

Postorgasmic Illness Syndrome (POIS) in a Chinese Man: No Proof for IgE-Mediated Allergy to Semen

Nannan Jiang, MD,^{*1} Guangpeng Xi, MD,^{*1} Hongjun Li, PhD,[†] and Jia Yin, MD^{*}

^{*}Department of Allergy, Peking Union Medical College Hospital, Beijing, China; [†]Department of Urology Surgery, Peking Union Medical College Hospital, Beijing, China

DOI: 10.1111/jsm.12813

ABSTRACT

Introduction. Postorgasmic illness syndrome (POIS) is a rarely described syndrome characterized by transient flu-like symptoms and cognition disorders. Recent studies suggest that immunogenic reactivity to autologous semen is the underlying mechanism in POIS. However, there are no data published on immunoglobulin E (IgE)-mediated allergy to autologous semen in men without POIS.

Aim. The purpose of the current work was to characterize the first diagnosed POIS patient in China and to study the allergic response of autologous semen in the affected patient and in three healthy males.

Methods. Specific IgE was tested with seminal fluid and common perennial aeroallergens in vitro. Skin prick tests and intracutaneous tests with autologous diluted semen were performed in the patient and three healthy donors. The pattern of IgE reactivity to patient's semen was identified using immunoblotting and ELISA.

Main Outcome Measure. Clinical features of POIS, skin reactions with autologous diluted seminal fluid, and the IgE reactivity patterns of immunoblotting and ELISA in vitro.

Results. A patient was diagnosed with POIS. The patient complained of lifelong premature ejaculation symptoms and allergic rhinitis. Routine laboratory and hormonal assessments were generally within normal range. The patient had a positive skin test with his own semen. Three healthy donors also showed positive skin tests. No semen-specific IgE to autologous semen was detected in the serum of the affected patient or healthy males.

Conclusions. This is the first report of a man with POIS in China. He had positive skin reactions after injection of autologous seminal fluid but no detectable serum concentrations of specific IgE antibodies. IgE-mediated semen allergy in men may not be the potential mechanism of POIS. **Jiang N, Xi G, Li H, and Yin J. Postorgasmic illness syndrome (POIS) in a Chinese man: No proof for IgE-mediated allergy to semen. J Sex Med **;**:**-**.**

Key Words. Postorgasmic Illness Syndrome (POIS); Seminal Fluid; Autologous Immunoreactions; Chemical Imbalances

Introduction

Postorgasmic illness syndrome (POIS), a rarely described syndrome, was first reported and named by Waldinger and Schweitzer in 2002 [1]. Its manifestations were local allergic symptoms and transient flu-like illness, occurring within 30–60 minutes after ejaculation. The symptoms

often reached peak severity at the second day and gradually diminished in 2–7 days. Most patients tried to abstain from sexual activities to prevent the symptoms [1–4]. Waldinger and Schweitzer [5] proposed five preliminary diagnostic criteria after summarizing a cohort of 45 Dutch Caucasian males with POIS.

The prevalence of POIS is unknown. There are only around 50 cases recorded in the literature over the last 10 years. In the United States, POIS

[†]These authors contributed equally to this work.

is recognized as a rare disorder by the National Institute for Health (NIH), Office of Rare Disease Research. However, the number of self-reported cases in internet forums is growing rapidly. It is likely that POIS might be underrecognized and underdiagnosed.

Despite its significant impact on quality of life, little is known about POIS's etiology. Initially, Waldinger and Schweitzer [1] stated that during ejaculation, many substances were released into the blood, and an allergic reaction might occur in response to one or more of them. Ashby and Goldmeier [3] proposed that there was a disordered cytokine or neuroendocrine response driving symptoms of POIS. Dexter [6] speculated that POIS could be caused by a lack of progesterone. In 2011, a study by Waldinger and collaborators [5] showed that 88% of affected patients had a positive skin test for autologous semen and concluded that type I and type IV allergy to their own semen may contribute to symptoms of the illness. The "immunogenic/allergy" mechanism was subsequently supported by successful hypsensitization treatment with increasing doses of autologous semen in two males [7]. There are obvious limitations to these two studies. One is that the absence of healthy male controls reduced the validity of skin test results. The second is that the latter study is not a randomized placebo-controlled clinical trial. Therefore, the treatment efficacy is uncertain.

Human seminal plasma allergy is a rare affair and has only been reported in women. Positive skin testing or serum-specific immunoglobulin E (IgE) to whole seminal fluid or fractionated seminal plasma proteins were demonstrated in women with seminal plasma hypersensitivity. Farley [8] proposed that men with POIS involved an autologous hyper-reactive immune response to semen fluid. Although Waldinger et al. [5] demonstrated POIS patients had a positive skin test for autologous semen, total IgE was low in both men with POIS and additional various forms of allergies, as in men with POIS without atopic constitution. However, their study did not measure serum-specific IgE in the POIS patients. Allergy data in healthy males without POIS have also never been published.

This study was performed with the following objectives: (i) to characterize a diagnosed POIS patient in China; (ii) to study the allergic response of autologous semen in a POIS patient and in healthy males; and (iii) to study semen-specific IgE in the sera of an affected patient.

Materials and Methods

Patient Presentation

A 61-year-old male visited our allergy department complaining of flu-like symptoms after ejaculation (including spontaneous ejaculations, masturbation, and intercourse) over 40 years. The symptoms began 60 minutes after ejaculation and were ranged from severe to moderate, mainly including extreme fatigue and exhaustion, feelings of extreme dryness—heat inside the body (particularly in the lower right back region), perspiration, muscle tension in the lower limbs, difficulty concentrating, general irritability, memory problems, foggy feeling in the head, nasal congestion, sneezing and running nose, sore throat, itching eyes, and photophobia. He had no rash or swelling around his genitalia or skin. This collection of symptoms peaked on day 2 or 3 and lasted to day 7, when the symptoms gradually disappeared simultaneously. The patient experienced the symptoms for the first time after spontaneous ejaculations in puberty. He often avoided sexual activity for fear of experiencing these terrible symptoms. He had normal erectile function and sexual desire but complained of premature ejaculation (PE). The intravaginal ejaculation latency time was less than 1 minute. The patient was in a stable marriage for 30 years, and his wife was currently 58 years old. The couple had two children and lived healthy life. He had a past medical history of allergic rhinitis, and the symptoms of rhinitis became worse when he entered a damp environment. He denied any regular or recreational drug use. On examination, the patient had fair general health and had complete secondary sex characteristics. The patient was diagnosed with insomnia, anxiety, and slight obsessive-compulsive disorder by a neurologist. The control group included three healthy male volunteers with a mean age of 28 years, who denied having experienced symptoms of POIS. They were all willing to take part in skin tests, but only two of them agreed to provide serum for testing. Informed consent for study participation was obtained by the patient and control group.

Semen Allergen Extract

Fresh seminal fluid was collected into 15-mL sterile centrifuge tubes by masturbation and allowed to liquefy undisturbed for 30 minutes at room temperature. The ejaculate was then diluted with 0.9% saline to a concentration of 1:1,000, 1:100, and 1:10 for skin testing. The remaining samples were stored at -80°C until use.

Table 1 Summary of routine laboratory investigations

Test	Affected patient result	Normal lab range
FSH (mIU/mL)	9.07	2.97–6.82
LH (mIU/mL)	4.25	1.18–3.54
PRL (ng/mL)	9.8	<18.5
E2 (pg/mL)	43.07	<31.64
T (ng/mL)	4.39	3.80–7.77
PSA (ng/mL)	2.49	0–4.00
FT3 (pmol/L)	4.76	2.62–6.49
FT4 (pmol/L)	10.82	9.01–19.04
STSH (μIU/mL)	1.49	0.35–4.94

The values in bold are results which level is higher than normal lab range

Skin Tests

The patient and three healthy volunteers underwent intracutaneous tests (IC) and skin prick tests (SPTs) with diluted seminal fluid, according to a standard protocol. Positive and negative controls consisted of histamine (0.1 mg/mL) and 0.9% saline solution, respectively.

Skin reactions to autologous semen were interpreted at 15 minutes after skin testing and found to be positive when the diameter of the wheal was >5 mm with local erythema. The following grading system was used [9]: (i) wheal <5 mm and no or small erythema = negative; (ii) wheal 5–10 mm and small erythema = 1+; (iii) wheal 10–15 mm and erythema >10 mm = 2+; (iv) wheal >15 mm and erythema >10 mm or with pseudopod formation = 3+; and (v) local response as grade 3+, accompanying systemic allergic reaction = 4+.

Specific IgE Determination

Specific IgE measurement against human seminal fluid, mites, molds, and cockroaches was carried out by using a fluorescent enzyme immunoassay (Unicap, Pharmacia, Sweden) using a standard procedure.

SDS-PAGE and Western Blotting

Semen extracts from the patient and two healthy controls were analyzed using SDS-PAGE with a NuPAGE® Novex 4–12% Bis-Tris precast gel (Invitrogen, Carlsbad, CA, USA) under reducing and nonreducing conditions. Twenty micrograms of protein was applied per lane. After electrophoresis, gels were stained with 0.1% Coomassie Brilliant Blue R-250 dissolved in a methanol/acetic acid/distilled water (4:1:5) solution. The proteins in the PAGE were transferred to a PVDF membrane. The membrane was saturated with 5% skim milk in PBST for 2 hours at room temperature and incubated with the serum of the affected patient and two

healthy controls at a dilution of 1:5 overnight at 4°C. The strips were washed with 0.05% Tween in PBS and incubated for 2 hours at room temperature with a 1:1,000 dilution of horseradish peroxidase (HRP) conjugate antihuman IgE (Abcam, Cambridge, UK). IgE-binding proteins were detected using BM Chemiluminescence Blotting Substrate (Roche Molecular Biochemicals, USA), according to the manufacturer's instruction.

ELISA

Autologous semen specific IgE was investigated using ELISA. Wells of a 96-well plate were coated with 10 μg of seminal fluid diluted in carbonate buffer (PH 9.6), incubated overnight at 4°C, washed with 0.5%-Tween-20/PBS (PBST) three times, and blocked 2 hours with 1% bovine serum albumin at 37°C. Autologous sera samples diluted 1:3 in blocking buffer were added and incubated overnight at 4°C, washed, and incubated with 100 μl of antihuman IgE–HRP conjugate (Abcam). The assay was developed with substrate solution (Sigma, St. Louis, MO, USA) in the dark and the enzymatic reaction stopped after 30 minutes of substrate incubation by addition of 0.5 M sulfuric acid. Absorbance was measured at 495 nm using a spectrophotometer (Spectra MAX 250, Molecular Device, Sunnyvale, CA, USA). All the determinations were done in duplicate.

Results

This patient was clinically diagnosed with POIS based on the five criteria published by Waldinger et al. and combined with lifelong PE and allergic rhinitis. Routine laboratory and hormonal assessments were generally normal except for a slightly higher serum concentration of FSH, LH, and E2 (Table 1). Prostate ultrasonography and brain MRI did not reveal any abnormality. The total IgE (3,292 KU/L) was higher than normal (<60 KU/L). Specific IgE against house dust mites, mold, and cockroaches were also detected. Specific IgE levels against seminal fluid were less than 0.35 KU/L. Detailed results of IgE testing are shown in Table 2.

Table 2 Total and specific IgE levels in the affected patient's serum

Specific IgE	Affected patient results	Normal lab range
Seminal fluid	0.03 KUA/L	<0.35 KUA/L
Cockroach	7.68 KUA/L	<0.35 KUA/L
Mold	1.09 KUA/L	<0.35 KUA/L
House dust mite	14.6 KUA/L	<0.35 KUA/L

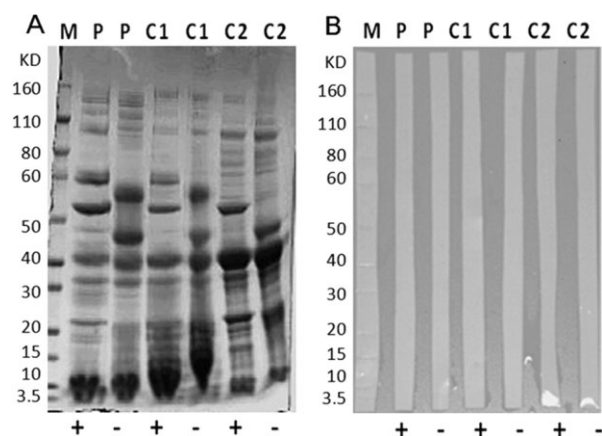


Figure 1 SDS-PAGE and IgE immunoblotting of the patient and two controls' seminal fluid. SDS-PAGE (A): lane M, molecular mass markers; lane P, affected patient's seminal fluid; lane C1, C2, control's seminal fluid. IgE Immunoblotting (B): lane M, molecular mass markers; lane P, electrophoresis with affected patient's seminal fluid and incubation with the patient's serum; lane C1, C2, electrophoresis with C1, C2's seminal fluid, and incubation with their own serum. The + and – symbols indicate the presence and absence of DTT, respectively.

SDS-PAGE and Western Blotting

SDS-PAGE of seminal fluid showed multiple protein bands with an apparent molecular mass ranging from 3.5 to 160 KD (Figure 1A). IgE immunoblotting of autologous seminal fluid samples under nonreducing and reducing conditions, incubated with the serum of the affected patient and two healthy controls, revealed no IgE-binding bands (Figure 1B).

ELISA

Semen-specific IgE was not demonstrated by ELISA in the affected patient or C1 and C2

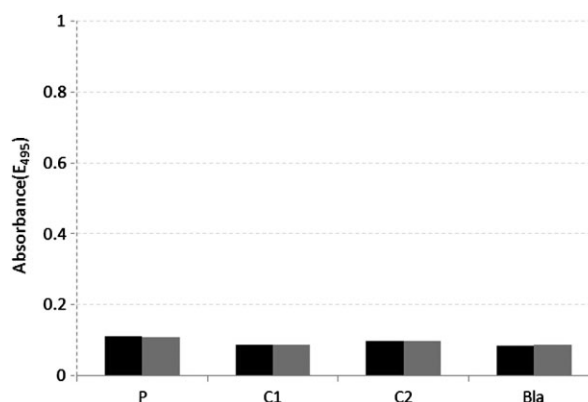


Figure 2 IgE reactivity of sera to autologous semen measured by ELISA. P, affected patient; C1, control 1; C2, control 2; Bla, blank control

(Figure 2). The absorbance of affected patient, control 1 and control 2, was similar to blank.

Skin Testing

The affected patient and three healthy volunteers received SPTs and ICs with autologous semen. The results are summarized in Table 3. The IC with dilutions of autologous seminal plasma from the affected patient resulted in an 9-mm wheal at a 1:100 dilution. SPTs revealed a 5-mm wheal at a 1:10 dilution. The ICs (titer 1:10 and 1:100) were positive in three healthy control volunteers. The SPT was negative in three healthy control volunteers.

Discussion

In the current study, a clinically diagnosed case of POIS in China is reported. Only around 50 known cases have been recorded in the literature over the

Table 3 Intracutaneous skin tests and skin prick tests

Skin test	Concentration	P		C1		C2		C3	
		W (mm)	E (mm)	W (mm)	E (mm)	W (mm)	E (mm)	W (mm)	E (mm)
ICs	1:10	UD	UD	UD	UD	12	35	13	25
	1:100	9	35	5	10	11	28	4	4
	1:1,000	7	20	6	6	3	3	3	3
	1:10,000	7	15	3	3	3	3	UD	UD
	0.01 mg/mL Histamine	9	30	7	20	11	23	12	28
	0.9% Saline	3	3	3	3	3	3	3	3
SPTs	1:1	3	3	UD	UD	UD	UD	UD	UD
	1:10	5	30	3	3	3	3	3	3
	1:100	5	7	3	3	3	3	3	3
	1:1,000	UD	UD	UD	UD	UD	UD	3	3
	0.01 mg/mL Histamine	5	30	3	20	7	25	7	31
	0.9% Saline	3	3	3	3	3	3	3	3

Results are expressed as wheal and erythema diameter, as described in a previous work [9]

The values in bold are results which level is higher than normal lab range

C = health control; E = erythema; IC = intracutaneous skin test; P = patient; SPT = skin prick test; W = wheal

last 10 years. Consistent with other reported cases [1–4], this patient had normal routine laboratory and hormonal assessments. Considering the patient's age, the slightly high concentrations of FSH, LH, and E2 were understandable. The patient had also experienced lifelong PE. This is consistent with results reported by Waldinger et al., who cited 56% patients of POIS had lifelong PE [5].

There is no data available on interactions between POIS and PE. The patient had atopic rhinitis caused by house mites and mold. In the group of 45 Caucasian males, reported by Waldinger et al. [5], 26 (58%) reported an atopic constitution, similar to other reported cases [4]. However, unlike the published cases, our patient suffered from slight obsessive-compulsive disorder and anxiety. The relationship between POIS and mental disorders has not been defined.

To date, little is known about the etiology of POIS. Waldinger et al. [5] hypothesized that males with POIS develop an immunogenic reactivity to their own semen. This was supported by the positive skin tests with diluted autologous seminal fluid and by successful hyposensitivity therapy in men with POIS [5,7].

We identified an affected patient with a mildly positive reaction (grade 1+) to intracutaneous skin injection and skin prick testing of seminal fluid at a 1:10 and 1:100 dilutions. Waldinger et al. [7] reported two patients with a significantly positive reaction (grade 4+) to seminal fluid at a 1:40,000 dilution. The current patient also underwent skin testing with a 1:40,000 dilution, but the result was negative (data not shown). Nguyen et al. [10] performed a skin prick and intradermal testing with a fresh sample of autologous semen in affected men, with mildly positive results. Intradermal testing, however, was significantly positive and associated with a larger reaction. Difference in the skin reactions to seminal fluid may be explained by the different grading systems and skin test procedures used.

One interesting finding of the current study was that three healthy control individuals had positive skin reactions to autologous seminal fluid. Their responses were more pronounced than that of the affected patient. The IC (titer 1:10 and 1:100) was grade 2+ positive, while the SPT was negative in three healthy control individuals.

Human seminal plasma has a variety of inflammatory cytokines and chemokines including TGF- β 1, CXCL8 (ex-IL-8), GRO (CXCL1/Th17), monocyte chemotactic protein 1 (MCP-1), IL-13,

and IL-17 [11], some of which can activate basophils or mast cells; for example, Conti et al. [12] showed that MCP-1 has chemotactic activity for mast cells and plays a fundamental role in the release of histamine. Geiser et al. [13] reported that IL-8 and GRO proteins were active toward basophils as indicated by chemotaxis and intracellular calcium changes in concentration. In addition to the presence of these immunologic factors in seminal plasma, high concentrations of spermine (2–15 mmol/L) were observed in seminal fluid [14]. This may injure endothelial cells. Yang et al. demonstrated that 200 μ mol/L exogenous spermine can induce injury to human umbilical vein endotheliocytes. It is here supposed that these substances may directly stimulate the skin and cause wheals and erythema when injected into the skin of both patients and healthy controls.

Semen allergy is a rare phenomenon. Previously, it has only been reported in women. Most of the symptoms are induced by classical IgE-mediated reactions. Women with seminal plasma hypersensitivity demonstrate positive skin tests or serum-specific IgE to whole seminal fluid or fractionated seminal plasma proteins. But there is no reported data regarding IgE detection in POIS. We did not detect seminal fluid-specific IgE in the serum of patients using ELISA or Western blotting.

The time course of POIS is consistent with that of type I allergic reaction, occurring either immediately or after 2–8 hours. However, the complaints and symptoms of POIS, especially the flu-like symptoms, are not consistent with a classic type I hypersensitivity reaction but consistent with type IV reaction according to Waldinger et al. [5]. Treatment with antihistamines is ineffective.

The symptoms of POIS are similar to those of "opioid withdrawal syndrome," which includes physical (flu-like symptoms, perspiration, and rhinitis) and psychological symptoms (anxiety, depression, and difficulty concentrating). These symptoms can last 2–7 days [15]. Opioids are involved in mediation of positive affective states generated by the execution of sexual behavior [16]. The μ -opioid receptors are thought to play a crucial role in controlling this behavior [17]. We supposed that patients suffering from POIS may have a disorder of the endogenous μ -opioid receptor system. Orgasm consumes large amounts of endogenous opioids in these patients, which causes a series of symptoms similar to opioid withdrawal symptoms. In addition, the patient was diagnosed with insomnia, anxiety, and slight obsessive–

compulsive disorder; these psychological factors may increase awareness to body's changes.

In conclusion, we present the first case of diagnosed POIS in China. Both the patient and healthy males had positive reactions to autologous seminal fluid. No semen-specific IgE was detected in men with POIS. IgE-mediated semen allergy in men might not be the mechanism of POIS as was found in the POIS cohort study published by Waldinger et al. [5]. It is here postulated that chemical imbalances in the brain might be the physiological basis for this condition and that psychological factors could be the risk factors. Further research into the neurobiochemical sequelae of orgasm might be useful in understanding the pathology of POIS.

Acknowledgment

We thank the patient and healthy controls for their contribution to the research, and we also want to thank Wei Zhang who performed the skin testing in this study, Prof. Xueyan Wu and Prof. Xinhua Wan who gave us great help in the consultation.

Corresponding Author: Jia Yin, MD, Department of Allergy, Peking Union Medical College Hospital (East), No.1 Shuaifuyuan Wangfujing, Dongcheng District, Beijing 100730, China. Tel: 86-10-65296346; Fax: 86-10-65296346; E-mail: doctoryinjia@163.com

Conflict of Interest: The author(s) report no conflicts of interest.

Statement of Authorship

Category 1

(a) Conception and Design

Jia Yin

(b) Acquisition of Data

Guangpeng Xi

(c) Analysis and Interpretation of Data

Nannan Jiang; Hongjun Li; Jia Yin

Category 2

(a) Drafting the Article

Nannan Jiang

(b) Revising It for Intellectual Content

Guangpeng Xi; Hongjun Li; Jia Yin

Category 3

(a) Final Approval of the Completed Article

Jia Yin

References

- 1 Waldinger MD, Schweitzer DH. Postorgasmic illness syndrome: Two cases. *J Sex Marital Ther* 2002;28:251–5.
- 2 Shigeta K, Kikuchi E, Matsushima M, Daimon T, Yazawa S, Ando T, Maeda T, Miyajima A, Nakagawa K, Oya M. A clinical case of suspected postorgasmic illness syndrome. *J Sex Med* 2013;10:220.
- 3 Ashby J, Goldmeier D. Postorgasm illness syndrome—a spectrum of illnesses. *J Sex Med* 2010;7:1976–81.
- 4 Attia A, Al-Ziny M, Yasien H. Post-orgasmic illness syndrome: A case report. *F1000 Research* 2013;2:113.
- 5 Waldinger MD, Meinardi MM, Zwinderman AH, Schweitzer DH. Postorgasmic illness syndrome (POIS) in 45 dutch Caucasian males: Clinical characteristics and evidence for an immunogenic pathogenesis (part 1). *J Sex Med* 2011;8:1164–70.
- 6 Dexter S. Benign coital headache relieved by partner's pregnancies with implications for future treatment. *BMJ Case Rep* 2010;2010.
- 7 Waldinger MD, Meinardi MM, Schweitzer DH. Hyposensitization therapy with autologous semen in two dutch Caucasian males: Beneficial effects in postorgasmic illness syndrome (POIS; part 2). *J Sex Med* 2011;8:1171–6.
- 8 Farley SJ. Postorgasmic illness syndrome. *Nat Rev Urol* 2011;8:121.
- 9 Ye S. Allergy. Beijing, China: Science Press; 1998.
- 10 Nguyen T, Dimov V, Bewtra A. Seminal fluid hypersensitivity in a man with postorgasmic illness syndrome (POIS). *Annals of Allergy Asthma & Immunology* 2011;107:A48.
- 11 Politch JA, Tucker L, Bowman FP, Anderson DJ. Concentrations and significance of cytokines and other immunologic factors in semen of healthy fertile men. *Hum Reprod* 2007;22:2928–35.
- 12 Conti P, Boucher W, Letourneau R, Feliciani C, Reale M, Barbacane RC, Vlagopoulos P, Bruneau G, Thibault J, Theoharides TC. Monocyte chemotactic protein-1 provokes mast cell aggregation and [3h]5ht release. *Immunology* 1995;86:434–40.
- 13 Geiser T, Dewald B, Ehrenguber MU, Clark-Lewis I, Baggiolini M. The interleukin-8-related chemotactic cytokines GRO alpha, GRO beta, and GRO gamma activate human neutrophil and basophil leukocytes. *J Biol Chem* 1993;268:15419–24.
- 14 Yang JX, Ma Y, Mu S, Liu DP, Liang CH, Xu CQ, Zhang ZR. Damaging effects of exogenous spermine on HUVECs and its possible mechanism. *Chinese Journal of Pathophysiology* 2009;25:1903–6.
- 15 Benich JJ III. Opioid dependence. *Prim Care* 2011;38:59–70. vi.
- 16 Parra-Gamez L, Garcia-Hidalgo A, Paredes RG. Infusion of endomorphin-1 (em-1) in the MPOA and the me modulate sexual and socio-sexual behavior in the male rat. *Brain Res* 2013;1517:36–43.
- 17 Pfaus JG. Pathways of sexual desire. *J Sex Med* 2009;6:1506–33.