Journal of Psychiatric Research 146 (2022) 264–271

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Influence of modafinil on early ejaculation – Results from a double-blind randomized clinical trial

Mohammad Haghighi [a], Leila Jahangard [a], Azadeh Mazahri Meybodi [b], Mehran Shayganfard [c], Mohammad Ahmadpanah [a], Mohammad Faryadres [d], Kenneth M. Dürsteler [e,f], Annette Beatrix Brühl [g], Dena Sadeghi-Bahmani [g,h,i], Serge Brand [g,i,j,k,l,*]

[a] Behavioral Disorder and Substance Abuses Research Center, Hamadan University of Medical Sciences, Hamadan, Iran
[b] Taleghani Hospital Research Development Committee and Department of Psychiatry, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Department of Psychiatry, Arak University of Medical Sciences, Arak, Iran
[d] Department of Biostatistics and Epidemiology, School of Public Health, Hamadan University of Medical Sciences, Hamadan, Iran
[e] Psychiatric Clinics, Division of Substance Use Disorders, University of Basel, 4002, Basel, Switzerland
[f] Center for Addictive Disorders, Department of Psychiatry, Psychotherapy and Psychosomatics, Psychiatric Hospital, University of Zurich, 8001, Zurich, Switzerland
[g] Center for Affective, Stress and Sleep Disorders (ZASS), Psychiatric University Hospital Basel, 4002, Basel, Switzerland
[h] Department of Psychology, Stanford University, Stanford, CA, USA
[i] Sleep Disorders Research Center, Kermanshah University of Medical Sciences, Kermanshah, 67146, Iran
[j] Substance Abuse Prevention Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, 67146, Iran
[k] Department of Sport, Exercise and Health, Division of Sport Science and Psychosocial Health, University of Basel, 4052, Basel, Switzerland
[l] School of Medicine, Tehran University of Medical Sciences, Tehran, 25529, Iran

ARTICLE INFO

Keywords:
Early ejaculation
Male sexual dysfunction
Modafinil
Double-blind clinical trial
Placebo

ABSTRACT

Background: For men, early ejaculation is a serious health concern. Here, we tested the influence of modafinil (Profinil®) on early ejaculation. To this end, we performed a double-blind randomized clinical trial among men with early ejaculation.

Methods: A total of 46 men with early ejaculation (mean age: 37.35 years) and in stable marital relationships with regular weekly penile-vaginal intercourse were randomly assigned either to the modafinil (100 mg) or to the placebo condition. Compounds were taken about 4–6h before intended penile-vaginal intercourse. At baseline and four weeks later at the end of the study, participants completed a series of self-rating questionnaires covering early ejaculation. Female partners also rated their male partners' early ejaculation profile.

Results: Dimensions of early ejaculation improved over time, but only so in the modafinil condition, while no improvements were observed in the placebo condition.

Conclusions: Among male adults in stable marital relationships with regular weekly penile-vaginal intercourse modafinil improved dimensions of early ejaculation, always compared to placebo. Given the strong effect of modafinil on cognitive-executive processes, it is conceivable, that modafinil acted both via physiological and cognitive-executive pathways.

1. Introduction

Among human beings and compared to all other species, penile-vaginal intercourse is outstanding in that it does not merely serve for reproduction (Buss, 2019; Meston and Buss, 2007; Miller, 2000): Indeed, among heterosexual couples, penile-vaginal intercourse is typically strictly private and thus undisclosed from even very close family members. Further, intercourse occurs when fertilization is highly unlikely such as before and after ovulation, during pregnancy and during post-menopausal stage. As such, penile-vaginal intercourse among heterosexual partners serves a strong pair-bonding function (Buss, 2019; Meston and Buss, 2007; Miller, 2000). Given this, there is sufficient evidence that among adults in heterosexual relationships overall satisfaction with life (Clayton et al., 2014; Contreras et al., 2016; Fisher et al., 2015; Rosen et al., 2016) and couple satisfaction (Blumenstock et al., 2020; Cao et al., 2019; Gewirtz-Meydan and Finzi-Dottan, 2018; Roels

* Corresponding author. Center for Affective, Stress and Sleep Disorders (ZASS), Psychiatric University Hospital Basel, 4002, Basel, Switzerland.
E-mail address: serge.brand@unibas.ch (S. Brand).

https://doi.org/10.1016/j.jpsychires.2021.11.015
Received 4 July 2021; Received in revised form 16 October 2021; Accepted 5 November 2021
Available online 9 November 2021

and Janssen, 2020; Yoo et al., 2014) is closely linked to sexual satisfaction.

However, among adults, sexual dysfunctions are highly prevalent (see below) and occur among both males and females, either as a single health issue or in combination with further somatic or psychological complaints (Berner and Kockott, 2019). Now, the ICD-11 labels sexual dysfunction as "conditions related to sexual health". To define sexual disorders, the DSM-5 (American Psychiatric Association, 2013) states that a 'sexual disorder' is understood as sexual behaviors and experiences characterized as insufficient in quality, duration or frequency. The frequency of occurrence of such unsatisfying sexual behaviors and experiences is between 75 and 100% of sexual behaviors and experiences (IsHak and Tobia, 2013), which further must be present for a minimum of six months, and which must also cause significant distress (see for comprehensive overview: Sadeghi Bahmani and Motl, 2021). If the duration of such unsatisfying sexual behaviors is less than six months or does not lead to serious distress, then this is labelled as a "dysfunction" (van Lankveld, 2018; American Psychiatric Association, 2013). Among women, sexual disorders include sexual interest/arousal disorder, genito-pelvic pain/penetration disorder, and female orgasmic disorder. Among men, sexual disorders include erectile disorder, male hypoactive sexual desire disorder, delayed ejaculation, and early (formerly: **p**remature) ejaculation.

In the present study, we focused on early ejaculation as one of the most prevalent male sexual dysfunctions. The prevalence rates of premature ejaculation range from 2% to 30% (McCabe et al., 2016), or from 5% (Simons and Carey, 2001) to 21% (Laumann et al., 1999). Typically, ejaculation occurs close to penetration to the vagina, or during penetration or shortly after penetration (Hartmann, 2015); men with early ejaculation appear to be unable to monitor their sexual arousal and sexual reactions. Accordingly, ejaculation occurs much earlier, compared to the period of time related to sexual stimulation, sexual play and intercourse and consensual accomplishing of sexual activity. Typically, intravaginal ejaculation latency often is below 1 min. Most often female partners complain to lose their sexual interests when their male partner has early ejaculations (Hartmann, 2015), while men not always experience early ejaculation as a "disorder" or "dysfunction". The etiological basis of premature ejaculation remains elusive; both genetic and behaviorally acquired causes are discussed, and antecedent or reactive anxiety are often reported (Hartmann, 2015).

Both non-pharmacological and pharmacological treatments are employed to treat early ejaculation. As regards non-pharmacological treatments, basically six interventions are considered: 1. Shifting the cognitive attention from sexual activity and content to non-sexual content, though, following Berner and Kockott (2019) such interventions appeared to be anecdotal and accompanied by higher anxiety. 2. Squeeze and stop-start (Kockott and Fahrner-Tutsek, 2015); 3. Sensate focus; 4. Stimulation device; 5. Pelvic floor rehabilitation (Cooper et al., 2015), and 6. Couple counseling (Fahrner and Kockott, 2003; Hartmann, 2015; Kockott and Fahrner-Tutsek, 2015). While Fahrner and Kockott (2003) reported that techniques such as squeeze and stop-start were efficient, Cooper et al. (2015) were less enthusiastic, as the evidence of the efficacy of physical behavioral techniques appeared to be limited and that behavioral therapies combined with drug treatments appeared to provide more encouraging results.

As regards the pharmacological treatments of early ejaculation, the following medications are reported: Serotonin-reuptake inhibitors (SSRIs such a paroxetine, citalopram, escitalopram, sertraline, to name but a few); serotonin-noradrenalin-reuptake-inhibitors (SNRIs such as duloxetine); phosphodiesterase-5 (PDE5) inhibitors such as vardenafil and tadalafil; opioid analgesics, and topical anesthetics - eutectic mixture of local anesthetics, and topical eutectic mixture for premature ejaculation (Cooper et al., 2015). Recently, a randomized, double-blind, placebo-controlled proof-of-concept trial showed that the oxytocin antagonist cligosiban prolonged intravaginal ejaculatory latency and improved self-reported outcomes of early ejaculation (McMahon et al., 2019). Further, the administration of lisdexamfetamine dymesilate improved dimensions of early ejaculation, compared to placebo (Haghighi et al., 2021). In the present study, we focused on the efficacy of a pharmacological compound, and on modafinil (Profinil®), more specifically.

Modafinil (2-[(Diphenylmethyl) sulfinyl] acetamide) is a medication with wake-promoting properties (Minzenberg and Carter, 2008). Results from animal and human studies suggest that modafinil appears to exert a concentration-altering effect on dopamine (increase), norepinephrine (increase), serotonin (both increase and decrease), glutamate (increase), GABA (decrease), and orexin (increase) (Minzenberg and Carter, 2008). Thus, the neurochemical properties of modafinil appear to impact on the catecholamine systems. The strong clinical efficacy of modafinil in people with narcolepsy suggests that modafinil has a relevant effect on the neurochemical system of orexin (Minzenberg and Carter, 2008). Modafinil has enhancing effects on behavior and above all on cognitive processes; such improvements are believed to be the effect of modafinil on the increased monoamine activity, including orexin, and not on the changes in the glutamate or GABA system (Minzenberg and Carter, 2008).

As regards the use of modafinil to treat early ejaculation, the thorough literature review showed that one animal study (Marson et al., 2010), one case report (Serefoglu, 2016) and one proof-of-concept study (Tuken et al., 2016) including 55 men with early ejaculation are available to the scientific community so far. Marson et al. (2010) showed that among rats and compared to placebo, administration of modafinil increased the ejaculatory latency time and increased the number of intromissions observed prior to ejaculation. Serefoglu (2016) reported on an apparently healthy 30 years-old man with early ejaculation. Three hours before penile-vaginal intercourse, the person took in 100 mg of modafinil. Two weeks after such a procedure, ejaculatory latency time increased from about 40 s to about 15 min, along with an increased overall satisfaction, as measured with the Premature Ejaculation Profile (Patrick et al., 2009). Tuken et al. (2016) assessed 55 me**a**n with lifelong early ejaculation; participants completed questionnaires related to early ejaculation both at baseline and 4 weeks later. Further, they took modafinil on demand some hours before penile-vaginal intercourse. Effect sizes (Cohen's ds) for dimensions of the Premature Ejaculation Profile (Patrick et al., 2009) were: Perceived control: 2.13; satisfaction: 2.15; personal distress: 2.08; interpersonal difficulties: 1.86; total score: 1.86; thus, all effect sizes were large. The advantages of the previous studies were that they offered some sparse, but encouraging indication that modafinil might favorably impact on early ejaculation. On the flip side, no study did systematically investigate, if modafinil was superior to placebo, when both participants and study investigators were blind to participants' treatment. To counter this, we performed a randomized, double-blind and placebo-controlled clinical trial. To this end, 46 men with early ejaculation were assessed and randomly assigned either to the modafinil condition or to the placebo condition.

Based on two previous studies (Serefoglu, 2016; Tuken et al., 2016), we predicted improvements of early ejaculation in the modafinil condition, compared to the placebo condition.

We hold that the result could be of practical and clinical importance, given that 2%–30% of the male general population may complain about early ejaculation (McCabe et al., 2016), and given that for instance the intake of SSRIs is associated with adverse side-effects.

2. Methods

2.1. Study design

Males with self-reported early ejaculation and treated at the outclinic of the Farshchian Hospital (Hamadan, Iran) were approached to participate in the present randomized and double-blind clinical trial on the effect of modafinil (Profinil®) on early ejaculation. Participants were fully informed about the aims of the study, the study procedure and

the confidential, secure and anonymized data handling. Next, participants signed the written informed consent. Participants were randomly assigned either to the modafinil or to the placebo condition. At the beginning and four weeks later at the end of the study participants completed a series of self-rating questionnaires covering sexual activity and ejaculation patterns. Female partners also rated participants' premature ejaculation profile both at the beginning and at the end of the study. The study was registered at that Iranian Register for Clinical Trials (IRCT registration number: IRCT20090304001743N15). The local ethics committee approved the study (register nr: IR.UMSHA.REC.1399,081), which was performed in accordance with the current and seventh revision (World Medical Association, 2013) of the Declaration of Helsinki.

2.2. Participants

A total of 46 males with self-reported premature ejaculation were assessed. Inclusion criteria were: 1. Male gender; 2: Age between 18 and 65 years; 3. Self-reported premature ejaculation (see below); 4. Clinical diagnosis of early ejaculation; 5. Stable heterosexual relationship; 6. Regular penile-vaginal intercourse at least twice the week for four consecutive weeks; 7. Compliance with the study conditions; 8. Signed written informed consent. Exclusion criteria were: 1. Use of additional pharmacological and non-pharmacological techniques to cope with early ejaculation. 2. Use of condoms; 3. Neurological disorders such as multiple sclerosis (MS), neuromyelitis optica spectrum disorder (NMOSD) or Parkinson's disease (PD), as ascertained by a thorough clinical-neurological interview; 4. Psychiatric disorders such as major depressive disorders, bipolar disorders, or substance use disorders, as ascertained by a thorough clinical-psychiatric interview (First, 2015) based on the DSM-5 (American Psychiatric Association, 2013). 5. Intake of psychoactive drugs such as antidepressants, mood stabilizers, sleep-inducing medications, or additional medications impacting on the dopamine- or orexin-system in an agonistic or antagonistic manner.

Of the 70 assessed, 46 (76.67%) were included in the study, and all completed the study. Statistics was performed per protocol. Fig. 1 shows the flow chart.

2.3. Sample size calculations

Based on a previous proof-of-concept-study (Tuken et al., 2016), we expected at least a medium effect size (partial eta-squared); the sample size calculation with G*Power (Faul et al., 2007) was as follows: Partial eta-squared: 0.07; effect size f: 0.274; alpha: 0.05; beta: 0.8; number of groups: 2; number of measurements: 2; total sample size: 34. However, to counterbalance possible dropouts, the sample size was set at 46 participants.

2.4. Randomization

A psychologist not otherwise involved in the study prepared 46 sealed envelopes containing 22 red and 23 blue cards; envelopes were put in an opaque ballot box and stirred. Participants picked-up an envelope and were assigned to the defined study conditions. Picked-up envelopes were then put aside.

2.5. Measurements

2.5.1. Demographic information

Participants reported their age (years), duration of marriage (years), highest educational degree (compulsory school; diploma; high-school degree; higher educational level such as bachelor, master or doctorate), the number of children and the socioeconomic status.

2.5.2. Information related to early ejaculation

At baseline and four weeks later at the end of the study participants completed the following self-rating questionnaires:

2.5.2.1. Premature ejaculation profile (PEP). To further assess early ejaculation, participants and their female partners completed the Premature Ejaculation Profile (PEP) (Giuliano et al., 2008; Patrick et al., 2005, 2009). The questionnaire consists of items covering the following four domains: Sense of control over ejaculation; personal distress related to ejaculation; interpersonal difficulty; satisfaction with sexual intercourse. Answers are given on five-points Likert scales ranging from 0 (= very poor/not at all/none) to 4 (= very good/extremely/severe). Interclass correlation coefficients ranged from 0.86 to 0.89.

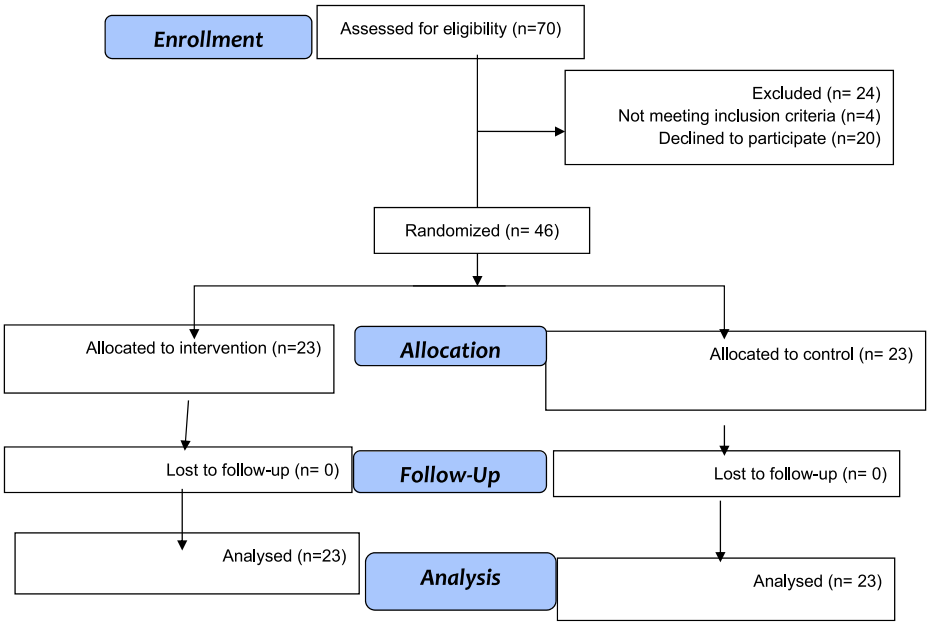

Fig. 1. Flow chart of participants' number and study allocation.

2.5.2.2. Index for premature ejaculation (IPE). The Index of Premature Ejaculation (IPE) is a self-report questionnaire developed to address issues (sexual satisfaction, control and distress) associated with premature ejaculation (Althof et al., 2006). The questionnaire consists of 10 items, and each item has 5 possible response options, ranging from 5 (= almost always/always/extremely distressed) to 1 (= almost never/never/not at all distressed). Items are aggregated to the following dimensions: Sexual satisfaction, control, and distress, higher scores reflected higher satisfaction, higher control and lower distress (Cronbach's alpha: 0.86).

2.5.2.3. Intravaginal ejaculation latency time. To assess the time lapse between the vaginal penetration and the intravaginal ejaculation, participants used a stop watch. The intravaginal ejaculation latency time was reported in seconds (Waldinger et al., 1994).

2.6. Modafinil; verum condition

Participants received a total of 12 tablets of 100 mg modafinil (Profinil®; manufacturer: Sobhan Darou, Tehran, Iran). Participants were instructed to intake a capsule about 6 h before when penile-vaginal intercourse was highly likely.

2.7. Placebo

Participants in the placebo condition received a total of 12 tablets of placebo. Participants were instructed to intake a capsule about 6 h before when penile-vaginal intercourse was highly likely. Placebo capsules consisted of lactose powder, glycerin, methylparaben, and propylparaben. Capsules of modafinil and placebo were identical in shape, color, weight, and smell.

2.8. Statistical analysis

Analyses were performed per protocol.

With a series of X^2-tests and t-tests sociodemographic information were compared between participants in the modafinil and placebo condition.

A series of ANOVAs for repeated measures was performed with the following factors: Time (baseline; study end), Group (verum vs. placebo) and the Time x Group-interaction; dependent variables were: Dimensions of early ejaculation, as reported in the questionnaires.

The nominal significance level was set at alpha <0.05. Effect sizes for F-statistics were reported as partial eta squared (ηp^2), with 0.019 = trivial effect size [T]; $0.020 < \eta p^2 < 0.059$ = small effect size [S], $0.06 < \eta p^2 < 0.139$ = medium effect size, [M], and $\eta p^2 \geq 0.14$ = large effect size [L]. Following the examples from previous studies (Sadeghi Bahmani et al., 2021, 2021), and based on Becker's approach to compare mean changes (Becker, 1988) Cohen's d effect sizes were reported for the pre-post change within the two groups, and between the two groups at the end of the study. Effect sizes for t-tests were reported as Cohen's d (Cohen, 1988) with the following ranges: d = 0–0.19: trivial effect sizes; d = 0.20–0.49: small effect sizes; d = 0.50–0.79: medium effect sizes; d ≥ 0.80: large effect sizes. All calculations were performed with SPSS® 25.0 (IBM Corporation, Armonk NY, USA) for Apple Mac®.

3. Results

3.1. General information

Table 1 provides the descriptive and inferential statistical overview of participants' sociodemographic and anthropometric information.

sociodemographic baseline characteristics of participants in the verum and placebo condition.

Participants in the modafinil and placebo condition did not differ as regards age, duration of marriage, the number of children, the socioeconomic status, and the highest educational level. Participants in the modafinil condition had a higher BMI, compared to participants in the placebo condition.

Table 1
Descriptive and inferential statistical overview of sociodemographic baseline characteristics between participants in the modafinil and the placebo condition.

Variables	Groups		Statistics
	Modafinil	Placebo	
N	23	23	
	M (SD)	M (SD)	
Age (years)	38.52 (8.25)	36.17 (8.25)	t(44) = 0.34, d = 0.39 [S]
Duration marriage (years)	12.60 (6.99)	10.86 (7.04)	t(44) = 0.41, d = 0.38 [S]
BMI (kg/m^2)	27.89 (4.04)	26.18 (2.57)	t(44) = 2.47*, d = 0.85 [L]
	n/n/n/n	n/n/n/n	
Children (0, 1, 2, 3, 4)	2/8/10/3/0	5/6/9/1/2	X^2(N = 46, df = 4) = 4.62
	n/n/n	n/n/n	
Education status (under diploma, diploma, academic degree)	5/9/9	3/10/10	X^2(N = 44, df = 4) = 0.40
Socioeconomic status (poor, moderate, good)	5/17/1	7/13/3	X^2(N = 46, df = 4) = 0.34

Notes: All ps > .40.

3.2. Early ejaculation-related information

Table 2 provides the descriptive statistical indices of early ejaculation-related information, while Table 3 reports the inferential statistical indices.

3.2.1. Premature ejaculation profile (PEP)

The premature ejaculation profile, as self-rated, increased over time (large effect size); there were no statistically significant group and no time by group-interactions effects (small effect sizes).

The premature ejaculation profile, as rated by participants' wives, increased over time (large effect size), with no group differences or with group differences over time (interaction); always trivial effect sizes.

Index of premature ejaculation (IPE).

Satisfaction, control, and distress improved over time (always large effect sizes), but more so in the modafinil condition, compared to placebo condition (always medium to large effect sizes).

Table 2
Descriptive statistical indices of dimensions of early ejaculation, at baseline and at the end of the study 4 weeks later, separately for participants in the modafinil and the placebo condition.

	Time pointsM (SD)			
	Baseline		Study end	
	Modafinil	Placebo	Modafinil	Placebo
N	23	23	23	23
	M (SD)	M (SD)	M (SD)	M (SD)
Premature ejaculation profile (self-rating)	5.26 (3.41)	3.73 (2.18)	6.00 (3.61)	4.17 (3.48)
Premature ejaculation profile (wives' ratings)	4.78 (3.46)	3.78 (2.95)	5.21 (3.14)	4.04 (3.02)
Index of premature ejaculation; satisfaction	41.57 (21.70)	34.23 (24.91)	49.22 (20.09)	36.18 (22.58)
Index of premature ejaculation; control	24.18 (21.91)	21.46 (19.56)	38.35 (20.11)	23.91 (15.72)
Index of premature ejaculation; distress	22.82 (21.20)	32.60 (23.75)	35.85 (18.47)	35.05 (23.05)
Intravaginal ejaculatory latency time (second)	36.95 (12.12)	31.52 (13.68)	66.95 (20.54)	34.34 (11.70)

Notes: M: mean, SD: standard deviation.

Table 3
Inferential statistical indices of dimensions of early ejaculation, at baseline and at the end of the study 4 weeks later, separately for participants in the modafinil and the placebo condition.

	Factors		
	Time	Group	Time × Group interaction
	F(1, 44) ηp^2	F(1, 44) ηp^2	F(1, 44) ηp^2
Premature ejaculation profile (self-rating)	13.92** .240 [L]	2.65 .057 [S]	0.94 .021 [S]
Premature ejaculation profile (wives' ratings)	4.07* .085 [M]	2.13 .053 [S]	0.26 .006 [T]
Index of premature ejaculation; satisfaction	12.30** .219 [L]	0.57 .015 [S]	4.39* .090 [M]
Index of premature ejaculation; control	27.91*** .338 [L]	1.59 .040 [S]	13.90** .240 [L]
Index of premature ejaculation; distress	27.36*** .383 [L]	0.27 .007 [T]	12.80** .225 [L]
Intravaginal ejaculatory latency time (seconds)	47.86*** .521 [L]	26.22*** .373 [L]	32.80*** .427 [L]

Note: [T] = trivial effect size [S] = small effect size; [M] = medium effect size; [L] = large effect size, *p < 0.05. **P < 0.01. ***P < 0.001.

Intravaginal ejaculation latency time (IELT).

Intravaginal ejaculation latency time increased over time (large effect size), but more so in the modafinil, compared to the placebo condition (large effect size of interaction). Scores were higher in the modafinil, compared to the placebo condition (large effect size).

3.3. Mean changes between the modafinil and the placebo condition at the end of the study, and within the modafinil and placebo condition from baseline to the end of the study

Table 4 provides the overview of effect size calculations between the modafinil and placebo condition at the end of the study, and within the modafinil and placebo condition from baseline to the end of the study.

Table 4
Overview of effect sizes; between group comparison at the end of the study; within group comparison from baseline to the end of the study.

	Effect size comparisons		
	Between the modafinil and placebo condition at the end of the study	Within the modafinil condition from baseline to the study end	Within the placebo condition from baseline to the study end
Premature ejaculation profile (self-rating)	0.65 [M]	0.26 [S]	0.15 [T]
Premature ejaculation profile (wives' ratings)	0.46 [M]	0.16 [S]	0.10 [T]
Index of premature ejaculation; satisfaction	0.81 [L]	0.53 [M]	0.12 [T]
Index of premature ejaculation; control	1.29 [L]	0.99 [L]	0.21 [S]
Index of premature ejaculation; distress	0.48 [M]	0.99 [L]	0.14 [T]
Intravaginal ejaculatory latency time (seconds)	3.89 [L]	2.05 [L]	0.33 [S]

Notes: [S] = small effect size; [M] = medium effect size; [L] = large effect size.

At the end of the study and compared to the placebo condition, modafinil improved early ejaculation, as assessed with the premature ejaculation profile (self-rating; female partners' ratings), premature ejaculation diagnosis profile, and intravaginal ejaculation latency (always medium to large effect sizes).

Within the modafinil condition, small effect sizes were observed for premature ejaculation profile (self-rating and female partner's rating), while medim to large effect sizes were observed for premature ejaculation, control, satisfaction and distress, and for the intravaginal ejaculation latency.

Within the placebo condition, all effect sizes were trivial or small.

4. Discussion

The key findings of the present study were that among men with early ejaculation and compared to a placebo condition, administration of modafinil (Profinil®) improved dimensions of early ejaculation over a time lapse of four weeks, when modafinil was taken about 6 h before penile-vaginal intercourse. In contrast, no improvements were observed in the placebo condition. The present results add to the current literature in five ways: 1. The intake of modafinil favorably impacted on ejaculation patterns among men with early ejaculation; 2. Such improvements were also perceived by their wives; 3. Early ejaculation appears to be treatable with pharmacological interventions; 4. In contrast to two previous publications, data were carried out from a double-blind, placebo-controlled clinical trial. 5. The underlying psychophysiological mechanisms remained unknown: Given that modafinil has a strong impact on cognition such as increased sustained attention, alertness and concentration, it is also conceivable that participants in the modafinil condition were more able to have control over their executive functions, to better control ejaculation processes and thus to be aware that they were given modafinil, and not placebo.

Based on two previous studies (Serefoglu, 2016; Tuken et al., 2016), we predicted improvements of early ejaculation in the modafinil condition, compared to the placebo condition, and data did fully support this. The present data expand upon the sparse literature on this topic, in that data were carried out from a double-blind and placebo-controlled clinical trial.

While the present data showed that modafinil favorably impacted on early ejaculation, the quality of the data does not allow a deeper neurophysiological and psychological introspection of such an impact. Given this, the following seven and admittedly speculative hypotheses are advanced.

First, Santilla et al. (2010) mentioned that early ejaculation appeared to be associated with the dopamine pathway; that is to say; it appears that a dysregulation in terms of inhibition of available dopamine concentrations in the regulatory neurophysiological system of the ejaculation could lead to early ejaculation. Further, in rats, the stimulation of dopamine auto-receptors led to early ejaculation (Napoli-Farris et al., 1984); this was understood as a process of inhibition of DA neurotransmission resulting in such "early ejaculation". Data from a large-scale study of 1290 men (mean age: 26.9 years) showed that compared to carriers of the 9R9R/9R10R genotype dopamine transporter gene (DAT1), carriers of the 10R10R genotype dopamine transporter gene (DAT1) had a lower threshold to ejaculate (Santtila et al., 2010). Santilla et al. (2010) concluded that the dopaminergic neurotransmission must be involved in the regulation of ejaculation. Next, the primary activation in the mesodiencephalic transition zone, including the ventral tegmental area, which is involved in a wide variety of rewarding behaviors (Holstege et al., 2003), is also associated with ejaculation. In the same vein, ejaculation was associated with the reward system, along with its emotional components of pleasure, joy and satisfaction, and along with the reward-enhancing action at a behavioral level, which is highly associated with the availability of dopamine concentrations in the nigrostriatal, tuberoinfundibular, mesolimbic and mesocortical pathways (Ng et al., 2019; van Calker, 2019).

In general, the findings described above suggest that the dopaminergic neurotransmission is involved in the ejaculation; specifically, the disbalance of the available dopamine concentrations appeared to be involved in the early ejaculation. In this view, given the properties of modafinil on the dopaminergic pathways and given that early ejaculation is also related to the dysregulation of the dopamine pathway, it appears plausible that modafinil favorably impacted on early ejaculation.

The background of the second hypothesis is as follows: Modafinil improves cognitive performance (Battleday and Brem, 2015; Brühl et al., 2019; Franke et al., 2017; Kredlow et al., 2019; Li et al., 2020; Repantis et al., 2010, 2021)*:* More specifically, modafinil favorably impacts on cognitive domains of attention, executive functioning, memory, and processing speed (Kredlow et al., 2019). With this background, the second hypothesis is: Modafinil improved dimensions of early ejaculation, because it improved the cognitive control over the process of sexual activity, in general, and the time point of ejaculation, in specific. Gaining higher control over the timepoint of ejaculation coincides with the cognitive-behavioral intervention of early ejaculation: Indeed, while men with early ejaculation experience ejaculation as a process out of their behavioral and cognitive control, interventions such as the squeeze technique and the stop-start-method confer to the individual (and his partner) a higher control over the process of ejaculation (Fahrner and Kockott, 2003; Kockott and Fahrner-Tutsek, 2015). We further claim that a higher control over the ejaculation timing should be associated with a lower feeling of helplessness and an increased the feeling of control and self-efficacy (Bandura, 1977). As such, it is conceivable that the administration of modafinil improved dimensions of early ejaculation via its cognition-enhanced effect in general, and its enhancing effect on increased on cognitive domains of attention, executive functioning, and processing speed (Kredlow et al., 2019).

The concept of the Health Belief Model (HBM) is the basis of the third hypothesis (Chiang et al., 2015; Janz and Becker, 1984; Rosenstock et al., 1988). The Health Belief Model identifies those cognitive-emotional processes (in terms of beliefs), which underlie health-related behavior. In this specific case, if early ejaculation is considered a "pure" physiological issue, then the administration of a pill should alleviate this sexual issue. Thus, the administration of a medical compound may coincide with the Health Belief Model (HBM), that early ejaculation is "merely" due to "biological" issues. In contrast, psychotherapeutic interventions presume a "psychological and psychosocial" basis of the early ejaculation. However, if this assumption were fully true, one would not expect differences of early ejaculation performances between the modafinil and the placebo condition.

The fourth hypothesis could be considered as an extension of the third hypothesis, and is based on the placebo research*:* The beneficial effect of a compound does not derive exclusively from its chemical and neurophysiological structures per se, but from the cognitive-emotional expectancies projected onto the compound (Evers et al., 2018; Gaab, 2019; Gaab et al., 2018). As such, the "mere" expectation that early ejaculation could be "solved" might have triggered relief, decreased psychophysiological tension and anxiety, and a favorable outcome. However, if this assumption were fully true, one would have expected also improvements in the placebo condition, which actually did occur only to a very small extent.

Relatedly, fifth, it is conceivable that the mere participation in such a study triggered positive expectations and an improvements on early ejaculation: Research on psychotherapy showed that treatment motivation was a reliable predictor of improved psychotherapy outcome (Grawe, 1994, 2004, 2007; Kanfer et al., 2011). In this line, only participants able and willing to comply with the study conditions were included in the study. As such, possible placebo and expectancy effects cannot be ruled out.

As regards the sixth hypothesis, it is conceivable that additional latent and unassessed neuroendocrinological and cognitive-emotional factors could be responsible for the present pattern of results. More specifically, it is conceivable that compared to the modafinil condition, more participants in the placebo condition suffered from varicocele, the abnormal enlargement of the pampiniform venous plexus in the scrotum. There is some evidence to suggest that varicocelectomy might improve early ejaculation (Martin et al., 2017). Thus, while highly unlikely, such methodological bias cannot fully be ruled out.

The seventh and last hypothesis is related to the second, third and fourth hypothesis: Given that modafinil improves the cognitive performance (Battleday and Brem, 2015; Brühl et al., 2019; Franke et al., 2017; Kredlow et al., 2019; Li et al., 2020; Repantis et al., 2010, 2021), and more specifically cognitive domains of attention, executive functioning, memory, and processing speed (Kredlow et al., 2019), participants in the modafinil condition should have been aware of their improvements in cognitive processes. As such, it is highly conceivable that such awareness and knowledge blurred the key concept of a double-blind study.

The novelty of the results should be balanced against the limitations mentioned above: First, while the overall pattern of results suggested that compared to placebo, modafinil improved dimensions of early ejaculation, the quality of the data does not allow a conclusive answer as to why this happened. A further passive control condition or a wait-list condition might have helped to sort out possible placebo effects. Second, modafinil is prescribed for individuals with narcolepsy (Golicki et al., 2010), with severe daytime sleepiness related to idiopathic hypersomnolence (Trotti et al., 2021), and with attention-deficit/hyperactivity disorder (Wang et al., 2017). Common side effects of modafinil are decreased appetite, insomnia (Wang et al., 2017), and, in some rare cases, the Steven-Johnson syndrome (Prince et al., 2018). Given this, a thorough assessment of perceived side-effects would have allowed to understand, if participants had noticed such side-effects, and if prevalence rates of such side-effects were higher in the modafinil condition, compared to the placebo condition. Third, psychotherapeutic interventions recommend to embed interventions to treat early ejaculation within a broader psychosocial and couple-related sexual therapy (Berner and Kockott, 2019; Fahrner and Kockott, 2003; Kockott and Fahrner-Tutsek, 2015); given this, next studies might consider to **introduce** further treatment arms or to involve in a broader fashion the female partner. Fourth, with modafinil early ejaculation latency time improved from about 37 s to about 67 s; mathematically, the latency time almost doubled; though, from the point of view of a broader quality of sexual activity consisting of foreplay, mutual satisfaction and coordinated joint orgasm, 67 s might be still unsatisfactorily. Fifth, there is evidence that early ejaculation is associated with a higher degree of anxiety and sociophobia (Berner and Kockott, 2019; Fahrner and Kockott, 2003; Kockott and Fahrner-Tutsek, 2015). As regards the association between anxiety and modafinil, findings from animal and human studies suggested, the administration of modafinil might bear the risk of increased anxiety (Hofmann et al., 2011, 2014); however, if true, we wouldn't have expected improvements in early ejaculation as a proxy of anxiety. As such, future studies should assess also assess anxiety and traits of sociophobia as possible confounders.

5. Conclusions

Compared to a placebo condition, modafinil (Profinil®) improved dimensions of early ejaculation in males with early ejaculation. Given the strong effect of modafinil on attention, alertness and executive control, it is conceivable that modafinil impacted on early ejaculation both via physiological and cognitive processes.

Declaration of competing interest

All authors declare no conflicts of interest. The whole study was performed without external funding.

Acknowledgement

We thank Balz Furlano (University of Basel, Basel, Switzerland) for manuscript formatting.

References

Althof, S., Rosen, R., Symonds, T., Mundayat, R., May, K., Abraham, L., 2006. Development and validation of a new questionnaire to assess sexual satisfaction, control, and distress associated with premature ejaculation. J. Sex. Med. 3 (3), 465–475.
American Psychiatric Association, 2013. Diagnostic and Statistical Manual of Mental Disorders, fifth ed., vol. 5. American Psychiatric Association, Arlington VA. DSM.
Bandura, A., 1977. Self-efficacy: toward a unifying theory of behavioral change. Psychol. Rev. 84 (2), 191–215.
Battleday, R.M., Brem, A.K., 2015. Modafinil for cognitive neuroenhancement in healthy non-sleep-deprived subjects: a systematic review. Eur. Neuropsychopharmacol 25 (11), 1865–1881.
Becker, B.J., 1988. Synthesizing standardized mean-change measures. Br. J. Math. Stat. Psychol. 41 (2), 257–278.
Berner, M.M., Kockott, G., 2019. Sexual dysfunctions. In: Berger, M. (Ed.), Psychiatric Disorders. Elsevier, Munich GER, pp. 591–613.
Blumenstock, S.M., Quinn-Nilas, C., Milhausen, R.R., McKay, A., 2020. High emotional and sexual satisfaction among partnered midlife Canadians: associations with relationship characteristics, sexual activity and communication, and health. Arch. Sex. Behav. 49 (3), 953–967.
Brühl, A.B., d'Angelo, C., Sahakian, B.J., 2019. Neuroethical issues in cognitive enhancement: modafinil as the example of a workplace drug? Brain Neurosci Adv 3, 2398212818816018.
Buss, D.M., 2019. Evolutionary Psychology. The New Science of the Mind, sixth ed. Routledge, New York.
Cao, H., Zhou, N., Fine, M.A., Li, X., Fang, X., 2019. Sexual satisfaction and marital satisfaction during the early years of Chinese marriage: a three-wave, cross-lagged, actor-partner interdependence Model. J. Sex. Res. 56 (3), 391–407.
Chiang, Y.Z., Bundy, C., Griffiths, C.E., Paus, R., Harries, M.J., 2015. The role of beliefs: lessons from a pilot study on illness perception, psychological distress and quality of life in patients with primary cicatricial alopecia. Br. J. Dermatol. 172 (1), 130–137.
Clayton, A.H., El Haddad, S., Iluonakhamhe, J.P., Ponce Martinez, C., Schuck, A.E., 2014. Sexual dysfunction associated with major depressive disorder and antidepressant treatment. Expet Opin. Drug Saf. 13 (10), 1361–1374.
Cohen, J., 1988. Statistical Power Analysis for the Behavioral Sciences, second ed. Lawrence Erlbaum Associates, Mahwah NJ.
Contreras, D., Lillo, S., Vera-Villarroel, P., 2016. Subjective sexual well-being in Chilean adults: evaluation of a predictive Model. J. Sex Marital Ther. 42 (4), 338–352.
Cooper, K., Martyn-St James, M., Kaltenthaler, E., Dickinson, K., Cantrell, A., Wylie, K., Frodsham, L., Hood, C., 2015. Behavioral therapies for management of premature ejaculation: a systematic review. Sex. Med. 3 (3), 174–188.
Evers, A.W.M., Colloca, L., Blease, C., Annoni, M., Atlas, L.Y., Benedetti, F., Bingel, U., Büchel, C., Carvalho, C., Colagiuri, B., Crum, A.J., Enck, P., Gaab, J., Geers, A.L., Howick, J., Jensen, K.B., Kirsch, I., Meissner, K., Napadow, V., Peerdeman, K.J., Raz, A., Rief, W., Vase, L., Wager, T.D., Wampold, B.E., Weimer, K., Wiech, K., Kaptchuk, T.J., Klinger, R., Kelley, J.M., 2018. Implications of placebo and nocebo effects for clinical practice: expert consensus. Psychother. Psychosom. 87 (4), 204–210.
Fahrner, E.-M., Kockott, G., 2003. Sexual Therapy. Textbook for the Treatment of Sexual Dysfunctions in Men. Hogrefe, Göttingen GER.
Faul, F., Erdfelder, E., Lang, A.G., Buchner, A., 2007. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav. Res. Methods 39 (2), 175–191.
First, M., 2015. Structured Clinical Interview for the DSM (SCID), pp. 1–6.
Fisher, W.A., Donahue, K.L., Long, J.S., Heiman, J.R., Rosen, R.C., Sand, M.S., 2015. Individual and partner correlates of sexual satisfaction and relationship happiness in midlife couples: dyadic analysis of the international survey of relationships. Arch. Sex. Behav. 44 (6), 1609–1620.
Franke, A.G., Gränsmark, P., Agricola, A., Schühle, K., Rommel, T., Sebastian, A., Balló, H.E., Gorbulev, S., Gerdes, C., Frank, B., Ruckes, C., Tüscher, O., Lieb, K., 2017. Methylphenidate, modafinil, and caffeine for cognitive enhancement in chess: a double-blind, randomised controlled trial. Eur. Neuropsychopharmacol 27 (3), 248–260.
Gaab, J., 2019. The placebo and its effects: a psychoneuroendocrinological perspective. Psychoneuroendocrinology 105, 3–8.
Gaab, J., Locher, C., Blease, C., 2018. Placebo and psychotherapy: differences, similarities, and implications. Int. Rev. Neurobiol. 138, 241–255.
Gewirtz-Meydan, A., Finzi-Dottan, R., 2018. Sexual satisfaction among couples: the role of attachment orientation and sexual motives. J. Sex. Res. 55 (2), 178–190.
Giuliano, F., Patrick, D.L., Porst, H., La Pera, G., Kokoszka, A., Merchant, S., Rothman, M., Gagnon, D.D., Polverejan, E., 2008. Premature ejaculation: results from a five-country European observational study. Eur. Urol. 53 (5), 1048–1057.
Golicki, D., Bala, M.M., Niewada, M., Wierzbicka, A., 2010. Modafinil for narcolepsy: systematic review and meta-analysis. Med. Sci. Mon. Int. Med. J. Exp. Clin. Res. 16 (8), Ra177–186.
Grawe, K., 2004. Psychological Therapy. Hogrefe Publisher, Göttingen GER.
Grawe, K., 2007. Neuropsychotherapy: How the Neurosciences Inform Effective Psychotherapy. Hogrefe Publisher, Göttingen GER.
Grawe, K.D., R, Bernauer, F., 1994. Development of Pychotherapy - from the Confession to Profession. Hogrefe, Göttingen GER.
Haghighi, M., Doostizadeh, M., Jahangard, L., Soltanian, A., Faryadres, M., Dürsteler, K. M., Beatrix Brühl, A., Sadeghi-Bahmani, D., Brand, S., 2021. Influence of lisdexamfetamine dimesylate on early ejaculation-results from a double-blind randomized clinical trial. Healthcare (Basel) 9 (7).
Hartmann, U., 2015. Sexual dysfunctions. In: Linden, M.H.M. (Ed.), Textbook of Behavioral Therapy. Springer, Berlin GER, pp. 585–590.
Hofmann, S.G., Fang, A., Gutner, C.A., 2014. Cognitive enhancers for the treatment of anxiety disorders. Restor. Neurol. Neurosci. 32 (1), 183–195.
Hofmann, S.G., Smits, J.A., Asnaani, A., Gutner, C.A., Otto, M.W., 2011. Cognitive enhancers for anxiety disorders. Pharmacol., Biochem. Behav. 99 (2), 275–284.
Holstege, G., Georgiadis, J.R., Paans, A.M., Meiners, L.C., van der Graaf, F.H., Reinders, A.A., 2003. Brain activation during human male ejaculation. J. Neurosci. 23 (27), 9185–9193.
IsHak, M.D.F.W., Tobia, G., 2013. DSM-5 changes in diagnostic criteria of sexual dysfunctions. Reprod. Syst. Sex. Disord. 2, 122.
Janz, N.K., Becker, M.H., 1984. The health belief Model: a decade later. Health Educ. Q. 11 (1), 1–47.
Kanfer, F.H., Reinecker, H., Schmelzer, D., 2011. Sebstmanagement-Therapie (Selfmanangement-Therapy), fifth ed. Springer, Berlin.
Kockott, G., Fahrner-Tutsek, E.-M., 2015. Ejcaculation control. In: Linden, M.H.M. (Ed.), Textbook of Behavioral Therapy. Springer, Berlin GER, pp. 101–103.
Kredlow, M.A., Keshishian, A., Oppenheimer, S., Otto, M.W., 2019. The efficacy of modafinil as a cognitive enhancer: a systematic review and meta-analysis. J. Clin. Psychopharmacol. 39 (5), 455–461.
Laumann, E.O., Paik, A., Rosen, R.C., 1999. The epidemiology of erectile dysfunction: results from the national health and social life survey. Int. J. Impot. Res. 11 (Suppl. 1), S60–S64.
Li, J., Yang, X., Zhou, F., Liu, C., Wei, Z., Xin, F., Daumann, B., Daumann, J., Kendrick, K. M., Becker, B., 2020. Modafinil enhances cognitive, but not emotional conflict processing via enhanced inferior frontal gyrus activation and its communication with the dorsomedial prefrontal cortex. Neuropsychopharmacology 45 (6), 1026–1033.
Marson, L., Yu, G., Farber, N.M., 2010. The effects of oral administration of d-modafinil on male rat ejaculatory behavior. J. Sex. Med. 7 (1 Pt 1), 70–78.
Martin, C., Nolen, H., Podolnick, J., Wang, R., 2017. Current and emerging therapies in premature ejaculation: where we are coming from, where we are going. Int. J. Urol. 24 (1), 40–50.
McCabe, M.P., Sharlip, I.D., Lewis, R., Atalla, E., Balon, R., Fisher, A.D., Laumann, E., Lee, S.W., Segraves, R.T., 2016. Incidence and prevalence of sexual dysfunction in women and men: a consensus statement from the fourth international consultation on sexual medicine 2015. J. Sex. Med. 13 (2), 144–152.
McMahon, C., Althof, S., Rosen, R., Giuliano, F., Miner, M., Osterloh, I.H., Muirhead, G. J., Harty, B., 2019. The oxytocin antagonist cligosiban prolongs intravaginal ejaculatory latency and improves patient-reported outcomes in men with lifelong premature ejaculation: results of a randomized, double-blind, placebo-controlled proof-of-concept trial (PEPIX). J. Sex. Med. 16 (8), 1178–1187.
Meston, C.M., Buss, D.M., 2007. Why humans have sex. Arch. Sex. Behav. 36 (4), 477–507.
Miller, G., 2000. The Mating Mind: How Sexual Choice Shaped the Evolution of Human Nature. Heineman, London.
Minzenberg, M.J., Carter, C.S., 2008. Modafinil: a review of neurochemical actions and effects on cognition. Neuropsychopharmacology 33 (7), 1477–1502.
Napoli-Farris, L., Fratta, W., Gessa, G.L., 1984. Stimulation of dopamine autoreceptors elicits "premature ejaculation" in rats. Pharmacol., Biochem. Behav. 20 (1), 69–72.
Ng, T.H., Alloy, L.B., Smith, D.V., 2019. Meta-analysis of reward processing in major depressive disorder reveals distinct abnormalities within the reward circuit. Transl. Psychiatry 9 (1), 293.
Patrick, D.L., Althof, S.E., Pryor, J.L., Rosen, R., Rowland, D.L., Ho, K.F., McNulty, P., Rothman, M., Jamieson, C., 2005. Premature ejaculation: an observational study of men and their partners. J. Sex. Med. 2 (3), 358–367.
Patrick, D.L., Giuliano, F., Ho, K.F., Gagnon, D.D., McNulty, P., Rothman, M., 2009. The Premature Ejaculation Profile: validation of self-reported outcome measures for research and practice. BJU Int. 103 (3), 358–364.
Prince, V., Philippidou, M., Walsh, S., Creamer, D., 2018. Stevens-Johnson syndrome induced by modafinil. Clin. Exp. Dermatol. 43 (2), 191–192.
Repantis, D., Bovy, L., Ohla, K., Kühn, S., Dresler, M., 2021. Cognitive enhancement effects of stimulants: a randomized controlled trial testing methylphenidate, modafinil, and caffeine. Psychopharmacology (Berl) 238 (2), 441–451.
Repantis, D., Schlattmann, P., Laisney, O., Heuser, I., 2010. Modafinil and methylphenidate for neuroenhancement in healthy individuals: a systematic review. Pharmacol. Res. 62 (3), 187–206.
Roels, R., Janssen, E., 2020. Sexual and relationship satisfaction in young, heterosexual couples: the role of sexual frequency and sexual communication. J. Sex. Med. 17 (9), 1643–1652.
Rosen, R.C., Heiman, J.R., Long, J.S., Fisher, W.A., Sand, M.S., 2016. Men with sexual problems and their partners: findings from the international survey of relationships. Arch. Sex. Behav. 45 (1), 159–173.
Rosenstock, I.M., Strecher, V.J., Becker, M.H., 1988. Social learning theory and the health belief Model. Health Educ. Q. 15 (2), 175–183.
Sadeghi Bahmani, D., Motl, R.W., 2021. Rate, burden, and treatment of sexual dysfunction in multiple sclerosis: the case for exercise training as a new treatment approach. Multiple sclerosis and related disorders 51, 102878.

Santtila, P., Jern, P., Westberg, L., Walum, H., Pedersen, C.T., Eriksson, E., Kenneth Sandnabba, N., 2010. The dopamine transporter gene (DAT1) polymorphism is associated with premature ejaculation. J. Sex. Med. 7 (4 Pt 1), 1538–1546.
Serefoglu, E.C., 2016. On-demand d-modafinil may be an effective treatment option for lifelong premature ejaculation: a case report. Andrologia 48 (1), 121–122.
Simons, J.S., Carey, M.P., 2001. Prevalence of sexual dysfunctions: results from a decade of research. Arch. Sex. Behav. 30 (2), 177–219.
Trotti, L.M., Becker, L.A., Friederich Murray, C., Hoque, R., 2021. Medications for daytime sleepiness in individuals with idiopathic hypersomnia. Cochrane Database Syst. Rev. 5 (5), Cd012714.
Tuken, M., Kiremit, M.C., Serefoglu, E.C., 2016. On-demand modafinil improves ejaculation time and patient-reported outcomes in men with lifelong premature ejaculation. Urology 94, 139–142.
van Calker, D., 2019. Psychopharmacology. In: Berger, M. (Ed.), Psychiatric Disorders. Elsevier, Munich GER, pp. 75–104.
van Lankveld, J.D.M., 2018. [Changes in classification of sexual dysfunction: from DSM-IV-TR to DSM-5]. Ned. Tijdschr. Geneeskd. 162.
Waldinger, M.D., Hengeveld, M.W., Zwinderman, A.H., 1994. Paroxetine treatment of premature ejaculation: a double-blind, randomized, placebo-controlled study. Am. J. Psychiatr. 151 (9), 1377–1379.
Wang, S.M., Han, C., Lee, S.J., Jun, T.Y., Patkar, A.A., Masand, P.S., Pae, C.U., 2017. Modafinil for the treatment of attention-deficit/hyperactivity disorder: a meta-analysis. J. Psychiatr. Res. 84, 292–300.
World Medical Association, 2013. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Jama 310 (20), 2191–2194.
Yoo, H., Bartle-Haring, S., Day, R.D., Gangamma, R., 2014. Couple communication, emotional and sexual intimacy, and relationship satisfaction. J. Sex Marital Ther. 40 (4), 275–293.