Arab Journal of Urology

ISSN: (Print) 2090-598X (Online) Journal homepage: https://www.tandfonline.com/loi/taju20

On-demand use of tramadol, sildenafil, paroxetine and local anaesthetics for the management of premature ejaculation: A randomised placebo-controlled clinical trial

Tarek A. Gameel, Ahmad M. Tawfik, Mohamed O. Abou-Farha, Mohamed G. Bastawisy, Mohamed A. El-Bendary & Abd El-Naser El-Gamasy

To cite this article: Tarek A. Gameel, Ahmad M. Tawfik, Mohamed O. Abou-Farha, Mohamed G. Bastawisy, Mohamed A. El-Bendary & Abd El-Naser El-Gamasy (2013) On-demand use of tramadol, sildenafil, paroxetine and local anaesthetics for the management of premature ejaculation: A randomised placebo-controlled clinical trial, Arab Journal of Urology, 11:4, 392-397, DOI: 10.1016/j.aju.2013.05.003

To link to this article: https://doi.org/10.1016/j.aju.2013.05.003

Published online: 05 Apr 2019.

Arab Journal of Urology (2013) **11**, 392–397

Arab Journal of Urology
(Official Journal of the Arab Association of Urology)

www.sciencedirect.com

ANDUROLOGY / SEXUAL MEDICINE
ORIGINAL ARTICLE

On-demand use of tramadol, sildenafil, paroxetine and local anaesthetics for the management of premature ejaculation: A randomised placebo-controlled clinical trial

Tarek A. Gameel, Ahmad M. Tawfik, Mohamed O. Abou-Farha *, Mohamed G. Bastawisy, Mohamed A. El-Bendary, Abd El-Naser El-Gamasy

Urology Department, Tanta University Hospitals, Tanta, Egypt

Received 25 February 2013, Received in revised form 22 May 2013, Accepted 23 May 2013
Available online 29 June 2013

KEYWORDS

Premature ejaculation;
Tramadol;
Sildenafil;
Paroxetine;
Local anaesthetics

ABBREVIATIONS

PE, premature ejaculation;
IELT, intravaginal ejaculation latency time;
SSRI, selective serotonin-reuptake inhibitor;

Abstract ***Objectives:*** To compare the clinical efficacy of the on-demand use of four drugs in the management of patients with premature ejaculation (PE), as the off-label use of selective serotonin-reuptake inhibitors and topical penile anaesthetics is frequently indicated for the management of patients with PE, and tramadol HCl and sildenafil citrate were also tried for managing this disorder, but with recommendations based on weak evidence.

Patients and methods: This was a single-centre, single-blind, placebo-controlled clinical trial conducted on 150 patients who had PE for >1 year. Patients were randomised equally into five groups. On-demand tramadol, sildenafil, paroxetine, local lidocaine gel or placebo was given for patients in groups 1–5, respectively. During the month before treatment, the intravaginal ejaculation latency time (IELT) and sexual satisfaction scores (on a 0–5-point scale) were measured and compared to the mean IELT and sexual satisfaction scores recorded during 4 weeks of on-demand drug administration, with monitoring of any possible side-effects.

Results: Tramadol-treated patients had a significantly longer mean (SD) IELT, of 351 (119) s, than the other groups. Local anaesthetic was significantly better than

* Corresponding author. Tel.: +20 1223950868.
E-mail address: m_farha1975@yahoo.com (M.O. Abou-Farha).
Peer review under responsibility of Arab Association of Urology.

Production and hosting by Elsevier

http://dx.doi.org/10.1016/j.aju.2013.05.003

ED, erectile dysfunction;
PDE-5i, phosphodiesterase-5 inhibitor;
IIEF-5, International Index of Erectile Function-5.

paroxetine in prolonging the IELT, at 278 (111) vs. 186 (65) s, respectively. The improvement in sexual satisfaction was significantly better in the sildenafil group, with a mean (SD) improvement of 2.9 (1) points, than in the paroxetine and local anaesthetic groups, at 2.2 (0.9) and 1.9 (0.9) points, respectively.

Conclusions: The four drugs significantly improved IELT values over placebo. Tramadol was associated with significantly longer IELT values, whilst sildenafil induced significantly better sexual satisfaction than the other drugs. The four drugs had tolerable side-effects.

Introduction

Premature ejaculation (PE) is one of the most common male sexual disorders, with prevalence rates of 20–30% in the general male population [1]. Although PE remains poorly defined and inadequately characterised, it represents a frustrating problem that can reduce the enjoyment of sex, harm relationships and impair the quality of life. To date, PE has no universally agreed diagnostic criteria or ideal definition. According to the Diagnostic and Statistical Manual of Mental Disorders [2], PE is defined as 'persistent or recurrent ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the subject wishes it', and is associated with 'marked distress or interpersonal difficulty'.

Recent guidelines [3–5] suggest combining the stopwatch-measured intravaginal ejaculatory latency time (IELT) with patient-reported outcome questionnaires. It was suggested that men with an IELT of <60 s and 60–120 s have 'definite' PE and 'probable' PE, respectively [6,7].

The treatment of PE should primarily attempt to alleviate concerns about the condition, as well as increase sexual satisfaction in patients and their partners. Many treatment options are described for those patients, including sexual education, behavioural therapy and pharmaceutical treatment [8–12].

Off-label use and/or clinical trials involving selective serotonin-reuptake inhibitors (SSRIs), e.g., paroxetine, or local penile anaesthetics, sildenafil citrate and tramadol HCl are frequently reported for managing PE [13–16], but the recommendations are based on weak evidence. In the present study we report the first placebo-controlled clinical trial comparing the clinical efficacy of these four agents in managing patients with PE, using the IELT as an objective outcome variable.

Patients and methods

Between November 2009 and January 2012, 150 sexually active healthy men with PE were recruited for this placebo-controlled clinical trial. The study protocol was reviewed and approved by the local ethics committee, with informed consent taken from all participants.

For all participants, a detailed medical and sexual history was taken (especially the onset, frequency and duration of PE, including the proportion of sexual attempts that are affected by PE), and discussed. In addition, a careful clinical examination was conducted to exclude patients with organic or neurological problems.

Patients included were those with PE for >1 year and who had an IELT of <2 min in $>75\%$ of episodes of vaginal sexual intercourse over a 2-week period. Patients excluded from the study were those with an International Index of Erectile Function-5 (IIEF-5) score of <22, an unstable relationship with the partner, or with drug abuse, diabetes mellitus, urogenital diseases, hepatic or renal impairments, or those receiving medication for psychiatric problems.

The study was designed as a single-blind placebo-controlled clinical trial in which patients were randomly divided into five groups (30 patients each), according to the treatment given. The sample size was assessed prospectively to provide a 95% power to detect a difference of 80–90 s between mean IELT values before and after treatment (with an expected change in SD of $\approx$90 s, based on previous studies comparing results before and after treatment with different agents), with a significance level (α) of 0.05.

The distribution of patients among the five groups was based on shuffling coded cards, so that patients were unaware of the nature of the drugs received. Group 1 was given on-demand tramadol HCl (50 mg tablets) 2 h before intercourse. Group 2 was given on-demand sildenafil citrate (50 mg tablets) 1 h before intercourse. Group 3 received on-demand paroxetine (20 mg tablets) 4 h before intercourse. Group 4 received a local anaesthetic in the form of lidocaine gel 2.5%, applied to the penile shaft and glans 15 min before intercourse. Group 5 was a placebo arm and received oral multivitamin pills 1–4 h before intercourse. To ensure that patients were unaware of the drug used, those receiving oral medication were also given local penile lubricating jelly before intercourse, whilst group 4 was also given oral multivitamin pills 1–4 h before intercourse.

During the 4 weeks before receiving the medication all patients were instructed to have twice weekly vaginal sexual intercourse and record their IELT (starting from

the time of intromission until ejaculation), using a stopwatch. Also, overall sexual satisfaction during the same period was assessed using 0–5-point scale, where '0' indicated never satisfied in any coital act, and '5' indicated very satisfied in all episodes of vaginal sexual intercourse. The mean IELT for each patient and his sexual satisfaction score were taken as the baseline (pre-treatment) record.

All drugs/treatments were taken for 4 weeks and patients were instructed to have twice weekly vaginal sexual intercourse. Patients were followed up weekly, when they were asked about their IELT values and any possible side-effects. At the end of the study the patients were again assessed for their overall sexual satisfaction, using the same 0–5-point scale.

The mean IELT and sexual satisfaction scores for each patient recorded during the study period were then taken as the post-treatment record. The improvement in the sexual satisfaction score for each patient was then calculated as the post-treatment score minus the pre-treatment score.

At the end of the study the number of nonresponders (defined as those who still had an IELT of <2 min in at least six of the eight vaginal sexual coital episodes) in each group was calculated. The overall success rate was defined as the proportion of responders in each group.

The variables, including age, and values measured before and after treatment, are presented as the mean (SD), with Student's paired *t*-test used to compare values within the same group, and a one-way anova and Scheffe test used to compare variables between the different groups. The chi-squared test was used to compare the overall success rates in different groups.

Results

The records of 144 patients (29, 30, 28, 30 and 27 in groups 1–5, respectively) were available at the end of the study. The mean (SD, range) age of the patients was 32.8 (3.8, 26–39) years. The mean patient age and duration of PE were similar amongst all the groups ($P > 0.05$).

There was no significant difference in the baseline IELT values of the five groups ($P > 0.05$; Table 1). The mean IELT values after treatment in the active-treatment groups (1–4), but not in group 5 (placebo) were significantly better than at baseline ($P < 0.05$; Table 1). Comparing the mean IELT values in different groups showed that tramadol-treated patients had a significantly longer IELT, of 351 (119) s, than had those treated with sildenafil, paroxetine or local anaesthetic, with values of 228 (69) s, 186 (65) s and 278 (111) s, respectively ($P < 0.05$; Table 1). In addition, the local anaesthetic was associated with a longer IELT than was paroxetine ($P < 0.05$). The increase in IELT in the sildenafil group was not statistically significantly different from that in the paroxetine or local anaesthetic groups ($P > 0.05$).

There were three, five, seven, six and 25 nonresponders in the five groups, respectively. The overall success rates (the proportion of responders) in the active treatment groups were 90%, 83%, 75% and 80%, respectively, which was significantly higher than in the placebo group ($P < 0.05$). There was no statistically significant difference in the success rates between the active-treatment groups ($P > 0.05$).

Systemic and local side-effects (e.g., headache, flushing, drowsiness, numbness, etc.) were monitored during the study period, and all of them were tolerable (Table 2).

The mean values for the overall sexual satisfaction scores were similar in all groups before the start of treatment (Table 1). At the end of the study the mean improvement in the sexual satisfaction scores of the active-treatment groups was significantly higher than in the placebo group ($P < 0.05$). The greatest improvement was in the sildenafil-treated patients, of 2.9 (1) points, which was significantly better than in the paroxetine and local anaesthetic groups, of 2.2 (0.9) and 1.9

Table 1 The IELT and the sexual satisfaction scores, before and after treatment in all groups.

Mean (SD)	Group				
	1 (Tramadol)	2 (Sildenafil)	3 (Paroxetine)	4 (Anaesthetic)	5 (Control)
IELT (s)					
Before	67.2 (26.6)	58.3 (29.3)	69.6 (28.1)	54.2 (29.8)	61.3 (30.5)
After	351.2 (119.3)[a]	228.3 (68.7)	186.3 (64.8)	278.1 (111.2)[b]	81.1 (32.3)[c]
Sexual satisfaction score					
Before	1.07 (0.78)	1.17 (0.75)	1.04 (0.64)	1.10 (0.80)	1.04 (0.64)
After	3.69 (0.71)[d]	4.10 (0.84)[e]	3.25 (0.65)	2.97 (0.49)	1.18 (0.72)

[a] IELT: significantly higher vs. other groups ($P < 0.05$).
[b] IELT: significantly higher vs. paroxetine group ($P < 0.05$).
[c] IELT: significantly lower vs. active-treatment groups ($P < 0.01$).
[d] Improvement in sexual satisfaction score: significantly higher vs. lidocaine group ($P < 0.05$).
[e] Improvement in sexual satisfaction score: significantly higher vs. paroxetine or lidocaine groups ($P < 0.05$).

Table 2 The side-effects in the different treatment groups during the study period.

Side-effect	Group				
	1	2	3	4	5
Sleep disturbance	16 (55)	6 (20)	8 (29)	0	0
Dry mouth	5 (17)	8 (27)	3 (11)	0	0
Nausea	10 (35)	13 (43)	3 (11)	0	0
Dizziness	4 (14)	7 (23)	3 (11)	0	0
Fatigue	7 (24)	12 (40)	6 (21)	0	0
Vomiting	3 (10)	4 (13)	3 (11)	1 (3)	0
Sweating	4 (14)	4 (13)	3 (11)	0	0
Constipation	4 (14)	0	5 (18)	0	2 (7)
Parathesia	0	0	1 (4)	1 (4)	0
Headache	3 (10)	13 (43)	8 (29)	0	0
Flushing	0	9 (30)	3 (11)	0	0
Nasal congestion	0	6 (20)	0	0	0
Hypotension	0	4 (13)	3 (11)	0	0
Penile anaesthesia	0	0	0	22 (73)	0
Allergy/reaction	0	2 (7)	0	1 (3)	0

(0.9) points, respectively ($P < 0.05$). Tramadol and paroxetine were associated with comparable drug-induced improvements in sexual satisfaction ($P > 0.05$), but tramadol was associated with significantly better sexual satisfaction scores than was the local anaesthetic ($P < 0.05$).

Discussion

The exact causes of PE are still considered unclear. Several mechanisms, including organic and psychogenic factors, have been proposed for this problem. For lifelong PE, animal and human psycho-pharmacological studies suggested that there are changes related to central serotonergic neurotransmission, e.g., 5-hydroxytryptamine-2C receptor hyposensitivity and/or 1A receptor hypersensitivity, as proposed mechanisms. An inherited predisposition was also suggested. Some reports showed a higher incidence of PE in Islamic countries [8].

As there is no definite cause, there is no standard treatment. Reports of medications used to manage PE are challenging both in treatment concepts and in speculation about the cause of the problem. Clinicians have long been aware that several drug classes improve PE, such as tricyclic antidepressants, SSRIs, and others [17].

Tramadol is a synthetic opioid-like drug, and the exact mechanism of action of tramadol in delaying ejaculation is not well known, but its weak serotonin- and noradrenaline-reuptake inhibitory action is unlikely to be the only explanation for its effectiveness in patients with PE. It is possible that it has other central actions on serotonin receptors, but this hypothesis requires further investigation [18].

Clinical reports of the on-demand use of 25–50 mg of tramadol HCl showed that it could significantly increase the IELT from baseline values, and when compared with control patients. In addition, it was found that patients who received tramadol HCl reported more satisfactory control over ejaculation [19].

As an opioid drug, drug dependence and other opioid side-effects were a major concern in patients treated with tramadol. A previous report confirmed that tramadol dependence required $\geqslant 3$ months of continuous drug administration at the maximum dose (400 mg/day) [20]. Thus for on-demand use, the risk of tramadol dependence is negligible. However, for patients with a history of drug abuse, care should be taken when tramadol is prescribed. Other opioid-like side-effects seen with tramadol included sleep disturbance, constipation, nausea and dry mouth, which were all tolerated by the present patients [21].

In the present study, tramadol-treated patients had the highest IELT amongst the five groups, but the overall sexual satisfaction score was no better than that with sildenafil. Sildenafil citrate is a phosphodiesterase-5 inhibitor (PDE-5i) which has been used for the on-demand treatment of erectile dysfunction (ED) [22]. According to recent international evidence-based expert recommendations, sildenafil should have a main role in managing acquired PE in men with comorbid ED [23]. Although these are evidence-based opinions, other reports, e.g., the panel summary of the recommendations on sexual dysfunctions in men [24], state that '.... the efficacy and safety of off-label on-demand or daily dosing of PDE5-inhibitors has been shown in the treatment of lifelong PE in men with normal erectile function, although the level of evidence is lower'.

In the present study we excluded patients with ED (an IIEF-5 score of <22), and for these men sildenafil provided the best overall sexual satisfaction scores (when compared with the other drugs), with a significantly longer IELT than with placebo. The proposed mechanisms of action of PDE-5i in managing PE is related to improving the erection and down-regulating the erectile threshold to a lower level of arousal, so that increased levels of excitation are required to achieve the ejaculation threshold [25]. The frequently encountered adverse effects of gastrointestinal problems, headache and flushing were all minor side-effects that were well tolerated by most of the present patients.

Unlike sildenafil and tramadol, which are not recommended as treatments for PE in many clinical guidelines, the off-label use of SSRIs (e.g., paroxetine) is recommended by the AUA and International Society of Sexual Medicine guidelines. Even dapoxetine was approved for on-demand use in many countries [12,24]. Studies showed that SSRIs (e.g., paroxetine) could be used either on-demand or daily. The administration of SSRIs 4–6 h before coitus was effective and well-tolerated (less anorexia, anejaculation, gastrointestinal upset and reduced libido),

although it was associated with less ejaculatory delay than with daily dosing [26–29].

Central blockage of 5-hydroxytryptamine receptors is the main mechanism underlying the use of SSRIs for managing PE [30]. Despite being widely described as the first choice of medication in patients with PE, the present results showed that paroxetine was no better than tramadol or local anaesthetics in terms of prolonging the IELT, although the IELT recorded when using paroxetine was nearly half that seen with tramadol. As a result, the overall sexual satisfaction score was much lower than that recorded with tramadol or sildenafil.

Compared to systemic treatments for PE, topical lidocaine can be applied when needed, and with minimal side-effects. The potential drawbacks include that the local agent can be messy, interfere with spontaneity, and can possibly cause sexual hypothesia for the man and/or his partner. Depending on the formulation, local anaesthetics also require a delay between application and the maximum effect, and need to either be used with a condom or to be washed or wiped off before intercourse, which might decrease arousal and reduce spontaneity [31].

The main adverse effect specifically occurring with lidocaine in the present study was loss of penile sensation (73% of patients) that interfered with sexual satisfaction. This effect was well documented in many previous studies, although some reports noted that the drug might lose its effect because of penile numbness, which could interfere with erection [32].

There are no reports of comparative studies of these four drugs together, and few data on the long-term outcome of using any of them. There is no universal agreement about the best treatment and whether to use it on-demand or continuously. Most guidelines for PE include local anaesthetics and SSRIs as off-label treatments of such cases. The present results showed that the clinical outcome when used on-demand was no better than with the off-label use of tramadol or sildenafil, and with comparable side-effects.

As a single-centre experience, the inclusion of further multicentre or meta-analytical studies is needed to strengthen the results. Also, further study designs, including a wider range of patient age (e.g., those aged 40–70 years) are required to provide more comparative results. Also, the present results should not be applied if the same drugs are used continuously, where side-effects might be major problems.

In conclusion, although tramadol and sildenafil have fewer evidence-based recommendations for managing PE, our results showed that the on-demand use of tramadol or sildenafil was associated with a better outcome. Tramadol was better for prolonging the IELT (nearly twice that for paroxetine), whilst sildenafil provided better sexual satisfaction scores (with acceptable prolongation of the IELT) than paroxetine and local penile anaesthetics. Each of the four drugs has advantages and disadvantages, and the choice of one of them should be made after discussing with the patient both the advantages and potential side-effects.

Conflict of interest

None.

Funding source

None.

References

[1] Porst H, Montorsi F, Rosen RC, Gaynor L, Grupe S, Alexander J. The premature ejaculation prevalence and attitudes (PEPA) survey: prevalence, comorbidities, and professional help-seeking. *Eur Urol* 2007;**51**:816–23.

[2] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Text Revision. (DSM-IV-TR). Washington, DC. American Psychiatric Association, 2000: 554.

[3] Hatzimouratidis K, Amar E, Eardley I, Giuliano F, Hatzichristou F, Montorsi F, et al. Guidelines on male sexual dysfunction: erectile dysfunction and premature ejaculation. *Eur Urol* 2010;**57**:804–14.

[4] Althof SE, Symonds T. Patient reported outcomes used in the assessment of premature ejaculation. *Urol Clin North Am* 2007;**34**:581–9.

[5] Porst H, Vardi Y, Akkus E, Melman A, Park NC, Seftel AD, et al. Standards for clinical trials in male sexual dysfunctions. *J Sex Med* 2010;**7**:414–44.

[6] Waldinger MD, Quinn P, Dilleen M, Mundayat R, Schweitzer M, Boolell M. A multinational population survey of intravaginal ejaculation latency time. *J Sex Med* 2005;**2**:492–7.

[7] Waldinger MD, Zwinderman AH, Olivier B, Schweitzer DH. Proposal for a definition of lifelong premature ejaculation based on epidemiological stopwatch data. *J Sex Med* 2005;**2**:498–507.

[8] Richardson D, Goldmeier D, Green J, Lamba H, Harris JR. Recommendations for the management of premature ejaculation. BASHH special interest group for sexual dysfunction. *Int J STD AIDS* 2006;**17**:1–6.

[9] Choi HK, Jung GW, Moon KH, Xin ZC, Choi YD, Lee WH, et al. Clinical study of SS-cream in patients with lifelong premature ejaculation. *Urology* 2000;**55**:257–61.

[10] Waldinger MD, Hengeveld MW, Zwinderman AH, Olivier B. Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine, and sertraline. *J Clin Psychopharmacol* 1998;**18**:274–81.

[11] McMahon CG, Stuckey BG, Andersen M, Purvis K, Koppiker N, Haughie S, et al. Efficacy of sildenafil citrate (Viagra) in men with premature ejaculation. *J Sex Med* 2005;**2**:368–75.

[12] Montague DK, Jarow J, Broderick GA, Dmochowski RR, Heaton JP, Lue TF, et al. AUA guideline on the pharmacologic management of premature ejaculation. *J Urol* 2004;**172**:290–4.

[13] Alghobary M, El-Bayoumy Y, Mostafa Y, Mahmoud HM, Amr M. Evaluation of tramadol on demand vs. daily paroxetine as a long-term treatment of lifelong premature ejaculation. *J Sex Med* 2010;**7**:2860–7.

[14] Bar-Or D, Salottolo KM, Orlando A, Winkler JV. A randomized double-blind, placebo-controlled multicenter study to evaluate the efficacy and safety of two doses of the tramadol orally disinte-

grating tablet for the treatment of premature ejaculation within less than 2 minutes. *Eur Urol* 2011.

[15] Atan A, Basar MM, Tuncel A, Ferhat M, Agras K, Tekdogan U. Comparison of efficacy of sildenafil-only, sildenafil plus topical EMLA cream, and topical EMLA-cream-only in treatment of premature ejaculation. *Urology* 2006;**67**:388–91.

[16] Chen J, Mabjeesh NJ, Matzkin H, Greenstein A. Efficacy of sildenafil as adjuvant therapy to selective serotonin reuptake inhibitor in alleviating premature ejaculation. *Urology* 2003;**61**:197–200.

[17] Segraves RT. Effects of psychotropic drugs on human erection and ejaculation. *Arch Gen Psychiatry* 1989;**46**:275–84.

[18] Lantz MS, Buchalter EN, Giambanco V. Serotonin syndrome following the administration of tramadol with paroxetine. *Int J Geriatr Psychiatry* 1998;**13**:343–5.

[19] Salem EA, Wilson SK, Bissada NK, Delk JR, Hellstrom WJ, Cleves MA. Tramadol HCL has promise in on-demand use to treat premature ejaculation. *J Sex Med* 2008;**5**:188–93.

[20] Barsotti CE, Mycyk MB, Reyes J. Withdrawal syndrome from tramadol hydrochloride. *Am J Emerg Med* 2003;**21**:87–8.

[21] Manchikanti L, Ailinani H, Koyyalagunta D, Datta S, Singh V, Eriator I, et al. A systematic review of randomized trials of long-term opioid management for chronic non-cancer pain. *Pain Physician* 2011;**14**:91–121.

[22] Boolell M, Allen MJ, Ballard SA, Gepi-Attee S, Muirhead GJ, Naylor AM, et al. Sildenafil. An orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int J Impot Res* 1996;**8**:47–52.

[23] Rowland D, McMahon CG, Abdo C, Chen J, Jannini E, Waldinger MD, et al. Disorders of orgasm and ejaculation in men. *J Sex Med* 2010;**7**:1668–86.

[24] Montorsi F, Adaikan G, Becher E, Giuliano F, Khoury S, Lue T, et al. Summary of the recommendations on sexual dysfunctions in men. *J Sex Med* 2010;**7**:3572–88.

[25] McMahon CG, McMahon CN, Leow LJ, Winestock CG. Efficacy of type-5 phosphodiesterase inhibitors in the drug treatment of premature ejaculation: a systematic review. *BJU Int* 2006;**98**:259–72.

[26] Waldinger MD, Berendsen HH, Blok BF, Olivier B, Holstege G. Premature ejaculation and serotonergic antidepressants-induced delayed ejaculation: the involvement of the serotonergic system. *Behav Brain Res* 1998;**92**:111–8.

[27] McMahon CG, Touma K. Treatment of premature ejaculation with paroxetine hydrochloride as needed: 2 single-blind placebo controlled crossover studies. *J Urol* 1999;**161**:1826–30.

[28] Waldinger MD, Zwinderman AH, Schweitzer DH, Olivier B. Relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation: a systematic review and meta-analysis. *Int J Impot Res* 2004;**16**:369–81.

[29] Benson GS. Treatment of premature ejaculation with paroxetine controlled crossover studies hydrochloride as needed: 2 single-blind placebo; editorial comment. *J Urol* 1999;**161**:1826–30.

[30] Giuliano F, Hellstrom WJ. The pharmacological treatment of premature ejaculation. *BJU Int* 2008;**102**:668–75.

[31] Henry R, Morales A. Topical lidocaine-prilocaine spray for the treatment of premature ejaculation: a proof of concept study. *Int J Impot Res* 2003;**15**:277–81.

[32] Atikeler MK, Gecit I, Senol FA. Optimum usage of prilocaine-lidocaine cream in premature ejaculation. *Andrologia* 2002;**34**:356–9.