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Effect of cranial electrotherapy stimulation (CES) in treatment of premature ejaculation: a randomized clinical trial

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Abstract

Background Premature ejaculation is one of the most common male sexual dysfunction, affecting approximately 30% of men. The aim of this study is to evaluate the efficacy and at the same time the safety of the cranial electrotherapy stimulation (CES) device in treatment of premature ejaculation disorder.

Methods Based on a randomized clinical trial, two groups were included in the study, so that the first group was treated with sertraline along with an ATANG (AT-9 model) CES, and the second group with sertraline and inactive the CES device (as the placebo group). The state of premature ejaculation after treatment (using the Premature Ejaculation Diagnostic Tool (PEDT) questionnaire) was evaluated and compared for both groups.

Results In the intervention and placebo groups, the average score of the PEDT questionnaire before the intervention did not differ significantly between the two groups (p -value equal to 0.93). However, the average score of the PEDT questionnaire after the intervention for CES group and placebo group was 10.28 ± 1.93 and 13.23 ± 3.05 , respectively, which demonstrated a significant decrease in the intervention group (p -value equal to 0.01).

Conclusion The use of CES device as a complementary treatment along with routine drug treatment (sertraline) is associated with a significant improvement in the condition of premature ejaculation of patients.

Trial registration Name of the registry: IRCT Iranian Registry of Clinical Trials.

Trial registration number: IRCT20210621051657N1.

Date of registration: December 11, 2022.

URL of trial registry record: <https://en.irct.ir/trial/57201>.

Keywords Electric stimulation therapy, Premature ejaculation, Randomized controlled trial

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Background

Premature ejaculation is one of the major sexual complaints in men all over the world. In the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) guideline, premature ejaculation is defined as a fixed or recurring pattern of ejaculation that occurs during sexual activity with a sexual partner within one minute after genital penetration and before the individual's desired time [1]. Various medicinal and non-medicinal methods have been used to treat this condition. In the drug treatment of this complaint, selective serotonin reuptake inhibitors and tricyclic antidepressants have been used [2, 3]; however, these approaches have been associated with relative response rates. In the case of non-pharmacological methods, the use of methods such as neuromuscular electrical stimulation on the bulbospongiosus muscle and subcutaneous ablation of the dorsal penile nerve have been tested [4, 5]. However, contradictory results were reported on the response rate of these methods in the treatment of premature ejaculation.

Cranial electrotherapy stimulation (CES) is a non-invasive method of delivering a low-intensity electrical current to the head through electrodes placed on the earlobes. This method differs from other forms of trans-cranial electrotherapy stimulations in which alternating micro currents are applied through the skin to the head. It is commonly believed that the effects are mainly through direct action on the brain in the limbic system, hypothalamus, thalamus, and/or the reticular activating system (RAS) [6]. Electrical stimulation of the skull increases the level of serotonin, norepinephrine, and beta-endorphin in the blood and cerebrospinal fluid [7, 8]. Increasing the level of serotonin and serotonin can play an inhibitory role in ejaculation [9]. In a meta-analysis, eight sham-controlled randomized clinical trials were analyzed for anxiety, two trials for brain dysfunction, two trials for headache, and two trials for insomnia [10]. A review of several studies proves that CES is effective for anxiety, headache, fibromyalgia, smoking cessation, drug withdrawal symptoms, and pain relief [11]. Overall, in USA, CES was approved by Food and Drug Administration (FDA) for treatment of insomnia and anxiety [12]. On the other hand, to the best of our knowledge, no study was performed to investigate the effect of application of CES on the brain on the treatment of premature ejaculation and also its role as an adjuvant treatment to achieve an effective treatment. The aim of this study is to investigate the effect of CES treatment compared to placebo for treatment of premature ejaculation.

Methods

Study samples

This randomized, double-blind clinical trial was performed in patients with the definitive diagnosis of premature ejaculation who were referred to Taleghani Hospital (Tehran, Iran) between 2022 and 2023. All patients aged 18 to 65 years and the premature ejaculation was defined as "uncontrollable ejaculation is said to occur before intercourse and for a very short period of time after with low stimulation and against a person's will" [1]. In this regard, recent history of receiving drug or non-drug treatments for premature ejaculation, history of cerebrovascular accidents or brain masses, history of sensitivity to sertraline, history of liver, heart or kidney diseases, having a specific etiology such as diabetes and blood pressure and other medical diseases affecting premature ejaculation disorder, having schizophrenia spectrum disorders, bipolar disorders, depression disorders, anxiety disorders, addiction and substance-related disorders and paraphilic disorders (based on DSM-V), history of head injury, history of convulsions, prostate problems, history of untreated thyroid disease, being in the period of drug or substance deprivation, and the use of drugs that had an effect on ejaculation were all considered as the exclusion criteria from the study evaluations. The study was approved by the research council of Shahid Beheshti University of Medical Sciences (with research ethics code IR.SBMU.MSP.REC.1400.147). The details of the study were recorded in the clinical trial registration system on December 11, 2022 (with clinical trial code of IRCT20210621051657N1) and are available at: <https://en.irct.ir/trial/57201>. Written informed consent was acquired from the research subjects, and they were given sufficient information about the study before the evaluation. The objectives of the research and its importance were explained to the research office. The subjects were given the right to choose to participate in the study and were assured that all the received information remain confidential. Upon request, they received the research results. It is necessary to mention that, in case of any side effects, the patients could be excluded from the study.

Study interventions

Patients participating in the study were classified into two groups using a transparent randomization technique. The Random Allocation Software (version 1.0, by Mahmood Saghaei) was used as the randomization tool [13]. Allocation concealment refers to the technique of randomizing study participants so that the assigned group was not known until the individual is assigned. Using opaque sealed envelopes in random order, in this technique, each random sequence generated was recorded on a card, and

the cards were placed in the envelopes in order. To preserve the random order, the outer surface of the envelopes was numbered in the same sequence. Finally, the envelope covers were glued together and boxed accordingly. Starting with the registration of participants, one of the envelopes was opened according to the order of registration, and the assigned group of that participant was revealed. This study was also blinded, so that the patients were unaware of the randomization method or the intended treatment groups (either intervention or placebo). The device was deactivated in such a way that the patient was not notified of its inactivity (the wire connection between the electrodes of the device and the ear was broken due to insulation. The device was turned on, but the current does not reach the patient's ear.

At the beginning of the study, before participating in the study, a signed written informed consent to participate was obtained from the patients. Then, through interviews with the patients, basic information including demographic characteristics and clinical and medication records of the patients were extracted and recorded in the study checklist. In order to screen patients for psychiatric diseases, in addition to interviews, patients' depression, anxiety, and stress were evaluated using the Depression, Anxiety and Stress Scale - 21 Items (DASS-21) questionnaire [14]. DASS-21 is the short form of the DASS-42 (DASS - 42 Items), which is a self-report scale for measurement of the negative emotional states including depression, anxiety, and stress. The standard PEDT questionnaire in Persian language was provided to the patients to complete it.

Then, through the simple random method, the patients were randomly classified into two groups, so that the first group was treated with sertraline along with application of CES, and the second group was treated with sertraline and application of the deactivated CES. In this regard, the protocol for using the device was defined as follows: ATANG CES device (AT-9 model, Wuhan ATANG Technology Co., China), with ISO, CE, and FDA certification (FDA registration number: 3015515517), was used. The pulse duration of the device was $150 \text{ ms} \pm 10 \text{ ms}$, and it had 6 adjustable power levels. The pulse repetition frequency was 250 Hz. The electroencephalography was performed for 3 weeks in two sessions a day, morning, and night (approximately 12 h apart) and for 20 min in each session. Power level of 3 was considered as the default for the device settings. The patients were given a complete explanation and training regarding the settings of the device and how to use it (turning it on, connecting the electrodes, etc.).

The device was provided to the patients, and the patients used it at their home. Monitoring on the use of

the device and compliance with the protocol was performed through regular phone calls with the patient. Regarding the complications, at the beginning of the study, the patients were given education about the possible complications and danger signs. At the time of the study, follow-up and reporting of possible side effects were performed by phone calls to the patient; in case of side effects reported by the patient, a psychiatric specialist doctor would visit him, and if further investigation was needed, the patient would be referred. Electrical stimulation was performed by the patient by connecting the ear electrodes to the earlobe and after setting the appropriate time and power (default 3). The ATANG CES (AT-9 model), including the main body, wires, and the electrodes which are connected to the patients' earlobes, is shown in Fig. 1. Drug treatment was done by conventional and standard drugs (sertraline 50 mg tablets should be taken as needed (PRN (pro re nata)) 4 h before intercourse) and was part of the patient's natural treatment process, and no new drug intervention was performed. In terms of examining the therapeutic effect, after the end of 3 weeks, the results were checked by completing the PEDT questionnaire again.

At the end, the treatment results of each group were compared for before and after treatment, and it was checked by the researcher to check whether the use of brain electrical stimulation could improve or accelerate the improvement of premature ejaculation or not. Additionally, during and after the end of the study, side effects (including headache, ear discomfort, dizziness, and stomach pain) were monitored through interviews and patient reports.

Statistical analysis

The obtained results were presented in terms of mean \pm standard deviation (SD) for the evaluated quantitative variables, and then the absolute frequencies and percentages for the categorical variables were reported. To be normal data distribution, Kolmogorov-Smirnov test was done and the data were analyzed using Statistical Package for the Social Sciences (SPSS) software (version 23.0 for windows, IBM, Armonk, New York). Classified data were analyzed based on chi-square analysis, and their information was written in the form of frequency and related percentages. Quantitative variables were also compared with the *t*-test if they showed a normal distribution. In the case of not showing a normal distribution, the Mann Whitney *U*-test was used. *p*-values of equal to or less than 0.05 were considered to show statistically significant difference.



Fig. 1 ATANG CES (AT-9 model), including the main body, wires, and the electrodes which are connected to the patients' earlobes

Results

In the present study, at first, 30 patients were randomly classified into two groups and including of 15 people (15 people were in the intervention group and 15 people were in the placebo group). During the study, 1 person in the intervention group was excluded from the study due to intolerance to the treatment, and 2 people in the placebo group were excluded from the study. Totally, 14 people in the intervention group and 13 people in the placebo group finished the study (Fig. 2). As indicated in Table 1, the two groups are similar in baseline characteristics including demographics, educational level, and history of disorders or medications.

In assessment of the characteristics of premature ejaculation, it was found no significant difference between the intervention and placebo group, in different aspects of this complaint at their baselines including the lack of feeling of ejaculation control, average time of onset of premature ejaculation, premature ejaculation before the desired time, or discomfort from premature ejaculation. As indicated in Table 2, no difference was revealed in the situation of premature ejaculation before intervention based on the PEDT questionnaire scoring. However, after the intervention, the patients who were treated with CES had lower mean PEDT score than the placebo group (10.28 ± 1.93 versus 13.23 ± 3.05 , p -value = 0.01). In addition, the rate of premature ejaculation was significantly lower in the intervention group than the placebo group postoperatively (57.1% versus 84.6%, p -value = 0.03).

Regarding the psychological condition of the patients after intervention, no significant difference was revealed between the two groups in the scores of depression, anxiety, and stress scores (Table 3).

Regarding post-treatment complications, some of the patients who were treated with CES experienced higher rates of headache and discomfort in the ear, but stomach pain or discomfort was more frequent in the placebo group. In total, the side effects in both groups were completely oriented and tolerable (Table 4).

Discussion

The results which were obtained in the first step of the study indicate that the use of CES intervention was associated with an increase in the response of routine treatments for premature ejaculation (in this study, the sertraline drug). In other words, the response rate of drug treatment shows a significant increase with the use of CES. Of course, it should be noted that it is necessary to mention a few points here. First, according to the screening of patients in terms of having diseases affecting premature ejaculation, especially depression and anxiety in this study, it can be concluded that the effect of CES on premature ejaculation disorder has been measured purely. Second, as seen in other studies, the result of electrical stimulation in the treatment of premature ejaculation is completely dependent on the frequency used for stimulation. However, in general, the addition of CES to the treatment of premature ejaculation seems to be effective from a clinical point of view. In similar studies, the

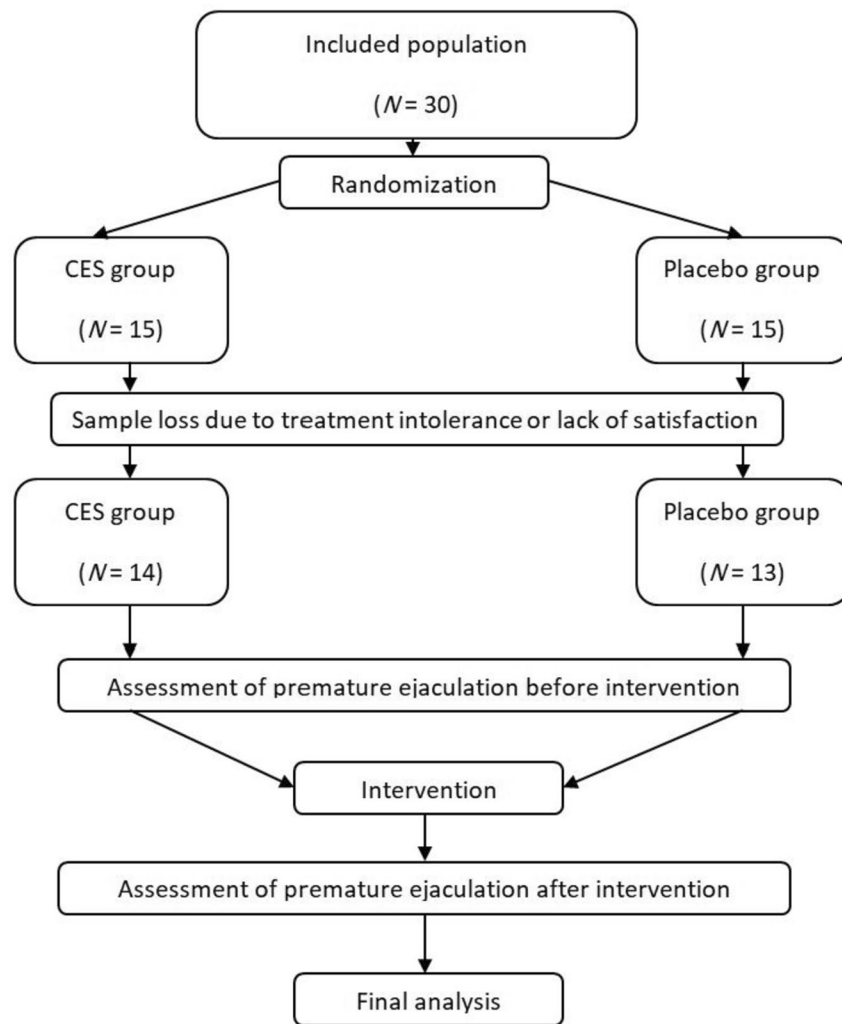


Fig. 2 Schematic design of how to enter patients and perform interventions

Table 1 Characteristics of study subjects

Characteristics	CES group	Placebo group	p-value
Mean age, year	30.43 ± 7.33	30.46 ± 6.77	0.99
Education level (%)			0.62
Undergraduate	1 (7.1%)	0 (0.0%)	
Diploma	2 (14.3%)	2 (15.4%)	
Academic degree	11 (78.6%)	11 (84.6%)	
Employment status (%)	10 (71.4%)	12 (92.3%)	0.16
History of smoking (%)	4 (28.6%)	5 (38.5%)	0.59
The mean time of marriage, month	36.79 ± 9.58	34.00 ± 11.87	0.86

primary goal was to use local (rather than cranial) electrotherapy stimulation to treat premature ejaculation.

In the study of Cizmeci et al. [15], after neuromuscular electrical stimulation of the bulbospongiosus

muscle in different modes and frequencies, a significant difference in ejaculation time was revealed between the study groups. In Uribe et al. study [16], subcutaneous electrical stimulation of the posterior tibial nerve was considered on the treatment of premature ejaculation, and following the electrical intervention, the intravaginal ejaculatory latency time (IELT) during 12, 24, and 48 weeks later has increased 4.8, 6.8, and 5.4 times, respectively. In the study by Balog et al. [17], neuromodulation using the regenerative electrical stimulation (RES) technique led to the final improvement of the patients' quality of life. In the study by Rislau et al. [18], electrical stimulation (ES) showed more effectiveness than aerobic exercise in the management of people with erectile dysfunction. Based on the results of the investigations by Brunoni et al. [19] and his colleagues, there were promising results regarding the safety and tolerability of noninvasive brain stimulation

Table 2 Ejaculation status before and after intervention

Characteristics	CES group	Placebo group	p-value
Before intervention			
Average PEDT score	13.57 ± 3.43	13.69 ± 3.35	0.927
The presence of premature ejaculation	12 (85.7%)	11 (84.6%)	0.511
Borderline status	2 (14.3%)	2 (15.4%)	0.612
Lack of premature ejaculation	0 (0.0%)	0 (0.0%)	0.124
After intervention			
Average PEDT score	10.28 ± 1.93	13.23 ± 3.05	0.008
The presence of premature ejaculation	8 (57.1)	11 (84.6)	0.034
Borderline status	5 (35.7)	2 (15.4)	0.027
Lack of premature ejaculation	1 (7.1)	0 (0.0)	0.124

Table 3 The psychological status after intervention

Characteristics	CES group	Placebo group	p-value
Depression			
Mean score	12.07 ± 2.43	11.23 ± 3.46	0.47
Lack of depression	2 (14.3%)	5 (38.5%)	0.28
Mild depression	8 (57.0%)	4 (30.8%)	0.23
Moderate depression	4 (30.7%)	4 (30.7%)	0.32
Anxiety			
Mean score	9.00 ± 1.46	8.92 ± 1.44	0.89
Lack of anxiety	3 (21.4%)	2 (15.4%)	0.84
Mild anxiety	6 (42.9%)	5 (38.4%)	0.67
Moderate anxiety	5 (35.7%)	6 (46.2%)	0.23
Stress			
Mean score	13.50 ± 3.00	12.69 ± 1.93	0.42
Lack of stress	10 (71.4%)	12 (92.3%)	0.34
Mild stress	3 (21.4%)	1 (7.7%)	0.23
Moderate stress	1 (7.2%)	0 (0.0%)	0.46

Table 4 Post-treatment complications

Characteristics	CES group	Placebo group	p-value
Headache	7 (50.0%)	2 (15.4%)	0.02
Ear discomfort	2 (14.3%)	0 (0.0%)	0.05
Dizziness	1 (7.1%)	0 (0.0%)	0.12
Stomach pain	0 (0.0%)	3 (23.1%)	0.03

methods, although the effect of this method still requires improvement.

In this study, due to the lack of access to the patients in the long term, the long-term follow-up of the response to the CES treatment was not possible, so it is suggested to evaluate the response from the intervention for the long term in future studies. Another limitation, due to the study time and drug limitations, the sertraline tablet used

by the patients was not of the same brand, which is suggested to be solved in the next studies. Due to cultural issues, it was not possible to determine the number of sexual intercourse during the study, so it is suggested that the number of sexual intercourse during the study should also be investigated in future studies. Furthermore, for further research in this area, it is proposed to compare the effect of the CES device with routine treatment (sertraline) and a non-medicated group.

Conclusion

As a final conclusion, it can be stated that the use of the CES device as a complementary treatment along with routine drug treatment (sertraline) is significantly related to the improvement of the premature ejaculation condition of the patients. In this regard, it is suggested to investigate the effect of CES for long duration in the next studies.

Abbreviations

CES	Cranial electrotherapy stimulation
PEDT	Premature Ejaculation Diagnostic Tool
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
RAS	Reticular activating system
FDA	Food and Drug Administration
DASS-21	Depression, Anxiety and Stress Scale - 21 Items
PRN	Pro re nata
SD	Standard deviation
SPSS	Statistical Package for the Social Sciences
IELT	Intravaginal ejaculatory latency time
RES	Regenerative electrical stimulation
ES	Electrical stimulation

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Authors' contributions

Hadi Delpasand had contribution in the conceptualization, methodology, formal analysis, investigation, writing of the original draft, and editing of the manuscript. Azadeh Mazaheri had contribution in the conceptualization, methodology, formal analysis, investigation, editing of the manuscript, and supervision. Ali Kheradmand had contribution in the conceptualization,

methodology, formal analysis, investigation, editing of the manuscript, and supervision. Mahdi Ghorbani had contribution in the conceptualization, methodology, investigation, editing of the manuscript, and funding acquisition. Amir Reza Abedi had contribution in the conceptualization, methodology, formal analysis, investigation, and editing of the manuscript. Mohsen Khosroabadi had contribution in the conceptualization, writing of the original draft, and editing of the manuscript.

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Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available due to personal reasons by the authors but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the research council of Shahid Beheshti University of Medical Sciences (with research ethics code IR.SBMU.MSP.REC.1400.147). Written informed consent was acquired from the research subjects.

Consent for publication

There is not any personal data being reported. Hereby, the authors approve their consent for publication of the manuscript.

Competing interests

The authors declare no competing interests.

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References

- Althof SE, McMahon CG, Rowland DL (2022) Advances and missteps in diagnosing premature ejaculation: analyzing and future directions. *J Sex Med* 19(1):64–73
- Mitsogiannis I, Dellis A, Papatsoris A, Moussa M (2022) An up-to-date overview of the pharmacotherapeutic options for premature ejaculation. *Expert Opin Pharmacother* 23(9):1043–1050
- Gul M, Bocu K, Serefoglu EC (2022) Current and emerging treatment options for premature ejaculation. *Nat Rev Urol* 19(11):659–680
- Huyghe E, Cuzin B, Grellet L, Faix A, Almont T, Burte C (2023) Recommendations for the treatment of premature ejaculation. *Prog Urol* 33(5):237–246
- Bukhari SR (2022) Psycho, pharmaco and sex therapy for the treatment of premature ejaculation. *Pak J Med Sci* 38(8):2350–2355
- Brotman P (1989) Low-intensity transcranial electrostimulation improves the efficacy of thermal biofeedback and quieting reflex training in the treatment of classical migraine headache. *Am J Electromed* 6(5):120–123
- Shealy C, Cady R, Wilkie RG, Cox RH, Liss S, Clossen W (1989) Depression: a diagnostic, neurochemical profile and therapy with cranial electrical stimulation (CES). *J Neur Orth Med Surg* 10:319–321
- Shealy C, Cady R, Culver-Veehoff D, Cox RH (1998) Cerebrospinal fluid and plasma neurochemicals: response to cranial electrical stimulation. *J Neurol Ortho Med Surg* 18(2):94–97
- Giuliano F, Clément P (2006) Serotonin and premature ejaculation: from physiology to patient management. *Eur Urol* 50(3):454–466
- Tsoucalas G, Karamanou M, Lympieri M, Gennimata V, Androutsos G (2014) The “torpedo” effect in medicine. *Int Marit Health* 65(2):65–67
- Kang N, Summers JJ, Cauraugh JH (2016) Transcranial direct current stimulation facilitates motor learning post-stroke: a systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry* 87(4):345–355
- Otal B, Dutta A, Foerster Á, Ripolles O, Kuceyeski A, Miranda PC et al (2016) Opportunities for guided multichannel non-invasive transcranial current stimulation in poststroke rehabilitation. *Front Neurol* 7:21
- Saghaei M (2004) Random allocation software for parallel group randomized trials. *BMC Med Res Methodol* 4:26–26
- Lovibond SH, Lovibond PF (1995) Manual for the depression anxiety stress scales. Sydney psychology foundation
- Cizmecci S, Ongun S, Sarac A, Sel E, Tozburun S, Durmus N (2023) Low frequency neuromuscular electrical stimulation applied to the bulbospongiosus muscle prolongs the ejaculation latency in a rat model. *Int J Impot Res*;1-4, Online a head of print.
- Uribe OL, Sandoval-Salinas C, Corredor HA, Martínez JM, Saffon JP (2020) Transcutaneous electric nerve stimulation to treat patients with premature ejaculation: phase II clinical trial. *Int J Impot Res* 32(4):434–439
- Balog BM, Deng K, Labhassetwar V, Jones KJ, Damaser MS (2019) Electrical stimulation for neuroregeneration in urology: a new therapeutic paradigm. *Curr Opin Urol* 29(4):458–465
- Rislanu A, Auwal H, Musa D, Auwal A (2020) Comparative effectiveness of electrical stimulation and aerobic exercise in the management of erectile dysfunction: a randomized clinical trial. *Ethiop J Health Sci* 30(6):961–970
- Brunoni AR, Sampaio-Junior B, Moffa AH, Aparício LV, Gordon P, Klein I et al (2019) Noninvasive brain stimulation in psychiatric disorders: a primer. *Braz J Psychiatry* 41(1):70–81

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