Psychiatry Research 276 (2019) 142–150

Contents lists available at ScienceDirect

Psychiatry Research

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

Ginseng treatment improves the sexual side effects of methadone maintenance treatment

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ARTICLE INFO

Keywords:
Ginseng
Opioid use disorder
Methadone maintenance therapy
Methadone-related sexual dysfunction

ABSTRACT

Background: While methadone maintenance therapy (MMT) in patients with opioid use disorder (OUD) decreases the risk of substance use relapses and criminal and risky sexual behavior, a major disadvantage is its negative impact on sexual function. In the present study we tested whether, compared to placebo, ginseng extract ameliorates methadone-related sexual dysfunction among female and male patients with OUD and receiving MMT.

Method: A total of 74 patients (26 females: mean age: $M = 39.0$ years; 48 males; mean age: 40.64 years) took part in a double-blind, randomized and placebo-controlled study. Female and male patients were separately randomly assigned either to the ginseng or to a placebo condition. At the beginning of the study and four weeks later, patients completed questionnaires on sexual function.

Results: Irrespective of gender, sexual function improved over time, but more so in the ginseng condition than in the placebo condition.

Conclusions: Ginseng appears to counteract the sexual dysfunction resulting from methadone use in both female and male patients with OUD and undergoing MMT.

1. Introduction

While in Western countries such as the USA the lifetime prevalence of substance use disorders (SUD) is about 3.9% (Grant et al., 2016), in Iran, the equivalent rate is about 2.44% (Amin-Esmaeili et al., 2016). Compared to other SUDs such as alcohol and stimulants (amphetamines), higher prevalence rates have been reported for individuals with opium use disorder (OUD), namely those who use opioids such as opium dross (the condensed extract of smoked opium ashes), methadone (not prescribed by a physician), heroin, or morphine (Amin-Esmaeili et al., 2016; Sharifi et al., 2015). Given the high prevalence rates of individuals with OUD, treatment merits particular attention.

Individuals with OUD may be treated with slow release oral morphine (Klimas et al., 2019) or with the methadone-maintenance therapy (MMT, Farnia et al., 2017a,b; Strain et al., 1999). Sun et al. (2015) showed in their meta-analysis, that MMT substantially reduced criminality, improved employment and social well-being, and helped individuals with OUD to reestablish a reasonable level of working and social life. Further, MMT helped to improve the ability to access HIV-related services, and to reduce needle sharing and the risk for further HIV-related behaviors such as hepatitis C virus infections (Boggiano et al., 2017). Additionally, Mattick et al. (2014) showed in their Cochraine meta-analysis that both methadone and buprenorphine were superior to placebo, while methadone was superior to buprenorphine in retaining people on treatment, and in suppressing illicit opioid use.

However, methadone also has side effects (Institute of Medicine Committee on Federal Regulation of Methadone, 1995), such as weight gain (Dursteler-MacFarland et al., 2010; Peles et al., 2016), weight loss, dizziness, headache, increased or decreased saliva, and dental problems (Dursteler-MacFarland et al., 2010). However, while sexual dysfunctions are observed in all opioids, including antagonists such as naltrexone (Abdel-Hamid et al., 2016; Grover et al., 2014; Varma et al., 2018), sexual dysfunction appears to be the most negative side effect of

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https://doi.org/10.1016/j.psychres.2019.05.004
Received 20 March 2019; Received in revised form 29 April 2019; Accepted 1 May 2019
Available online 02 May 2019
0165-1781/

MMT (Dursteler-MacFarland et al., 2010). To illustrate, males with OUD and under MMT reported problems with orgasm (39.7%) and problems with erections (29%), while the females reported irregular menstruation (63%), pain before and after menstruation (41%), and bleeding between menstruations (8%) (Dursteler-MacFarland et al., 2010). Similarly, sexual dysfunction was one of the most common side effects among males with OUD (Yee et al., 2014), and sexual dysfunction has been well documented both for males (Hallinan et al., 2008; Quaglio et al., 2008; Tatari et al., 2010; Teoh et al., 2016; Zhang et al., 2014), and for females with OUD undergoing MMT (Farnia et al., 2017b).

The neurophysiological mechanisms underlying the effect of methadone on sexual functioning are not fully understood, though the following model appears to be the most reasonable. As briefly summarized elsewhere (Farnia et al., 2017a), methadone is a long-lasting and slow-acting opioid-agonist, which stimulates opioid-receptors in the central nervous system (CNS), and which affects both the tuberoinfundibular and hypothalamic-pituitary-gonadal axes. As a consequence, sex hormones such as prolactin levels increase, while levels of gonadotropin-releasing hormone decrease, as also do levels of luteininzing (LH) and follicle-stimulating hormones (FSH), leading to a downregulation of sex hormones such as testosterone (de la Rosa and Hennessey, 1996). Furthermore, decreases in LH and FSH lead to a down-regulation of progesterone and estradiol, two key hormones particularly involved in females' sexual behavior (Caruso et al., 2014; Durante and Li, 2009). At a behavioral level, sexual assertiveness and sexual drive decrease (Smith and Elliott, 2012; Yee et al., 2016, 2014). Additionally, Bawor et al. (2015) showed in their systematic review and meta-analysis that all opioids suppress the testosterone levels of males with OUD, though this testosterone suppression is not observed among females with OUD.

To our knowledge, there has been little research into measures that might counter methadone-related sexual dysfunction. As regards such dysfunction in males with OUD and undergoing MMT, Farnia et al. (2017a) identified two studies (Tatari et al., 2010; Tatari et al., 2013), in which adjuvant trazodone and adjuvant bupropion improved erectile dysfunctions when compared to a placebo. In a study of their own, Farnia et al. (2017a) showed that adjuvant Rosa Damascena oil, when compared to a placebo, improved erectile and sexual dysfunction among men with OUD, undergoing MTT and suffering from methadone-related sexual dysfunction. The same study design was employed with an equivalent sample of women (Farnia et al., 2017b), and the results were again encouraging; over time and compared to a placebo, adjuvant Rosa Damascena oil produced improvements on dimensions of female sexuality such as sexual desire, arousal, lubrication and orgasm, while pain during sexual intercourse was reduced.

A major disadvantage of Rosa damascena oil is its limited availability to a broader market of costumers, while this is not the case for Ginseng (Baeg and So, 2013).

Several reviews (Choi, 2008; Kitts and Hu, 2000; Nocerino et al., 2000) have reported the beneficial effects of ginseng for a broad variety of somatic complaints including lack of energy and pain, along with benefits for brain function, immune system function, anti-oxidative and anti-aging effects, anti-tumor activity, anti-diabetic effects and adjusted blood pressure. Furthermore, ginseng is known to improve sexual function in males with low sexual drive and erectile dysfunctions (Murphy and Lee, 2002; Nocerino et al., 2000; Shamloul, 2010).

The hypothesis was as follows. Following others (Murphy and Lee, 2002; Nocerino et al., 2000; Shamloul, 2010), we anticipated that, compared to placebo, adjuvant ginseng would improve sexual function in males with OUD and undergoing MMT. Whether adjuvant ginseng would also improve sexual function among females with OUD and undergoing MMT was treated as a research question.

We believe that the results have the potential to improve sexual function in individuals with OUD and undergoing MMT, the importance of which is that a satisfying sexual life is associated with better health and improved quality of life. In contrast, sexual dysfunction carries the risk of damaging both individual and couple-related quality of life (Clayton et al., 2014; Contreras et al., 2016; Fisher et al., 2015; Rosen et al., 2016).

2. Method

2.1. Procedure

Outpatients with opioid use disorder (OUD) and receiving methadone maintenance therapy (MMT) were approached to participate at the present randomized, double-blind, placebo-controlled clinical trial. Eligible participants were fully informed about the study aims, the study design and the confidential and anonymous data handling. Thereafter, participants signed a written informed consent, and they were randomly assigned either to the adjuvant ginseng or to a placebo condition. At the beginning of the study (baseline) and four weeks later (end of the study), male participants completed two self-rating questionnaires covering sexual dysfunction (Brief Sexual Function Inventory; BSFI, see below) and erectile function (International Index of erectile function; IIEF, see below), while female patients completed a self-rating scale on sexual function (Female Sexual Function Index (FSFI; see below). The ethical committee of the Kermanshah University of Medical Sciences (KUMS; No IR.KUMS.REC.1395.178) approved the study, which was performed in accordance with the rules laid down in the Declaration of Helsinki and its later amendments. The study was registered at the Iranian Registry of Clinical Trials (IRCT) with the following number: IRCT2016062523705N5 (www.irct.ir).

2.2. Sample

A total of 240 male and female patients with opioid-dependency and currently undergoing methadone-maintenance treatment (MMT) were approached; of these 91 (37.92%; 54 males and 37 females) were finally enrolled in the study and randomly assigned to one of the two study conditions (see Figs. 1 and 2; CONSORT flow diagram).

As in our previous studies (Farnia et al., 2017a,b), inclusion criteria were as follows: 1. Suffering from opioid use disorder (OUD), as ascertained by a trained psychiatrist or clinical psychologist and based on a thorough psychiatric interview, together with medical records, and according to the DSM 5 (American Psychiatric Association, 2013). 2. Suffering from MMT-related sexual dysfunction, again based on the DSM 5 (American Psychiatric Association, 2013), and on the clinical interview. More specifically, participants had to clearly indicate that their sexual function significantly decreased after the start of the MMT. 3. Currently undergoing stable MMT for at least six months. 4. Age between 18 and 50 years. 5. Willing and able to comply with the study conditions. 6. Currently in a stable heterosexual relationship, as ascertained via a thorough clinical and sociopsychological interview. 7. Signed written informed consent. Exclusion criteria were as follows: 1. Psychiatric comorbidities such as other SUDs (alcohol, cannabis, amphetamines) or a current state of depression or mania. 2. Acute suicidality. 3. Intake of medication affecting sexual drive such as selective serotonin reuptake inhibitors. 4. Somatic issues such as spinal cord injury or radical prostatectomy. 5 Current marital issues (such as verbal and physical aggressions; conflicts concerning financial resources, children's education and school achievements, substance use, family of origin, and similar), as explored during the clinical interview. 6. Allergy to ginseng constituents (that is to say: On request, participants had to report previous ginseng intake and possible adverse effects).

2.3. Sample size analysis

The sample size calculation was performed with G*Power® (Faul et al., 2007). Based on previous results (Farnia et al., 2017b), the following parameters were defined: Effect size: 0.25 (Cohen's f for

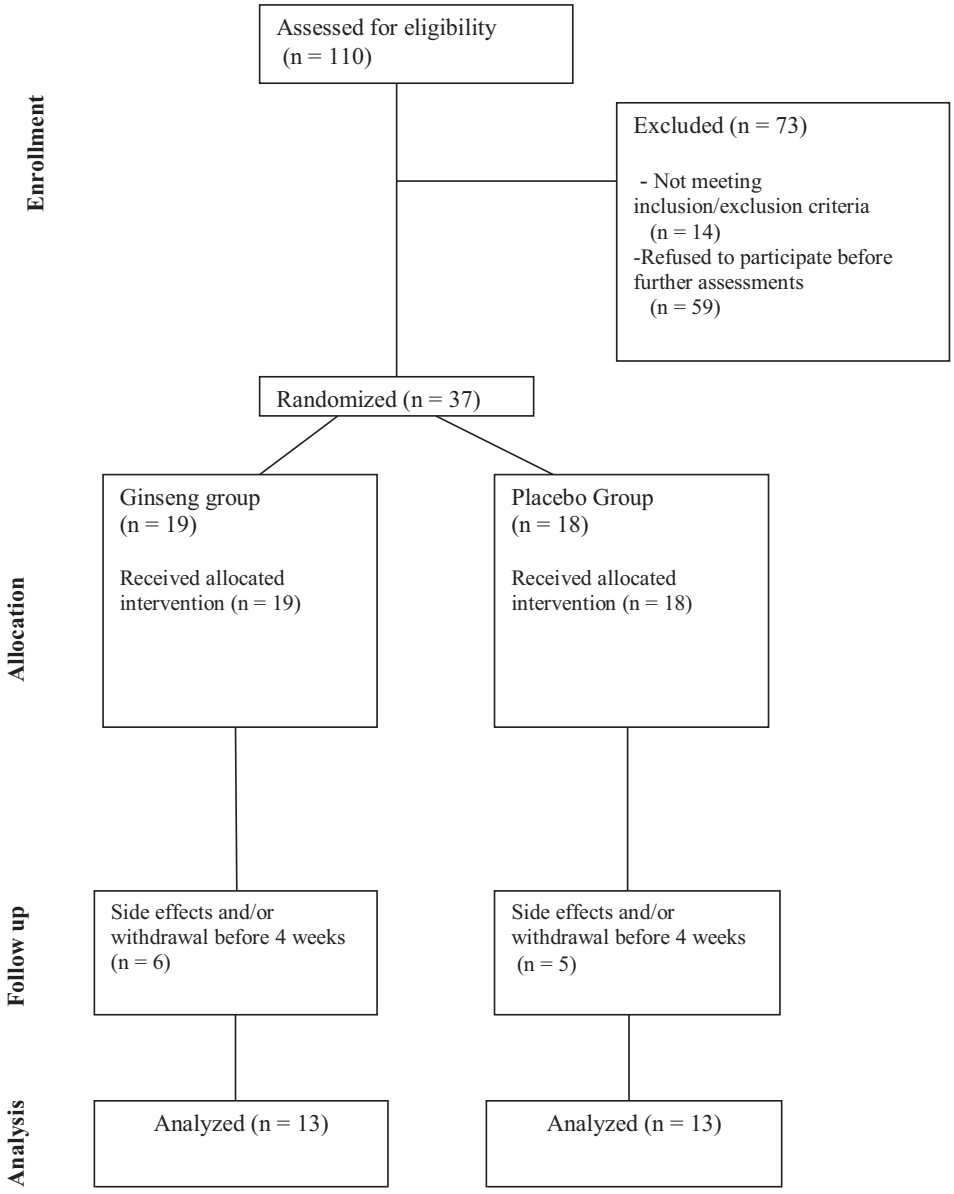

Fig. 1. CONSORT diagram showing the flow of female participants through each stage.

ANOVAs); alpha error probability: 0.05; power: 0.95; number of groups: 2: number of measurements: 2; the total sample size was 54. However, to counter possible drop-outs and to perform statistical analyses separately for male and female patients, the sample size was set at 74 participants.

2.4. Randomization

As in previous studies (Jahangard et al., 2018), randomization was achieved with the software randomization.com. Based on two separate lists for male and female participants, a psychologist not otherwise involved in the study assigned participants to the two study conditions. Participants, hospital members and medical doctors responsible for patients' treatments were kept unaware of participants' study assignment.

2.5. Medication

2.5.1. Standard medication

Medication consisted of standard methadone treatment at therapeutic dosages (see Tables 1 and 4). Other medications were explicitly excluded, as agreed in the written informed consent.

2.5.2. Ginseng and placebo

The ginseng group received four capsules of ginseng daily (each capsule contained 250 mg dry powder of ginseng radix). The ginseng capsules were manufactured by Goldaru Herbal Pharmaceutical Company, Esfahan, Iran (http://www.goldaru-co.com).

The placebo group received four placebo capsules daily (lactose powder, 5% gelatin solution and cellulose powder). Ginseng and placebo capsules were identical in shape, size, color, weight, and scent.

2.6. Side effects

To provide a check on possible side effects, participants completed, at baseline, one week and four weeks later (study end), a questionnaire covering possible side effects, as proposed by the British Medical Association and the Royal Pharmaceutical Society of Great Britain (British Medical Association, 2004). The list included the following items: rash, drowsiness, anxiety, dizziness, headache, insomnia,

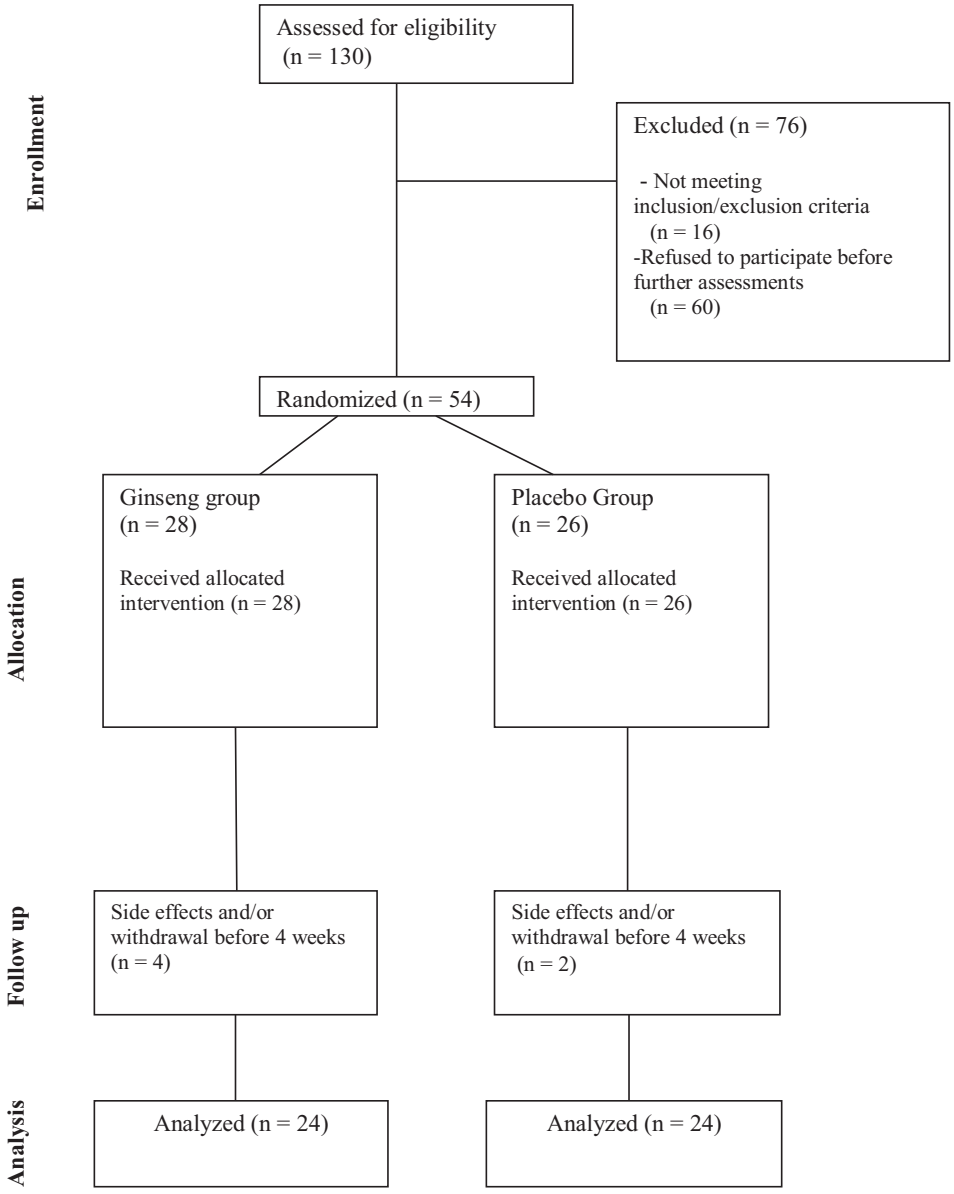

Fig. 2. CONSORT diagram showing the flow of male participants through each stage.

Table 1
Sociodemographic and illness-related characteristics of female patients, separately for patients in the Ginseng condition (n = 19) and in the placebo condition (n = 18).

Dimensions	Groups		Statistics
N	Ginseng 19	Placebo 18	
	M (SD)	M (SD)	
Age (years)	38.11 (6.58)	38.00 (6.65)	t(35) = 0.05, p = .96
Duration of marriage (years)	16.37 (6.46)	15.61 (7.88)	t(35) = 0.32, p = .75
Number of children	2.11 (0.88)	2.00 (0.97)	t(35) = 0.35, p = .73
Age of first opium/opioid use (years)	30.84 (6.19)	30.17 (7.45)	t(35) = 0.30, p = .77
Duration of opium/opioid use (years)	7.00 (3.23)	7.72 (5.40)	t(35) = 0.50, p = .62
Methadone dosage (mg)	54.74 (23.42)	37.50 (21.78)	t(35) = 2.32, p = .03
Years of methadone substitution	2.84 (1.83)	2.67 (1.85)	t(35) = 0.29, p = .77
	N	*N*	
Opioids prevalently used: Opioid/opium; opioid and tramadol/heroin	17/2/0	17/0/1	$\chi^2(N = 35, df = 2) = 1.87, p = .51$
Highest educational level: Primary school/secondary school diploma/ high school diploma/ bachelor or higher degree	6/4/9/0	8/4/4/1	$\chi^2(N = 35, df = 3) = 2.38, p = .13$
Occupation: Employed/unemployed	0/19	0/18	–
Income: Low/middle/high income	7/9/3	2/15/1	$\chi^2(N = 35, df = 2) = 4.32, p = .53$

agitation and/or hallucinations, nervousness, vomiting, light-headedness, vertigo, weakness, chest pain and peripheral edema, constipation, diarrhea, dyspepsia, flatulence, nausea, flu-like syndrome, allergic reaction, arthralgia, irregular heart beating, hypertension.

2.7. Tools

2.7.1. Sociodemographic and illness-related information

Participants reported on their sex, age in years, duration of marriage (years) and number of children, highest educational degree (primary school; secondary school; high school diploma; bachelor or master degree), the current job position (employed vs. unemployed), and their income (low income = less than 200 USD/month); middle income = 200 to 500 USD/month); high income = 500 or more USD/month).

Illness-related information were taken from the medical records and participants' information: Age of first opium/opioid use (years); duration of opium/opioid use (years), methadone dosage (mg), years of methadone substitution.

2.8. Assessing female sexual dysfunction: Female Sexual Function Index (FSFI)

As in the previous two studies (Farnia et al., 2015a, 2017b) we employed the Farsi version of the Female Sexual Function Index (FSFI; Bhasin et al., 2007). It contains 19 questions covering six domains of sexual function: sexual desire, sexual arousal, lubrication, orgasm, sexual satisfaction, and pain. An overall score was also computed. Answers are given on 5-point Likert-scales ranging from 0 (=almost never or never/very low or none at all/ or similar) to 4 (=almost always/very high and similar; for the items related to pain, scoring was reversed), with lower mean scores reflecting greater sexual dysfunction (Cronbach's alpha = 0.90).

2.9. Assessing male sexual dysfunction: Brief Sexual Function Inventory (BSFI)

As in the previous two studies (Farnia et al., 2015b, 2017a), male patients completed the Brief Sexual Function Inventory (BSFI) (Mykletun et al., 2006), which contains eleven questions that cover five domains of sexual function: 1) sexual drive (two items); 2) erectile function (three items); 3) ejaculatory function (two items); 4) sexual problem assessment (three items); and 5) sexual satisfaction (one item). Answers are given on a 5-point Likert scale with scores ranging from 0 (= none, big problem, or no activity) to 4 (= always, no problem, or high activity) and with *lower mean scores* reflecting *greater sexual dysfunction* (Cronbach's alpha = 0.85).

2.10. Assessment of erectile function (International Index of Erectile Function; IIEF)

As in the previous two studies (Farnia et al., 2015b, 2017a) the International Index of Erectile Function (IIEF; Rosen et al., 1997) was employed to assess erectile dysfunctions. The IIEF consists of 15 items focusing on erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. A typical item is: "How often were you able to get an erection during sexual activity?", with response options as follows: 0 = no sexual activity, 1 = almost never; 2 = a few time (much less than half the time); 3 = sometimes (about half the time); 4 = most times (much more than half the time), 5 = almost always/always. The labels of the anchor points vary depending on the questions, though a higher value always reflects lower erectile dysfunction. Consequently, a *higher sum score* reflects *lower erectile dysfunction*, which is to say, *better erectile function* (Cronbach's alpha = 0.90).

2.11. Statistical analyses

Male and female participants completed different questionnaires on sexual dysfunction. Accordingly, statistical procedures were run separately for female and male participants. With a series of *t*-tests and χ^2-tests we examined differences between the ginseng and placebo conditions with respect to sociodemographic and illness-related information. Similarly, *t*-tests and a χ^2-test were performed to compare study completers and study non-completers. A series of ANOVAs for repeated measures with the factors Time (baseline vs. study end), Condition (ginseng vs. placebo) and Time by Condition interaction were employed to examine differences in sexual dysfunction. Due to drop-outs between baseline and study end, ANOVAs were performed following the intention-to-treat (ITT) analysis with the last observation carried forward (LOCF). Effect sizes were reported as partial eta-squared (η_p^2): $0.01 \leq \eta_p^2 \leq 0.059$ = small [S]; $0.06 \leq \eta_p^2 \leq 0.139$ = medium [M]; $\eta_p^2 \geq 0.14$ = large [L]. The level of significance was set at alpha $\leq$ 0.05. Statistics was performed with SPSS® 25.0 (IBM Corporation, Armonk NY, USA) for Apple® Mac®.

3. Results

3.1. Drop-out rates

In the sample of female patients ($N = 37$), 19 were randomized to the adjuvant ginseng condition, and 18 to the placebo condition. In the adjuvant ginseng condition, six (32%) patients dropped out of the study, while in the placebo condition, five (28%) patients dropped out (see Fig. 1). Female study completers and study non-completers did not differ as regards age, duration of consumption, duration of methadone substitution, methadone dosage, and levels of sexual dysfunctions (all t's < 0.81, p's > 0.65) and side-effects ($\chi^2(N = 37, df = 4) = 0.17$, $p = .99$). Likewise, male study completers and study non-completers did not differ as regards age, duration of consumption, duration of methadone substitution, methadone dosage, and levels of sexual dysfunctions (all t's < 0.90, p's > 0.68) and side-effects ($\chi^2(N = 54$, $df = 5) = 1.40$, $p = .56$).

In the sample of male patients ($N = 54$), 28 were randomly assigned to the adjuvant ginseng condition, and 26 to the placebo condition. In the adjuvant ginseng condition, four (14%) patients dropped out, while in the placebo condition, two (8%) patients dropped out (see Fig. 2).

Reasons for drop-out were either side effects or failure to comply with the study conditions.

3.2. Female participants

3.2.1. Sociodemographic and illness-related information

Table 1 gives the descriptive and inferential statistical indices for sociodemographic and illness-related information.

Female patients with adjuvant ginseng did not differ from those with placebo as regards age, duration of marriage, number of children, age of first opioid use, duration of consumption, years of methadone substitution, type of substance, highest educational level, occupation, or income. Compared to female participants in the ginseng-condition, female participants in the placebo condition received a significantly lower dosage of methadone.

3.2.2. Female sexual function

Tables 2 and 3 gives a descriptive and inferential statistical overview (Intent-To-Treat (ITT) with last observation carried forward (LOCF)) of sexual function, separately for adjuvant ginseng and placebo conditions, and for the two time-points (baseline and week 4).

Over time, desire, arousal, lubrication, orgasm, and total score increased significantly, but more so in the adjuvant ginseng than the placebo condition (significant interaction effects). Significant interactions were also observed for pain. Effect sizes were large. No time

Table 2
Descriptive overview of female sexual function scores, separately by assessment time (baseline and week 4), and group (ginseng vs. placebo).

	Assessment times			
	Baseline		Week 4	
	Ginseng	Placebo	Ginseng	Placebo
N	19	18	19	18
	M (SD)	M (SD)	M (SD)	M (SD)
Desire	4.16 (1.12)	4.56 (1.34)	5.74 (1.24)	5.00 (1.03)
Arousal	8.05 (2.68)	8.44 (2.18)	9.79 (2.18)	8.44 (1.79)
Lubrication	9.00 (3.20)	8.56 (3.11)	10.26 (3.16)	8.83 (2.57)
Orgasm	7.42 (2.22)	6.67 (2.03)	8.79 (2.10)	7.00 (1.46)
Satisfaction	7.32 (2.26)	7.17 (2.09)	7.53 (1.54)	7.17 (1.58)
Pain	8.16 (3.18)	8.67 (2.81)	9.42 (1.80)	7.44 (1.92)
FSFI total	43.47 (10.33)	44.06 (10.15)	49.84 (7.08)	43.89 (7.57)

Note: Higher scores reflect better sexual function.

Table 3
Overview of inferential statistics for female sexual function as a function of Time (baseline, week 4) and Group (ginseng, placebo) and the Time by Group-interaction.

	Time		Group		Time × Group interaction	
Degrees of freedom	(1, 35)		(1, 35)		(1, 35)	
	F	η_p^2 [EF]	F	η_p^2 [EF]	F	η_p^2 [EF]
Desire	22.42***	0.39 [L]	0.27	0.01 [S]	7.05*	0.17 [L]
Arousal	10.42**	0.23 [L]	0.49	0.01 [S]	10.42**	0.23 [L]
Lubrication	6.33*	0.15 [L]	0.98	0.03 [S]	2.59	0.07 [M]
Orgasm	12.94***	0.27 [L]	4.41*	0.11 [M]	4.79*	0.12 [M]
Satisfaction	0.13	0.00 [S]	0.21	0.01 [S]	0.13	0.00 [S]
Pain	0.00	0.00 [S]	1.11	0.03 [S]	8.16*	0.19 [L]
FSFI total	9.85**	0.22 [L]	0.95	0.03 [S]	10.94**	0.24 [L]

Notes: FSFI = Female Sexual Function Inventory.
EF = effect size; S = small effect size, M = medium effect size; L = large effect size.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

effects were observed for satisfaction or pain. Higher scores for the ginseng group were observed for orgasm (medium effect size).

3.3. Male participants

3.3.1. Sociodemographic and illness-related information

Table 4 provides descriptive and inferential statistical indices for sociodemographic and illness-related information.

Male patients with adjuvant ginseng did not differ from those with placebo as regards duration of marriage, number of children, age of first opioid use, duration of consumption, years of methadone substitution, type of substance, highest educational level, occupation, or income. Descriptively, male patients in the placebo condition were older and had more children; additionally, this group was receiving a significantly higher methadone dosage, and had a significantly longer duration of opioid consumption.

Table 5
Descriptive overview of male sexual function scores, separately by assessment time (baseline and week 4), and group (ginseng vs. placebo).

	Assessment times			
	Baseline		Week 4	
	Ginseng	Placebo	Ginseng	Placebo
N	28	26	28	26
	M (SD)	M (SD)	M (SD)	M (SD)
Excitement	5.07 (1.96)	5.04 (1.64)	5.68 (2.14)	4.88 (1.34)
Erection	7.39 (2.99)	7.62 (2.28)	8.29 (3.39)	6.77 (2.07)
Ejaculation	5.46 (2.59)	5.46 (1.27)	6.50 (2.69)	5.38 (1.39)
Perception of the problem	6.64 (3.05)	7.50 (1.88)	8.32 (3.78)	6.12 (1.31)
Satisfaction	2.71 (0.90)	2.77 (0.59)	3.36 (0.83)	2.54 (0.95)
BSFI total	25.93 (10.02)	28.08 (5.29)	31.71 (11.86)	25.81 (5.64)
IIEF total	13.39 (2.79)	13.35 (2.68)	15.14 (3.99)	12.04 (2.46)

Notes: BSFI = Brief Sexual Function Inventory. IIEF = International Index of Erectile Function.

3.3.2. Male sexual dysfunction

Tables 5 and 6 give a descriptive and inferential statistical overview (Intent-To-Treat (ITT) with last observation carried forward (LOCF)) of sexual function and erectile dysfunction, separately for the adjuvant ginseng or placebo conditions and for the two time points (baseline and week 4).

Over time, ejaculation and total sexual function improved. Compared to the placebo condition, higher scores were observed in the ginseng condition for satisfaction and erectile function. Medium to large effect sizes and significant changes over time were observed in the ginseng condition for erection, ejaculation, perception of the problem, satisfaction, and overall scores for sexual dysfunction and erectile function (significant Time × Group-interactions).

Table 4
Sample characteristics of male patients, separately for patients in the ginseng condition ($n = 28$) and in the placebo condition ($n = 26$).

	Groups		Statistics
Dimensions	Ginseng	Placebo	
N	28	26	
	M (SD)	M (SD)	
Age (years)	38.25 (6.59)	42.27 (9.88)	$t(52) = 1.77$, $p = .08$
Duration of marriage (years)	12.21 (7.77)	15.04 (10.91)	$t(52) = 1.10$, $p = .28$
Number of children	1.14 (1.08)	1.65 (1.50)	$t(52) = 1.45$, $p = .15$
Age of first opium/opioid use (years)	27.07 (6.59)	23.88 (8.31)	$t(52) = 1.59$, $p = .12$
Duration of opium/opioid use (years)	8.82 (6.27)	14.35 (9.10)	$t(52) = 2.61$, $p = .01$
Methadone dosage (mg)	71.43 (24.38)	85.38 (19.89)	$t(52) = 2.29$, $p = .03$
Years of methadone substitution	3.57 (1.89)	3.54 (2.34)	$t(52) = 0.06$, $p = .96$
	N	N	
Opioids prevalently used: Opium/ opioid/ opium, opioid and tramadol/ heroin / opioid and heroin / methadone	1/22/2/0/2/1	1/17/4/2/1/1	$\chi^2(N = 54, df = 5) = 3.94$, $p = .61$
Highest educational level: Primary school/ secondary school / high school diploma/ bachelor or higher degree	4/12/11/1	4/7/11/4	$\chi^2(N = 54, df = 3) = 4.85$, $p = .18$
Occupation: Employed/unemployed	0/28	1/25	$\chi^2(N = 54, df = 1) = 1.02$, $p = .31$
Income: Low/middle/high income	9/16/3	9/13/4	$\chi^2(N = 54, df = 2) = 0.85$, $p = .78$

Table 6
Overview of inferential statistics for male sexual and erectile function as a function of Time (baseline, week 4), Group (ginseng, placebo) and the Time by Group interaction.

Degrees of freedom	Time (1, 52) F	η_p^2 [EF]	Group (1, 52) F	η_p^2 [EF]	Time × Group interaction (1, 52) F	η_p^2 [EF]
Excitement	1.00	0.02 [S]	0.90	0.02 [S]	2.82(*)	0.05 [S]
Erection	0.00	0.00 [S]	0.95	0.02 [S]	6.20*	0.11 [M]
Ejaculation	3.91(*)	0.07 [M]	1.15	0.02 [S]	5.27*	0.09 [M]
Perception of the Problem	0.22	0.00 [S]	1.01	0.02 [S]	23.81***	0.31 [L]
Satisfaction	2.16	0.04 [S]	10.15**	0.18 [L]	9.72**	0.16 [L]
BSFI total	4.23*	0.08 [M]	0.71	0.01 [S]	22.17***	0.30 [L]
IIEF total	0.19	0.01 [S]	5.65*	0.10 [M]	9.22**	0.15 [L]

Notes: BSFI = Brief Sexual Function Inventory. IIEF = International Index of Erectile Function.
EF = effect size; S = small effect size, M = medium effect size; L = large effect size.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

3.4. Side effects and drop-outs (female and male samples)

All participants completed questionnaires on side effects. Table 7 reports the number of participants per study condition, and the drop-out rates due to side-effects and non-compliance with the study conditions.

Adjuvant ginseng condition (number of patients): high blood pressure (1); sleeplessness (3); agitation (2); rash (1); diarrhea (2); stomach ache (2); total: 11 (multiple answers possible).

Placebo condition (number of patients): rash (2); stomachache (2) total: 4 (multiple answers possible).

Drop-out rate did not differ significantly or descriptively between the two groups (ginseng: drop-outs: 10 out of 37; placebo: drop-outs: 7 out of 37; $X^2(N = 91, df = 1) = 0.43, p = .512$).

4. Discussion

The key findings of the present double-blind, placebo-controlled clinical trial were that, compared to a placebo condition, adjuvant ginseng improved sexual function in both female and male patients with opioid use disorder (OUD), undergoing methadone-maintenance treatment (MMT), and with methadone-related sexual dysfunction. In our opinion, the present results add to the current literature in an important way as sexual dysfunctions are health concerns for both female and male opioid-dependent patients undergoing MMT.

We hypothesized that, compared to placebo, adjuvant ginseng would have a positive impact on sexual function among males with methadone-induced sexual dysfunction, and this was fully confirmed. Accordingly, the present findings match those of previous studies (Choi, 2008; Leung and Wong, 2013; Nocerino et al., 2000). However, the present findings expand upon previous results in that we were able to demonstrate such improvements among males with OUD and undergoing MMT.

Our research question was whether ginseng would also have benefits for female sexual function, and the answer was positive. To the best of our knowledge, this is the first randomized, double-blind clinical study to provide evidence for the positive influence of ginseng on the sexual functioning of females with OUD and undergoing MMT.

The data available to us could not provide any direct insight into the neurophysiological mechanisms underlying the positive effect of ginseng on the sexual functioning of the patients we studied. We therefore draw upon previous work for possible explanations. Following Leung and Wong (2013), sexual drive and sexual arousal are complex cognitive-emotional and neurophysiological processes. As regards neurotransmitters, increased dopamine (DA) release is associated with higher levels of desire, while higher acetylcholine levels (ACh) are associated with higher sexual arousal in those brain areas associated with pleasure and reward such as the nucleus accumbens (Berridge and Kringelbach, 2013, 2015; Kringelbach and Berridge, 2017); similarly, higher GABA levels in the same brain areas associated with pleasure and reward are associated with better odds of orgasm. In a study with rodents, ginsenoside Re, a major agent of ginseng, increased the level of extracellular DA and ACh (Shi et al., 2013) in the hippocampus and the mPFC. Likewise, Benishin (1992) reported that ginsenoside Rb1 improved the choline uptake of central cholinergic nerve endings in the hippocampus and to a lesser extent to the cortex in rat brains. Next, Leung and Wong (2013) reported in their review that ginsenosides Rb1, Rb2, Rc, Re, Rf, and Rg1 increased the levels of dopamine, acetylcholine and GABA(A) in the hippocampus and the mPFC; likewise, Rc is also an agonist for GABA(B) receptors, thus increasing the overall availability of GABA in the intracellular system (Yuan et al., 1998). It therefore appears that ginseng can regulate the hypothalamic-pituitary-gonadal axis (Kimura et al., 1994). This finding is of particular interest as methadone is a long-lasting and slow-acting opioid-agonist which stimulates the opioid-receptors in the CNS and which affects both the tuberoinfundibular and hypothalamic-pituitary-gonadal axes (de la Rosa and Hennessey, 1996). Ito et al. (2001) investigated the role of ginsenosides on the nitric oxide (NO) level, and summarized that ginsenosides increase NO, which is the key mediator for the up-regulation of cyclic guarosine monophosphate (cGMP), which in turn mediates circulation and sexual function, as NO appears to be highly involved in neurophysiological pathway of female sexual arousal. Though

Table 7
Overview of side effects and drop-out, separately for female and male participants and separately for the adjuvant ginseng or placebo condition.

Condition	Adjuvant ginseng				Placebo				Total DO SE	Total DO NON-C
	BL	End	DO SE	DO NON-C	BL	End	DO SE	DO NON-C		
Females	19	13	5	1	18	13	3	2	8	3
Males	28	24	4	0	26	24	0	4	4	4
Total	47	37	9	1	44	37	3	6	12	7

Notes: BL = baseline; DO = drop-out; SE= side effects; NON-C = non-compliance to the study conditions.

speculative, one might therefore argue that the active agents of ginseng such as ginsenosides Rb1, Rb2, Rc, Re, Rf, and Rg1 have the power to counteract methadone-induced downregulation of the hypothalamic-pituitary-gonadal axis. Last, in a clinical study of 66 males (30 with oligoastenospermic sine causa; 16 oligoastenospermic with idiopathic varicocele; 20 healthy controls) increases in plasma total and free testosterone, dihydrotestosterone (DHT), FSH and LH levels was observed after treatment with ginseng (Salvati et al., 1996).

Overall, while the present study provides no direct proof, it is quite possible that the active agents of ginseng such as ginsenosides Rb1, Rb2, Rc, Re, Rf, and Rg1 might have directly increased the release and availability of DA, Ach, GABA, DHT, FSH and LH, thus suggesting that ginsenosides counter-balanced a methadone-induced down-regulation of the hypothalamic-pituitary-gonadal axis. We believe this is why improvements in sexual function were observed in both male and females with OUD and undergoing MMT.

Individuals with OUD and undergoing MMT can struggle with a broad variety of health problems including malnutrition, hepatitis C virus (Altice et al., 2016; Novick and Kreek, 2008), and weight gain (Dursteler-MacFarland et al., 2010; Peles et al., 2016). Given this range of problems, it might be felt that sexual dysfunction should be of minor concern. However, as discussed in more detail elsewhere (Farnia et al., 2017a,b), couples' sexual activity serves a strong bond-reinforcing function (Buss, 2015; Meston and Buss, 2007). Not surprising, sexual satisfaction and overall satisfaction with life are closely linked (Clayton et al., 2014; Contreras et al., 2016; Fisher et al., 2015; Rosen et al., 2016). Given this, we believe that improving the sexual function of individuals with OUD and undergoing MMT is a legitimate treatment goal.

Despite the novelty of the findings they should be balanced against the following limitations. First, while we were able to show *that* ginseng had a favorable impact on sexual dysfunction, we were unable to explain at a physiological level, *why* this occurred. Future studies might therefore also assess biomarkers such as inflammatory markers, brain-derived neurotrophic factor (BDNF), cortisol, and hormones such as testosterone, prostaglandin, progesterone and estrogen. Second and more specifically, assessing female and male sexual hormones would have allowed us to determine whether changes observed at the behavioral level were mirrored at the hormonal level. Third, the inclusion and exclusion criteria were such that only a quite narrow range of patients were included. The present pattern of results may not therefore generalize to older or younger patients with OUD and under MMT, or to those with longer OUD durations or with other comorbidities such as neurodegenerative disorders, mood disorders, personality disorders, or impaired cognitive performances. Fourth, the particular pharmacological treatment and psychophysiological status of the female participants in this sample precludes generalizability of the findings to the female population as a whole. Fifth, since people taking other medications were excluded, it remains unclear how well these findings would generalize to people prescribed other medications, particularly medications that may interact with methadone and/or ginseng, or which independently affect sexual function. Sixth, Gerra et al. (2016) have queried whether a purely physiological explanation is sufficient to explain sexual dysfunction in male individuals undergoing MMT, as in their study erectile dysfunction was predicted by methadone dosages, while this was not the case for other aspects of sexual dysfunction, leading to the conclusion that sexual dysfunction, psychological issues and MMT are interlinked, and that more than physiological factors are involved. Seventh, as in previous studies (Farnia et al., 2015a,b, 2017a; Farnia et al., 2017b), there was no assessment of whether increased sexual desire had any impact on sexual behavior. It therefore remains unclear whether the participants in the present study more frequently sought intimate activity with their partners, and if so, whether they were successful or rejected, or whether they wanted more frequently extramarital affairs, or whether the odds of risky sexual behavior decreased. In our opinion, answering such questions is critical, as both males and females pursue long-term, but also short-term strategies to attract (sexual) partners (Buss, 2015; Meston and Buss, 2007). Eighth, given the adaptogenic properties of ginseng and its possible influence on learning and memory (Baeg and So, 2013), it would have been interesting to know whether participants also showed increases in physical activity or cognitive performance (Nocerino et al., 2000).

5. Conclusions

The present pattern of results suggests that, compared to placebo, adjuvant ginseng can counteract methadone-related sexual dysfunction in both female and male patients with opioid use disorder (OUD) and receiving methadone maintenance therapy (MMT).

Acknowledgments

We would like to thank Nick Emler (University of Surrey, Surrey UK) for proofreading the manuscript, and Laura Marbacher and Marika Thomaser (University of Basel, Basel, Switzerland) for data description. Further, we thank the Substance Abuse Prevention Research Center (SAPRC) and Clinical Research Development Unit (CRDU) of Emam Khomeini Hospital, University of Medical Sciences, Kermanshah (Iran) for their support, cooperation and assistance throughout the execution of the study (Grant number: 95179).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.05.004.

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