The effect of drug holidays on sexual dysfunction in men treated with selective serotonin reuptake inhibitors (SSRIs) other than fluoxetine: An 8-week open-label randomized clinical trial

Arman Alipour-Kivi
Iran University of Medical Sciences
Negin Eissazade
Iran University of Medical Sciences
Seyed Vahid Shariat
Iran University of Medical Sciences
Razieh Salehian
Iran University of Medical Sciences
Shiva Soraya
Iran University of Medical Sciences
Sanaz Askari
Iran University of Medical Sciences
Mohammadreza Shalbafan (Shalbafan.mr@iums.ac.ir)
Iran University of Medical Sciences

Research Article

Keywords: Selective Serotonin Reuptake Inhibitors, Drug Holidays, Sexual Dysfunction, Erection, Satisfaction, Ejaculation

Posted Date: August 23rd, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3175920/v1

Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at BMC Psychiatry on January 23rd, 2024. See the published version at https://doi.org/10.1186/s12888-024-05507-7.

Abstract

Introduction: Mental disorders are a significant global burden, with selective serotonin reuptake inhibitors (SSRIs) being widely used for treatment. However, SSRIs are associated with various side effects, including sexual dysfunction. Common and persistent, these side effects often lead to poor adherence and treatment discontinuation. While several strategies have been employed to manage SSRI-induced sexual dysfunction, drug holidays have not been extensively studied for this purpose. Therefore, this clinical trial aims to assess the effect of drug holidays on sexual dysfunction in men treated with SSRIs, excluding fluoxetine.

Methods: This 8-week double-center, randomized, open-label, controlled trial was conducted in the outpatient clinics of Iran Psychiatric Hospital and Tehran Institute of Psychiatry, from January 2022 to March 2023. The study included married men between the ages of 18 and 50 years who had experienced sexual dysfunction during treatment with an SSRI. The Male Sexual Health Questionnaire (MSHQ) and the 28-Question General Health Questionnaire (GHQ-28) were used as assessment tools. Participants were randomized into two groups: the drug holidays group and the control group. The drug holidays group was instructed not to take their medications on the weekends. The control group was asked to continue their regular medication regimen without any changes. Both groups were assessed at baseline, and weeks 4 and 8.

Results: Sixty-three patients were included and randomly assigned to drug holidays (N=32) or control (N=31) groups, and 50 patients (25 in each group) completed the trial. The participants' mean (±SD) age was 37.22 (±12.181). Drug holidays significantly improved erection, ejaculation, satisfaction, and overall sexual health of the participants (P<0.001).. No significant change was observed in the drug holidays group's mental health. No major side effects were recorded.

Conclusions: Based on the results of our study, drug holidays was significantly in favor of 'erection', 'ejaculation', 'satisfaction' and 'total' scores of the MSHQ, indicating improvement in sexual health of men, without significant worsening of mental health status. Further research is needed to reach a certain conclusion.

Trial registration: The trial was registered at the Iranian Registry of Clinical Trials on 25/10/2021 (www.irct.ir; IRCT ID: IRCT20170123032145N6) before the trial.

Background

Mental disorders are among the top ten leading causes of burden worldwide [1]. Selective serotonin reuptake inhibitors (SSRIs) are a cornerstone class of medications in psychopharmacology used to treat conditions like depression, anxiety disorders, and obsessive-compulsive disorder. However, they are commonly associated with varying degrees of side effects that significantly affect the patients' daily lives and lead to poor adherence and treatment discontinuation [2]. Sexual dysfunction is among the most common side effects of SSRIs, and it can become permanent in some cases [3].

SSRIs can affect any of the sexual cycle phases and cause various types of sexual dysfunction. Delayed ejaculation and absent or delayed orgasm are the most common side effects. They can also cause decreased or loss of libido, painful orgasm, anorgasmia, impotency, priapism, painful erection, problems of sexual arousal, and reduced sexual satisfaction and lubrication [3–5].

The mechanism of SSRIs causing sexual dysfunction is not yet fully understood. However, it is thought to be related to alterations in the level of serotonin, acetylcholine, noradrenaline, dopamine, nitric oxide, and prolactin [6]. Some of the medications that have been proposed to neutralize this effect are sildenafil, tadalafil and vardenafil (phosphodiesterase 5 inhibitors), amantadine (dopamine and norepinephrine agonist), cyproheptadine (5-HT blocker), buspirone (5-HT1A receptor partial agonist), and bupropion (norepinephrine and dopamine agonist), mirtazapine (serotonin and norepinephrine agonist), modafinil (dopamine agonist), agomelatine (MT1 and MT2 receptors agonist and 5-HT2 receptors antagonist), yohimbine (alpha-2 blocker), bethanechol (acetylcholine agonist) and ginkgo biloba (herbal medication). However, additional treatments may have adverse effects and tolerability problems [3, 4].

So far, the following strategies have been employed to manage SSRI-induced sexual dysfunction: the ‘wait-and-see’ strategy, behavior-changing techniques and psychotherapy, reducing the dose of medication, delaying the use of medication until after sexual activity, using a different antidepressant, adjuvant therapy, and drug holidays [3, 4, 7].

Drug holidays is defined as temporarily stopping or reducing the dose of medication. It has previously been used to help alleviate side effects or improve treatment effectiveness for various mental disorders and medications [8, 9].

Thus far, only one 4-week clinical trial (1995) has evaluated the effect of drug holidays on sexual side effects of SSRIs and reported that sertraline and paroxetine users experienced an improvement in their sexual function, and fluoxetine users did not, which may be due to fluoxetine long half-life [10].

SSRI-induced sexual dysfunction continues to be a major issue leading to discontinuation of treatment, and drug holidays has not been extensively studied for this purpose. Therefore, we conducted this open-label clinical trial aiming to assess the effect of drug holidays on sexual dysfunction in men treated with SSRIs, excluding fluoxetine, as the previous clinical trial reported no effect.

Methods

Trial setting and design

This 8-week double-center, randomized, open-label, controlled trial was conducted in the outpatient clinics of Iran Psychiatric Hospital and Tehran Institute of Psychiatry (both affiliated with Iran University of Medical Sciences, Tehran, Iran) from January 2022 to March 2023.

Participants

Participants were married men, aged between 18–50 years, having experienced sexual dysfunction during the course of treatment with an SSRI. Patients were in their maintenance course of treatment, and base on the history taking of a board certified psychiatrist and medical records, they had stable condition over the past two month and no change in their drug dose was made. The exclusion criteria were: 1) the use of fluoxetine (as due to its long half-life, drug holidays is not effective), 2) the use of medications with known sexual side effects (such as tricyclic antidepressants, typical antipsychotics, risperidone, biperiden and anticholinergics), and 3) poor medication adherence (reported by the treating psychiatrist).

Demographic data were recorded. The Male Sexual Health Questionnaire (MSHQ) was filled out at baseline and weeks 4 and 8. The 28-Question General Health Questionnaire (GHQ-28) was filled out at baseline and endpoint of the study to evaluate the change in mental health of participants.

Participants were randomized using the block method (blocks of four) in two groups: drug holidays group and control group. The allocation sequence was concealed in sequentially numbered, opaque, sealed envelopes. Randomizer and statistical analyzer were separate individuals blinded to allocation.

Instruments

We used a demographic questionnaire to record the age, education level, employment status, medication and past psychiatric history of participants.

The GHQ-28 consists of four subscales: somatic symptoms, anxiety and insomnia, social dysfunction, and depression. Each question is scored from 0 to 3. Lower scores indicate better state of health. The validity and reliability of the Persian version of GHQ-28 have been confirmed by the study of Taqvai et al. [11].

MSHQ is a self-administered questionnaire used to assess sexual function in men. It consists of 25 questions assessing erection (4 questions), ejaculation (8 questions) and satisfaction (13 questions) over the past month, scored on a five or six-point Likert scale. Higher scores indicate better sexual health. Fakhri et al have previously measured the validity and reliability of the Persian version of MSHQ. Content validity index (CVI), content validity ratio (CVR), Spearman-Brown coefficient, and Cronbach's alpha coefficient were reported as 0.9, 0.78, 0.79, and 0.84, respectively [12].

Interventions

The participants in the drug holidays group were asked not to take their medications on Thursdays and Fridays (as they are the weekends in Iran and having sexual intercourse is more likely to occur) for eight weeks. Participants in the control group were asked not to make any changes in their medications and use their medications as they were prescribed.

Outcomes

The primary outcome measure was the difference between the MSHQ’s total and its subscales scores of the two groups from baseline to the eighth week. The secondary outcome measures were the difference

of GHQ-28scores between the two groups from baseline to the eighth week and the frequency and severity of side effects in the two groups.

Sample size and statistical analysis

Based on the previously done clinical trial, a sample size of 50 (25 in each group) was calculated [10]. All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS) software for Windows (version 24, SPSS Inc., Chicago, IL, USA). Continuous variables are presented as mean ± standard deviation. The continuous score variables were tested for sphericity by using the Mauchly's test. Repeated-measures ANOVA and Friedman test were used to evaluate the effect of demographics and drug holidays with time on the MSHQ scores. Independent T-test and Mann-Whitney U-test were used to compare the mean scores between the two groups at different time periods. A p-value of < 0.05 was considered statistically significant.

Results

Participants

Sixty-three patients were included and randomly assigned to drug holidays (N = 32) or control (N = 31) groups, and 50 patients (25 in each group) completed the trial. The participants' mean (± SD) age was 37.22 (± 12.181). The demographic characteristics of the participants are presented in Table 1. The flow diagram of the participants is presented in Fig. 1. The baseline mean scores of MSHQ were not significantly different between the two groups (Table 2).

Table 1
Demographic data of the participants

		Drug holidays group (N = 25)		Control group (N = 25)	
		Mean (± SD)	Count (%)	Mean (± SD)	Count (%)
Age (years)		36.44 (± 6.049)		35.04 (± 6.693)	
Education	**Illiterate**		-		1 (4%)
	High school diploma or lower		5 (20%)		10 (40%)
	Higher education		20 (80%)		14 (56%)
Employment	**Employed**		20 (80%)		19 (86%)
	Unemployed		5 (20%)		6 (24%)
Medication	**Sertraline**		11 (44%)		9 (36%)
	Escitalopram		7 (28%)		9 (36%)
	Paroxetine		1 (4%)		1 (4%)
	Citalopram		4 (16%)		4 (16%)
	Fluvoxamine		2 (8%)		2 (8%)
Previous psychiatric diagnosis	**Depressive disorders**		13 (52%)		6 (24%)
	Anxiety disorders		10 (40%)		12 (48%)
	Obsessive-compulsive and related disorders		2 (8%)		7 (28%)

Table 2
MSHQ scores of the participants in total, and the erection, ejaculation and satisfaction subscales (mean ± standard deviation) and comparison between the groups at baseline and weeks 4 and 8

		Drug holidays group (N = 25)	Control group (N = 25)	P-value
Erection	**Baseline**	10.96 ± 2.865	10.04 ± 2.541	0.23
	Week 4	11.80 ± 2.598	9.08 ± 2.768	0.001*
	Week 8	12.52 ± 2.044	8.72 ± 2.807	< 0.001*
Ejaculation	**Baseline**	25.20 ± 5.612	26.60 ± 5.958	0.39
	Week 4	26.80 ± 5.881	25.60 ± 6.357	0.49
	Week 8	28.32 ± 5.336	26.08 ± 6.041	0.171
Satisfaction	**Baseline**	21.08 ± 5.220	19.24 ± 5.995	0.26
	Week 4	23.00 ± 4.435	17.80 ± 6.813	0.005*
	Week 8	25.72 ± 4.078	18.28 ± 6.580	< 0.001*
Total	**Baseline**	57.24 ± 11.780	55.88 ± 12.022	0.68
	Week 4	60.88 ± 11.114	52.52 ± 13.194	0.019*
	Week 8	66.56 ± 9.820	53.12 ± 12.982	< 0.001*

*P-values less than 0.05

MSHQ total scores

The mean total score increased from 57.24 ± 11.780 at baseline to 66.56 ± 9.820 at the end of trial in the drug holidays group, and decreased from 55.88 ± 12.022 to 53.12 ± 12.982 in the control group, respectively (Fig. 2). Comparison of the means revealed significant difference between the groups at weeks 4 (P = 0.019) and 8 (P < 0.001) (Table 2).

In total, the mean score changes between the groups, were statistically significant (Huyn-Feldt F(1.774, 85.174) = 9.44, P < 0.001). Repeated-measures ANOVA analysis detected a significant Time X Treatment interaction in both drug holidays group, (F(2, 48) = 24.60, P < 0.001), and the control group (Huynh-Feldt F(1.653, 39.663) = 5.728, P = 0.010).

MSHQ erection scores

The mean satisfaction score increased from 10.96 ± 2.865 to 12.52 ± 2.044 in the drug holidays group, and decreased from 10.04 ± 2.541 to 8.72 ± 2.807 in the control group (Fig. 3) (Table 2). Comparison of the means revealed significant difference between the groups at weeks 4 (P = 0.001) and 8 (P < 0.001) (Table 2).

Repeated-measures analysis revealed that the mean erection score change was statistically significant between the groups (Huyn-Feldt F(1.354, 32.505) = 4.899, P = 0.024). In addition, the mean score change

was significant among the drug holidays group ($F(2, 48) = 10.134$, $P < 0.001$), and non-significant among the control group (Greenhouse-Geisser $F(1.309, 31.422) = 4.899$, $P = 0.26$).

MSHQ ejaculation scores

The mean of satisfaction scores increased from 25.20 ± 5.612 to 28.32 ± 5.336 in the drug holidays group, and slightly decreased from 26.60 ± 5.958 to 26.08 ± 6.041 in the control group (Fig. 4) (Table 2). Unlike comparison of the means by Mann-Whitney U-test that did not reveal any significant difference (Table 2), repeated-measures ANOVA detected that mean score change was statistically significant between the groups, $F(2, 96) = 17.494$, $P < 0.001$. Additionally, the Time X Interaction effect was significant among the drug holidays group ($F (2, 48) = 26.484$, $P < 0.001$), and non-significant among the control group ($F(2, 48) = 2.294$, $P = 0.112$).

MSHQ satisfaction scores

The mean of satisfaction scores increased from 21.08 ± 5.220 to 25.72 ± 4.078 in the drug holidays group, and decreased from 19.24 ± 5.995 to 18.28 ± 6.580 in the control group (Fig. 5) (Table 2). Comparison of the means revealed significant difference between the groups at weeks 4 ($P = 0.005$) and 8 ($P < 0.001$) (Table 2).

Friedman test's revealed a significant change in the mean satisfaction score in both drug holidays ($\chi^2(2, N = 25) = 28.295$, $P < 0.001$) and control ($\chi^2(2, N = 25) = 6.997$, $P = 0.31$) groups during the course of trial. Friedman test's mean rank scores are presented in Table 3.

Table 3
Friedman test's mean rank scores for the satisfaction subscale of MSHQ

	Drug holidays group (N = 25)	Control group (N = 25)
Baseline	1.36	2.36
Week 4	1.84	1.66
Week 8	2.8	1.98

GHQ-28 scores

GHQ-28 scores decreased in both groups, indicating improvement of mental health, which was not significant in the drug holidays group ($P = 0.066$).

Side effects

Patients in the drug holidays group reported experiencing nausea (16%, N = 4), headache (24%, N = 6) and mild restlessness (24%, N = 6). None of the patients in the control group reported any additional side effects.

Discussion

Based on the results of our study, drug holidays was significantly in favor of ‘erection’, ‘satisfaction’, ‘ejaculation’ and ‘total’ scores of the MSHQ, indicating improvement of sexual health.

Thus far, only one clinical trial conducted by Rothschild et al. (1995) has investigated the effect of the drug holidays on the sexual dysfunction induced by SSRIs. This study was shorter than our study (four weeks) and had a smaller sample size (14 men). They recruited 14 men and 16 women under treatment with sertraline, paroxetine, and fluoxetine. None of the patients took high doses of SSRIs, so the withdrawal symptoms were not likely to appear. Patients were asked not to take their medications after the Thursday morning dose until Sunday noon for four weeks. Male patients who were taking sertraline and paroxetine reported improved orgasm function (60%), sexual satisfaction (50%), and libido (50%) without a significant increase in mean Hamilton depression score. However, fluoxetine users did not report any improvements, which may be due to the long half-life of fluoxetine. Similarly, we found improvement in erection, satisfaction and overall sexual health, without significant worsening of mental health status. Although, we did not assess libido [10].

The exact mechanism of how SSRIs cause sexual dysfunction is not clear. The proposed contributing mechanisms are as follows: serotonin receptor down-regulation, decreased levels of dopamine and norepinephrine, up-regulation of prolactin (leads to increased levels of sexual hormone-binding globulin (SHBG) and reduced levels of free testosterone), disruption of oxytocin signaling (reduced blood flow to genitals), altered activity of hypothalamic-pituitary-gonadal axis (decreased levels of testosterone and estrogen), disruption of nitric oxide pathway (reduced blood flow to genitals), and impacting the autonomic nervous system (e.g., genital numbness). Additionally, this process can be complicated by genetic variations (e.g., CYP2C19 and CYP3A4) alternating the metabolism of SSRIs and comorbid psychological (treated with SSRIs) contributing to sexual dysfunction [13–19].

A Cochrane review (2013) was conducted on the management strategies of the SSRI-induced sexual dysfunction. Other than drug holidays, the ‘wait-and-see’ strategy, behavior-changing techniques and psychotherapy, reducing the dose of medication, delaying the use of medication until after sexual activity, using a different antidepressant, adjuvant therapy have been proposed. Most interventions have not been studied in clinical trials. Limited evidence, potential side effects, and variable mechanisms of action make it challenging to make a comprehensive comparison and come to conclusion [3, 7].

The ‘wait-and-see’ strategy, ‘behavior-changing techniques’ and ‘psychotherapy’ may lead to a gradual resolution of sexual dysfunction. However, they usually require a significant amount of time and commitment, and may lead to prolonged dissatisfaction. ‘Reducing the dose of medication’ and ‘delayed doses of medication until after sexual activity’, can potentially disrupt the stability of mental health treatment and lead to a recurrence of symptoms or withdrawal symptoms. Moreover, they may require close monitoring by healthcare professionals. ‘Switching to a different antidepressant’ can involve a period of adjustment, and the new medication may still have potential side effects. ‘Adjuvant therapy’ can also introduce new potential side effects. For instance, sildenafil, tadalafil, and vardenafil (phosphodiesterase 5 inhibitors) have a rapid onset of action, but they can commonly cause headache,

flushing and dyspepsia. Buspirone (5-HT1A receptor partial agonist) can cause dizziness, nausea, and headaches. Bupropion (norepinephrine and dopamine agonist) can cause insomnia, agitation, and increased heart rate [3–8, 20].

Compared to the previous strategies, drug holidays is simple and it may improve treatment adherence and reduce the likelihood of treatment discontinuation due to sexual dysfunction by providing a temporary respite from the side effects. It has been recommended to be used for unwanted orgasm delay or anorgasmia. It is important to note that the costs and benefits of the drug holiday method should be carefully weighed on an individual basis. The decision to implement this method should be made in collaboration between the patient and their healthcare provider, taking into account the specific characteristics of the mental disorder, the severity of sexual dysfunction, and the potential risks and benefits of temporary medication discontinuation [5, 20]. Our study provided evidence for the positive effect of drug holidays on erection, satisfaction and overall, sexual mental health in men. However, further research is needed to determine the safety and efficacy of this method.

Limitations

Our study was limited by a small sample size, short follow-up period, the use of different SSRIs among patients, the use of different doses of SSRIs among the patients, not including patients with comorbidities, and self-report bias. Additionally, our study was not double blinded. Multi-center clinical trials with extended follow-up period and large sample size are needed to help shape the body of evidence for the safety and efficacy of drug holidays.

Conclusions

Based on the results of our study, drug holidays was significantly in favor of ‘erection’, ‘satisfaction’ and ‘total’ scores of the MSHQ. It did not have a significant effect on the ‘ejaculation’ scores. Further research is needed to reach a certain conclusion.

List Of Abbreviations

SSRI
Selective Serotonin Reuptake Inhibitor
MSHQ
Male Sexual Health Questionnaire
GHQ-28
28-Question General Health Questionnaire
CVI
Content validity index
CVR
content validity ratio

SPSS
Statistical Package for the Social Sciences
SHBG
sexual hormone-binding globulin

Declarations

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to confidentiality concerns (in the informed consent, we have made a commitment to the participants to publish only the general and group results of the study) but are available from the corresponding author on reasonable request.

Authors' contributions

AA, SVS, RS, SS and MS made substantial contributions to the conception and design of the work. AA, SA, and MS have substantial contribution in data gathering. NE and SVS analyzed and interpreted the data. NE, SVS and MS have major contribution in writing the manuscript. All authors read and approved the final manuscript.

Acknowledgement

This study was Dr. **Arman Alipour-Kivi's** postgraduate thesis toward the Iranian Board of Psychiatry.

Funding

The authors disclose receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by Iran University of Medical Sciences (Grant no: 1402-1-90-25886).

Ethics approval and consent to participate

The trial was approved by the ethics committee of the Iran University of Medical Sciences institutional review board (IR.IUMS.FMD.REC.1400.130) and carried out based on the Declaration of Helsinki and subsequent revisions. Written informed consent obtained from all subjects or, if subjects are illiterates then from a legal guardian. Patients were reassured that their participation was voluntary and that they had the right to return to their usual treatment at any point of the study. The trial was registered at the Iranian Registry of Clinical Trials on 25/10/2021 (www.irct.ir; IRCT ID: IRCT20170123032145N6) before the trial.

Consent for publication

Not applicable

Competing interests

The authors have no conflicts of interest to report.

References

1. GBD 2019 Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet Psychiatry. 2022;9(2):137–50. 10.1016/S2215-0366(21)00395-3. Epub 2022 Jan 10.
2. Edinoff AN, Akuly HA, Hanna TA, Ochoa CO, Patti SJ, Ghaffar YA, Kaye AD, Viswanath O, Urits I, Boyer AG, Cornett EM, Kaye AM. Selective Serotonin Reuptake Inhibitors and Adverse Effects: A Narrative Review. Neurol Int. 2021;13(3):387–401. 10.3390/neurolint13030038.
3. Taylor MJ, Rudkin L, Bullemor-Day P, Lubin J, Chukwujekwu C, Hawton K. Strategies for managing sexual dysfunction induced by antidepressant medication. Cochrane Database of Systematic Reviews 2013, Issue 5. Art. No.: CD003382. DOI: 10.1002/14651858.CD003382.pub3. Accessed 29 March 2023.
4. Montejo A, Majadas S, Rizvi SJ, Kennedy SH. The effects of agomelatine on sexual function in depressed patients and healthy volunteers. Hum Psychopharmacol. 2011;26(8):537–42. 10.1002/hup.1243. Epub 2011 Nov 21.
5. Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. J Clin Psychopharmacol. 1999;19(1):67–85. 10.1097/00004714-199902000-00013.
6. Jing E, Straw-Wilson K. Sexual dysfunction in selective serotonin reuptake inhibitors (SSRIs) and potential solutions: A narrative literature review. Ment Health Clin. 2016;6(4):191–6. 10.9740/mhc.2016.07.191.
7. Moore BE, Rothschild AJ. Treatment of antidepressant-induced sexual dysfunction. Hosp Pract (1995). 1999;34(1):89–91, 95 – 6. doi: 10.3810/hp.1999.01.127.
8. Shalbafan M, Saeedi V, Kamalzadeh L. Significant improvement of risperidone-induced retrograde ejaculation on drug holidays: a case report. Psychiatry and Clinical Psychopharmacology. 2019;29(1):120–2.
9. de Filippis R, Solerdelcoll M, Shalbafan M. Editorial: Safety and side effects of psychotropic medications. Front Psychiatry. 2023;14:1148158. https://doi.org/10.3389/fpsyt.2023.1148158.
10. Rothschild AJ. Selective serotonin reuptake inhibitor-induced sexual dysfunction: efficacy of a drug holidays. Am J Psychiatry. 1995;152(10):1514–6. 10.1176/ajp.152.10.1514.
11. Taghavi M. Assessment of the Validity and Reliability ofthe General Health Questionnaire. J Psychol. 2001;5(3):381–98.
12. Fakhri A, Morshedi H, Soleymanian A. Psychometric Properties of Iranian Version of Male Sexual Function Index. Jundishapur Sci Med J. 2014;12(6):655–63.

13. Keltner NL, McAfee KM, Taylor CL. Mechanisms and treatments of SSRI-induced sexual dysfunction. Perspect Psychiatr Care. 2002 Jul-Sep;38(3):111–6.
14. Nitkowska M, Tomasiuk R, Czyżyk M, Friedman A. Prolactin and sex hormones levels in males with parkinson's disease. Acta Neurol Scand. 2015;131:411–6.
15. Abbasinazari M, Heidari-Kord M, Mazaheri-Meybodi A, Eshraghi A, Bayati N. Plasma Oxytocin Level and Sexual Dysfunction in Depressed Women Treated by Either Fluoxetine or Citalopram: a Pilot Clinical Trial. Iran J Pharm Res 2018 Winter;17(1):408–14.
16. Pavlidi P, Kokras N, Dalla C. Antidepressants' effects on testosterone and estrogens: What do we know? Eur J Pharmacol. 2021;899:173998. 10.1016/j.ejphar.2021.173998. Epub 2021 Mar 4.
17. Dhir A, Kulkarni K. Nitric Oxide (NO) System in Major Depression: Studies on NO Synthase Inhibitors as Antidepressant Agents. Curr Enzym Inhib. 2016;12(1):40–8. http://dx.doi.org/10.2174/1573408012666151126185543.
18. Healy D, LaPalme J, Levin M, Post-SSRI, Sexual Dysfunction. A Bioelectric Mechanism? Bioelectricity. 2020;2(1):7–13. 10.1089/bioe.2019.0010. Epub 2020 Mar 18.
19. Campos AI, Mulcahy A, Thorp JG, Wray NR, Byrne EM, Lind PA, Medland SE, Martin NG, Hickie IB, Rentería ME. Understanding genetic risk factors for common side effects of antidepressant medications. Commun Med (Lond). 2021;1:45. 10.1038/s43856-021-00046-8.
20. Montejo AL, Prieto N, de Alarcón R, Casado-Espada N, de la Iglesia J, Montejo L. Management Strategies for Antidepressant-Related Sexual Dysfunction: A Clinical Approach. J Clin Med. 2019;8(10):1640. 10.3390/jcm8101640.

Figures

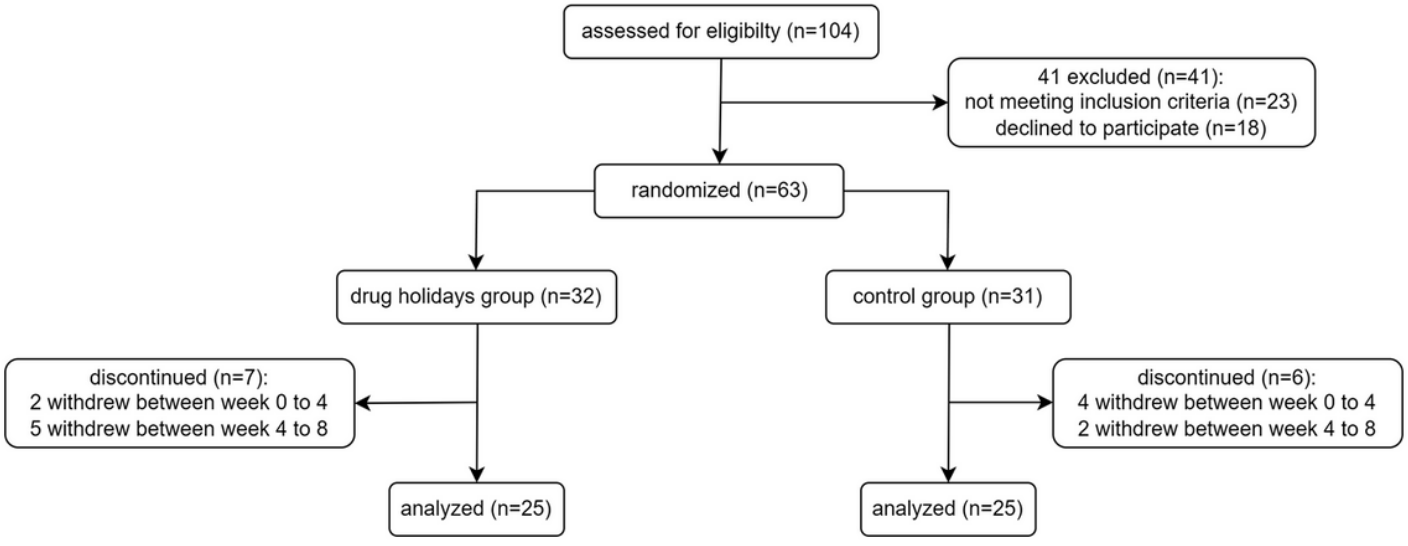
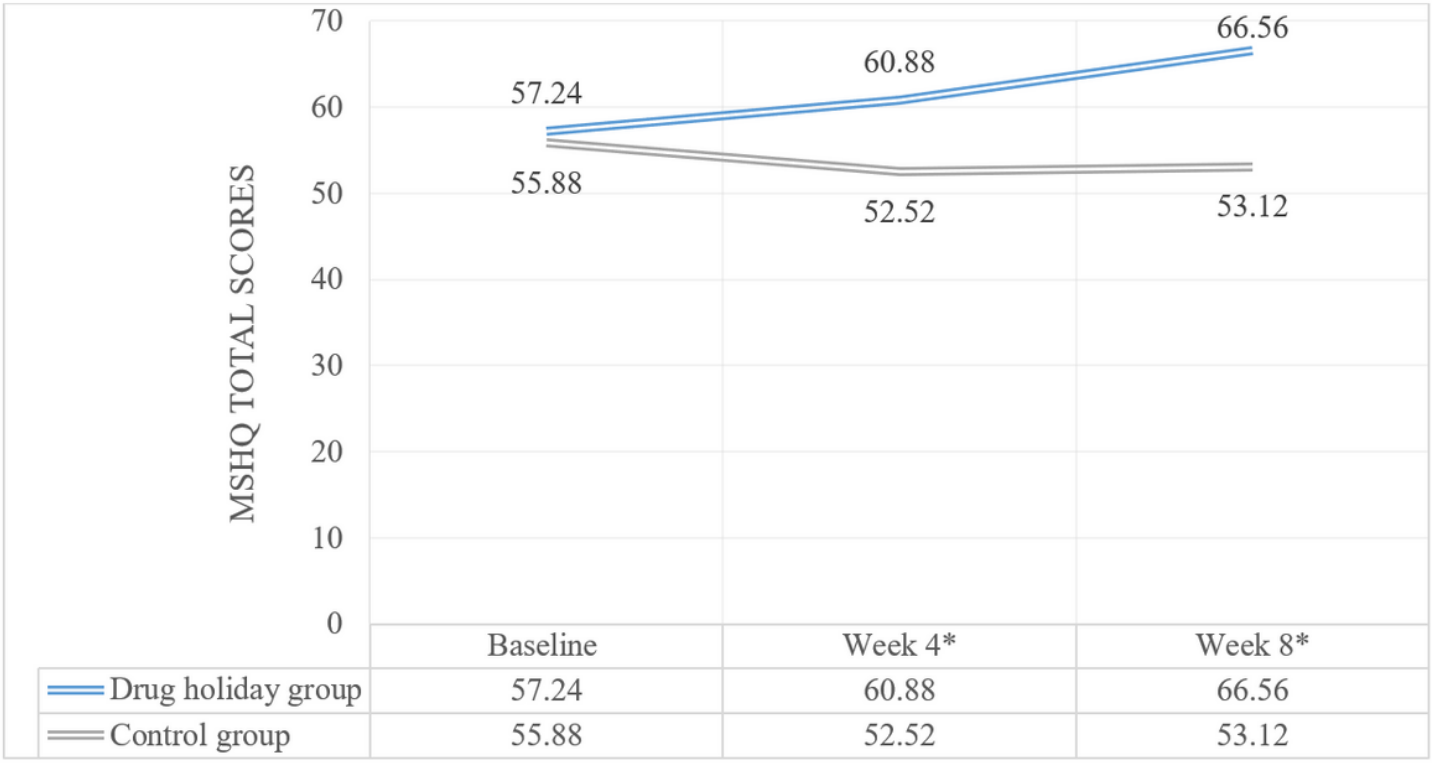


Figure 1

Flow diagram of the participants of the trial

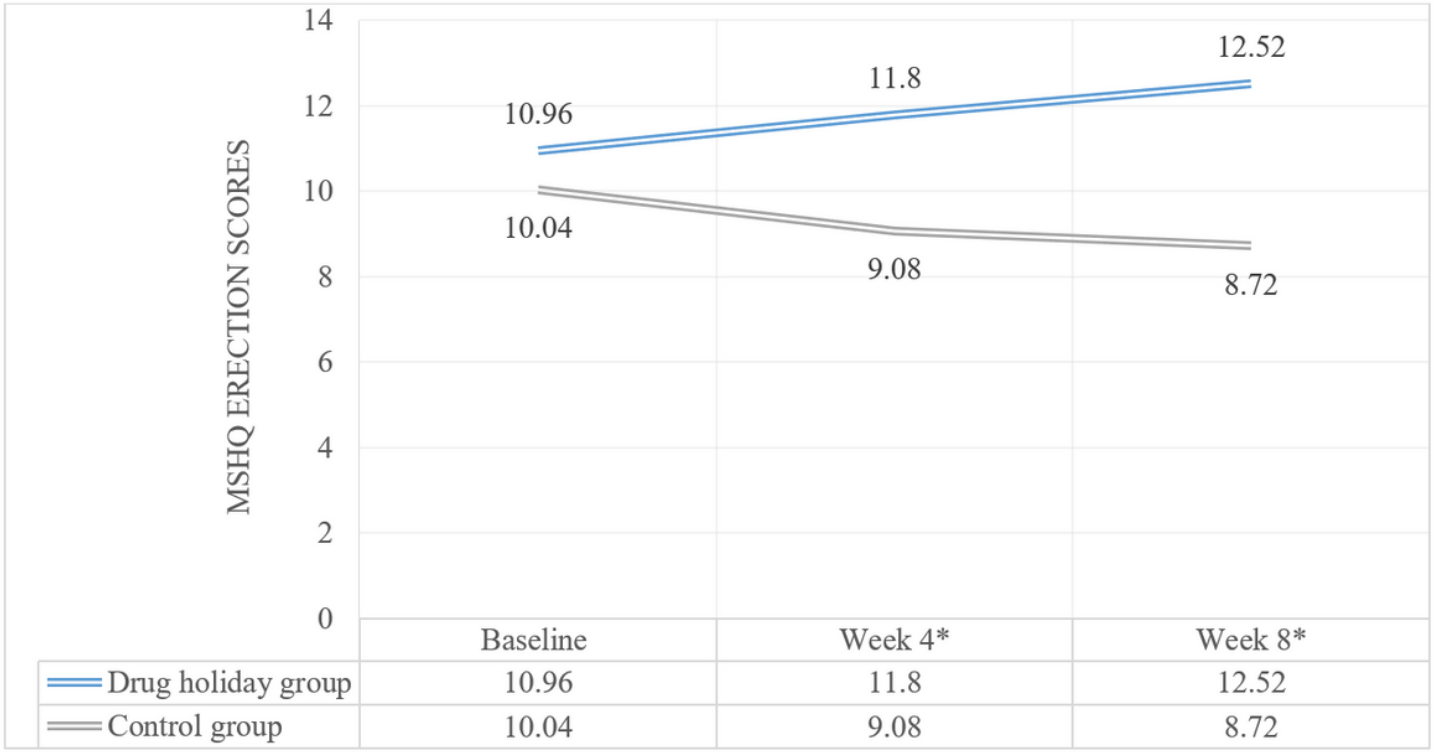


	Baseline	Week 4*	Week 8*
Drug holiday group	57.24	60.88	66.56
Control group	55.88	52.52	53.12

Figure 2

MSHQ total score changes of the participants during the course of trial.

*significant difference between the two groups



	Baseline	Week 4*	Week 8*
Drug holiday group	10.96	11.8	12.52
Control group	10.04	9.08	8.72

Figure 3

MSHQ erection score changes of the participants during the course of trial.

*significant difference between the two groups

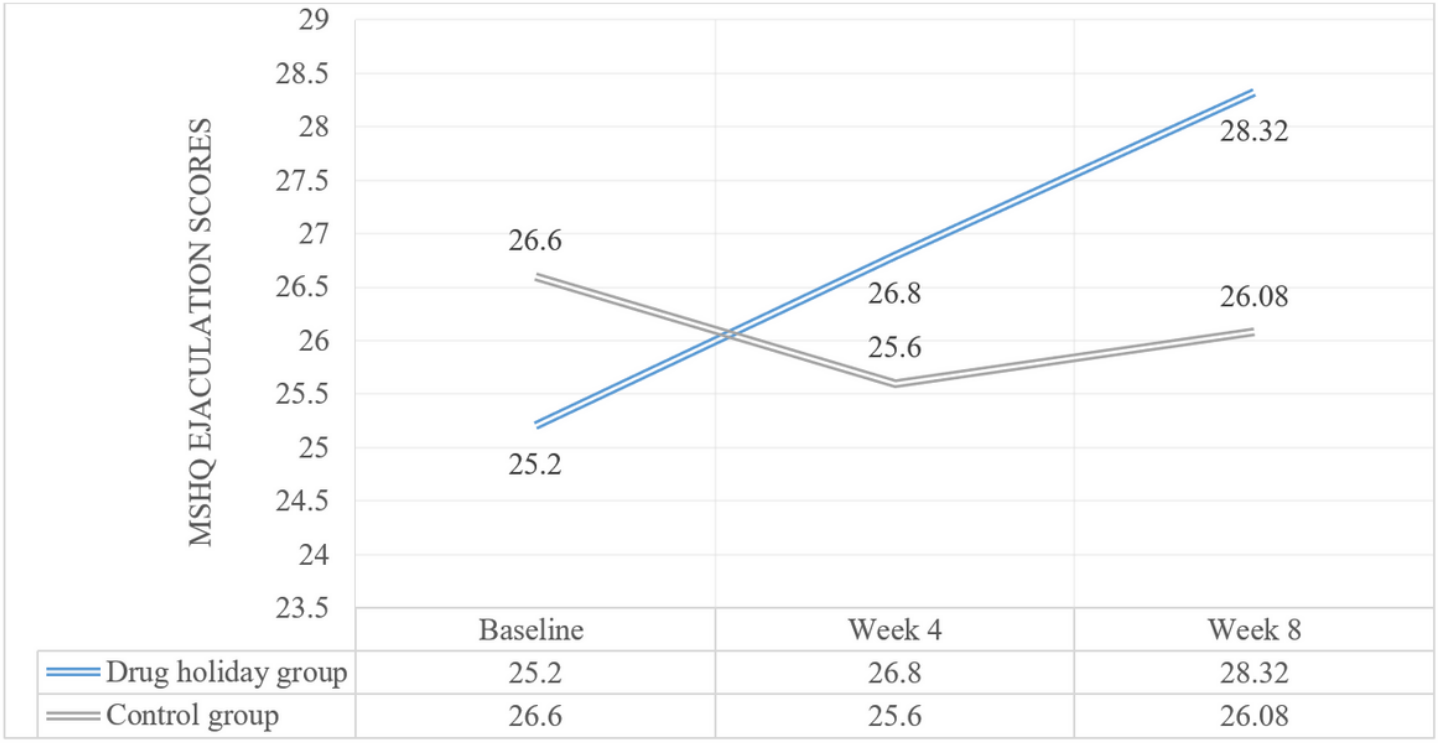


Figure 4

MSHQ ejaculation score changes of the participants during the course of trial.

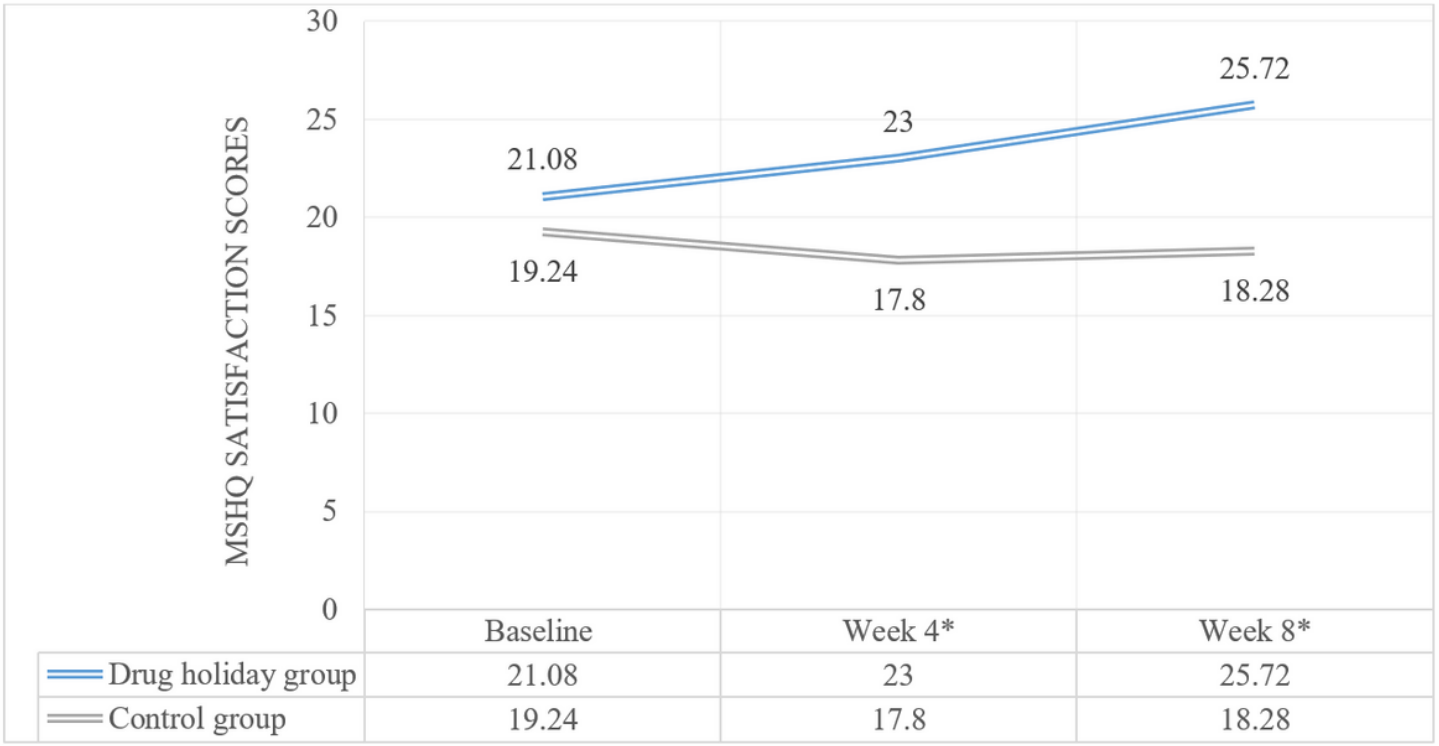


Figure 5

MSHQ satisfaction score changes of the participants during the course of trial.

*significant difference between the two groups