreover, at the end of 1 month, patients reported in the PEP questionnaire better control over ejaculation (0.75 ± 0.67 vs 1.35 ± 0.91, $P = .0001$), improved satisfaction with sexual intercourse (0.98 ± 0.78 vs 1.40 ± 0.85, $P = .0001$), lesser personal distress (0.42 ± 0.69 vs 0.89 ± 1.01, $P = .0001$), and reduced interpersonal difficulty (1.69 ± 1.48 vs 1.95 ± 1.47, $P = .0001$).

CONCLUSION In an uncontrolled proof-of-concept study of men with treatment-naïve lifelong PE where IELT was self-reported without a stopwatch, modest improvements of both IELT and patient-reported outcome measures were observed. Future controlled clinical trials are necessary to confirm these findings. UROLOGY 94: 139–142, 2016. © 2016 Elsevier Inc.

Lifelong premature ejaculation (PE) is defined as "a male sexual dysfunction characterized by ejaculation that always or nearly always occurs prior to or within about one minute of vaginal penetration; the inability to delay ejaculation on all or nearly all vaginal penetrations; and negative personal consequences such as distress, bother, frustration, and/or the avoidance of sexual intimacy."[1] In spite of its high prevalence,[2,3] the US Food and Drug Administration (FDA) has not approved any pharmaceutical agent for the treatment of PE. However, there are a variety of "off-label" therapeutic options,[4] and recent guidelines underline that pharmacotherapy should theoretically be the treatment of choice for lifelong PE patients.[5]

Modafinil is an FDA-approved wake-promoting agent,[6] and it interacts with dopaminergic, norepinephrinergic, histaminergic, and orexinergic systems.[7] In a validated animal model study, Marson et al demonstrated that acute oral administration of an isomer of modafinil (d-modafinil) can increase the ejaculation latency in rats, without suppressing sexual behavior.[8] Moreover, the beneficial effects of on-demand modafinil treatment were reported on a lifelong PE patient.[9]

Because modafinil interacts with various neurotransmitters, which play a role in the ejaculation reflex, this study aims to evaluate the effects of modafinil on the intravaginal ejaculatory latency time (IELT) and patient-reported outcomes in a cohort of patients with lifelong PE.

PATIENTS AND METHODS

A total of 55 treatment-naïve lifelong PE patients were prospectively included to this proof-of-concept study conducted at two urology centers between December 2014 and December 2015. After obtaining written informed consents from the patients, their self-estimated IELTs were recorded and the Turkish validation of Premature Ejaculation

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Table 1. Comparison of pretreatment and posttreatment outcome measures

	Pretreatment	Posttreatment	P*
IELT (s)	24.82 ± 16.1	49.82 ± 31.46	**.0001**
Perceived control (PEP 1)	0.75 ± 0.67	1.35 ± 0.91	**.0001**
Satisfaction (PEP 2)	0.98 ± 0.78	1.4 ± 0.85	**.0001**
Personal distress (PEP 3)	0.42 ± 0.69	0.89 ± 1.01	**.0001**
Interpersonal difficulty (PEP 4)	1.69 ± 1.48	1.95 ± 1.47	**.0001**
PEP total	3.91 ± 2.37	5.72 ± 3.28	**.0001**

IELT, intravaginal ejaculatory latency time; PEP, Premature Ejaculation Profile.
The statistically significant *P* values are presented in bold numbers.
* Wilcoxon and Mann-Whitney *U* tests.

Profile (PEP) questionnaire was administered.[10] The PEP is a four-item (each assessed on 5-point response scales) self-administered questionnaire designed for evaluating the key elements of PE, notably control, distress, interpersonal difficulty, and sexual satisfaction.[11] A detailed medical history (which included sexual history) was obtained and a complete physical examination was performed. All patients were married heterosexual potent men in a stable relationship for at least 6 months. Patients who did not meet the lifelong PE definition criteria[1] were not included in the study. Moreover, patients with concomitant erectile dysfunction or any other types of sexual problems, prostatitis, major psychiatric disorder, drug abuse, hormonal problem, and a history receiving other treatments for PE were excluded from the study.

The patients were given on-demand modafinil 100 mg (Modiwake, Generica, Istanbul, Turkey) treatment and instructed to use the medication before noontime of the days that they were in anticipation of having sex, in order to prevent potential sleeping disturbances, considering the biological half-life of modafinil, which is around 15 hours from administration.[12] Subjects were also requested to have at least two coitus attempts each week during the month. Moreover, they were prohibited to use condoms or topical anesthetic creams, and were advised not to have pauses during intercourse or to have interrupted intromission. At the end of a 1-month treatment period, self-estimated IELTs were recorded again, along with the posttreatment PEP outcomes. In addition, the side effects that occurred during the treatment period were recorded.

The drugs were supplied by the researchers and the participants were not provided any incentives. The study protocol was approved by the institutional review board. The statistical analyses were carried out with Number Cruncher Statistical System 2007 Statistical Software program (NCSS, Kaysville, UT). In addition to the descriptive statistics, Wilcoxon and Mann-Whitney *U* tests were used for comparison of variables. Pearson's correlation test was conducted to assess the association between the baseline IELT values and treatment outcomes. The statistical significance level was set at $P < .05$.

RESULTS

The mean age of the patients was 35.07 ± 7.80 years (range: 22-58). On-demand modafinil treatment modestly increased the mean self-estimated IELT at the end of 1 month (24.82 ± 16.10 seconds vs 49.82 ± 31.46 seconds, $P = .0001$). Moreover, scores obtained from each PEP question and from the total PEP score significantly improved ($P = .0001$ for all, Table 1).

Pearson's correlation test revealed that pretreatment IELT was negatively and moderately correlated with the percentage of IELT change after the treatment ($r = -0.428$, $P = .001$), indicating that patients with shorter IELT benefited more from the treatment. Similarly, mild correlations were observed between the shorter IELT values and better improvements in PEP questions related to perceived control over ejaculation ($r = -0.268$, $P = .048$), interpersonal difficulty related to ejaculation ($r = -0.301$, $P = .026$), and total PEP score ($r = -0.274$, $P = .041$) (Table 2). Moreover, the changes in PEP scores were positively correlated with the change in IELT (Table 2).

Sleeping difficulties during the treatment were reported by six patients (10.91%); however, none of them quit the study because of these side effects. No other adverse events were reported.

DISCUSSION

Although many management options for PE have been proposed, none of these treatment modalities have been well accepted by patients and sexual medicine experts because of their limited efficacy, side effects, or unproven safety.[13] There are concerns on the standards and efficacy of psychotherapy.[14-16] The delay in IELT under topical local anesthetics does not satisfy the majority of the PE patients.[17] Although the efficacy of daily or on-demand selective serotonin reuptake inhibitor treatment has been established, the majority of patients discontinue this treatment because of the cost of the drugs, their side effects, or limited efficacy.[18,19] In addition, potential fertility problems associated with selective serotonin reuptake inhibitor treatment prevent the chronic use of these medications.[20-23] Tramadol, an opioid analgesic, is another effective PE treatment;[24] however, the possibility of drug addiction and side effects limits its use. Therefore, the unmet need of PE treatment triggers researchers to search for a more ideal therapy for this prevalent sexual dysfunction.

Modafinil (diphenylmethyl sulfinyl-2-acetamide) is a wake-promoting agent and has been approved by the FDA for the treatment of narcolepsy, shift work sleep disorder,

Table 2. Correlation between pretreatment intravaginal ejaculatory latency time (IELT) and Premature Ejaculation Profile (PEP) outcomes (Pearson's correlation test)

		Pretreatment IELT	% Change in IELT
% Change PEP 1 (perceived control)	*r*	**–0.268**	**0.663**
	P	**0.048**	**0.0001**
% Change PEP 2 (satisfaction)	*r*	–0.116	**0.508**
	P	0.399	**0.0001**
% Change PEP 3 (personal distress)	*r*	–0.212	**0.603**
	P	0.121	**0.0001**
% Change PEP 4 (interpersonal difficulty)	*r*	**–0.301**	**0.459**
	P	**0.026**	**0.0001**
% Change PEP Total	*r*	**–0.274**	**0.674**
	P	**0.041**	**0.0001**

The statistically significant *P* values are presented in bold numbers.

and obstructive sleep apnea or hypopnea.[6] Although its exact mode of action is not fully elucidated, modafinil has been shown to activate dopaminergic, norepinephrinergic, histaminergic, and orexinergic systems.[7] Modafinil is a race mate composed of two stereoisomers, and the impact of the d-modafinil isomer on male rat sexual behavior has been analyzed by Marson et al,[8] who demonstrated that d-modafinil increases the latency to ejaculation. Because the initiation of mounting behavior and the postejaculatory interval were not altered in rats receiving oral modafinil, the authors concluded that this treatment did not alter the sexual behavior. The d-modafinil isomer has a much shorter half-life, which the authors proposed may be suited for the treatment of PE. Serefoglu reported significant improvement in IELT and PEP measures of a lifelong PE patient who initiated on-demand modafinil therapy.[9] To our knowledge, the efficacy and safety of on-demand modafinil have not been assessed in a clinical study before.

The findings of this proof-of-concept, open-label study revealed that on-demand modafinil may be considered as a novel approach for the treatment of lifelong PE. Modafinil therapy increases the IELT significantly and is associated with significant improvements in the PEP measures. The percentage of IELT change was greater in patients with shorter IELT, indicating that patients with shorter IELT had more significant improvements from modafinil therapy. Better improvements in the PEP questions related to perceived control over ejaculation, interpersonal difficulty related to ejaculation, and total PEP score in these patients confirm these assertions. These findings are in accordance with the observations of Marson et al,[8] who demonstrated that rats with shorter baseline ejaculatory latencies had more pronounced increases in the latency to ejaculation after modafinil treatment.

On the other hand, the improvements in the IELT and PEP measures observed with modafinil in the present study seem to be lesser compared with on-demand dapoxetine treatment, which is the first oral medication specifically developed for the treatment of PE.[25] Several well-controlled studies have demonstrated that dapoxetine, 30 mg or 60 mg taken orally 1-2 hours prior to intercourse, is associated with a 2.5- to 3.0-fold IELT increase in the IELT, as well as improved PEP outcomes.[26-28] Although recent guidelines recommend the use of dapoxetine in the treatment of PE,[5] this medication has not been approved by the FDA yet. Moreover, recent postmarketing surveillance studies reported high discontinuation rates and limited efficacy of dapoxetine,[18,19] indicating that this drug did not meet the expectations of the majority of the PE patients and the unmet need for an effective PE treatment still exists.

Our study is not without limitations. First, the use of self-estimation rather than the use of a stopwatch for measuring the IELT may raise concerns on the reliability of our findings. Unfortunately, our previous attempts in using a stopwatch for PE studies were not successful as the majority of PE patients in our population were reluctant to use this method.[29] However, recent studies have shown a good correlation between self-estimated and stopwatch measured IELT,[30] and this must be considered in interpreting our data. Second, it may be argued that the amount of increase in IELT (more than twofold) is not sufficient for patients with lifelong PE. Although we would agree with this critique, we believe that the efficacy of this therapy may be improved with optimizing the time and dosing of the treatment. As indicated in the Patients and Methods section, these patients were instructed to take the modafinil before noontime in order to prevent potential sleeping disturbances, which may limit the efficacy of the treatment. Considering the pharmacokinetic properties of modafinil and assuming that the majority of patients had sexual encounters in the evening, daily modafinil treatment or taking the medication sooner (eg, 3 hours) before intercourse may result in more significant increase in the IELT values. However, this must be carefully balanced by its vigilance promoting effects. Similarly, increasing the dose of the medication may also improve the efficacy of on-demand modafinil treatment. Finally, having a control group that consisted of placebo or other on-demand treatment option (eg, dapoxetine) would significantly increase the reliability of our findings. Therefore, we believe that future randomized controlled studies are necessary to elucidate the actual benefit of modafinil in the treatment of lifelong PE.

CONCLUSION

In this uncontrolled proof-of-concept study of men with treatment-naïve lifelong PE where IELT was self-reported without a stopwatch, modest improvements of both IELT and patient-reported outcome measures were observed. Future clinical studies are required to establish the optimal dosing scheme of this medication in patients with lifelong PE.

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APPENDIX

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.urology.2016.04.036.