REVIEW

Sexual dysfunction in 2013: Advances in epidemiology, diagnosis and treatment

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Abstract Objectives: To provide a contemporary review of the epidemiology, diagnosis and treatment of premature ejaculation (PE) and erectile dysfunction (ED).
Methods: We searched for English-language articles published in the past 12 months using the PubMed database. Relevant articles on the subjects of sexual dysfunction, ED and PE were selected for review.
Conclusions: Recent studies on male sexual dysfunction have provided new therapeutic possibilities. Tramadol, a well-used analgesic, has a new role in the treatment of PE. Super-selective targeting of dorsal penile nerves by surgery or cryoablative technologies might become a viable treatment option for refractory PE in the future. The role of ED as a harbinger of important comorbidities allows for the early detection and intervention of these conditions, which can optimise therapeutic outcomes. The long-term effect of chronic phosphodiesterase-5 inhibitors on endothelial dysfunction, the angiogenic potential of low-intensity extracorporeal shock wave therapy, and further advances in drug-eluting endovascular stents might in future allow clinicians to treat ED more definitively.

Introduction

The field of male sexual dysfunction is constantly developing. In recent years research has been targeted at not only developing better treatments, but also at enhancing the understanding of the epidemiology and pathophysiology of these conditions. Algorithms and tools for diagnosis are constantly being evaluated and refined to fine-tune clinical practice, yielding optimal results with
Table 1: An overview of newer developments in the treatment of sexual dysfunction.

| Clinical therapy | Comments |
|------------------|----------|
| Topical eutectic mixture for PE in the treatment of PE | Can use as an alternative to SSRIs and other conventional therapy |
| On-demand tramadol in the treatment of PE | Can use as an alternative to SSRIs and other conventional therapy |
| Selective dorsal nerve resection in the treatment of PE | Use only in centres with experience in this technique |
| CT-guided unilateral cryoablation of DPN to treat PE | Experimental |
| Daily low-dose tadalafil to treat ED with coexistent LUTS | Can use as monotherapy targeting both ED and LUTS simultaneously |
| Li-ESWT in the treatment of ED | Use only in centres with experience in this technique |
| Drug-eluting stents in the treatment of ED | Experimental and only in selected ED patients |

PE

PE affects up to 30% of men worldwide [2], but despite its prevalence, the cause remains unclear. Genetic polymorphism in the dopamine and serotonin transporter genes has been identified in patients with lifelong PE [3,4], with additional findings to suggest that variations in oxytocin and vasopressin-receptor genes might also have a role [5]. By contrast, acquired PE has been associated with urological, endocrine, neurological and psychological causes.

Patients with PE form a heterogeneous group. The assessment of men with self-reported PE usually includes a full medical and sexual history to identify the onset and character of PE, with a focused physical examination of the man’s level of virilisation, the penis, testes, epididymides, prostate, and a check of his reflexes [6]. Limited laboratory or vascular assessments are typically required, apart from biothesiometry in some centres, measuring the vibratory threshold.

The tools available to help assess PE objectively include the Arabic Index of Premature Ejaculation [7], the Premature Ejaculation Profile [8], and the Premature Ejaculation Diagnostic Tool [9]. The last is a useful and validated questionnaire to identify men with suspected PE, and has been widely used in studies on this subject.

A stopwatch-measured or self-estimated intravaginal ejaculatory latency time (IELT), which is defined as the time from the start of vaginal intromission to the start of intravaginal ejaculation [10], is a useful tool that can be used routinely to measure the success of treatments for PE.

Female sexual dysfunction, such as vaginismus and hypoactive sexual desire disorder, might be involved in the pathogenesis of PE. A short screening tool, such as the abridged Female Sexual Function Index-6, can be clinically useful for evaluating the sexual partner [11].

Symptomatic hyperthyroidism can be diagnosed by the presence of psychic hyperactivity, such as anxiety, increased heart rate, sweating, tremors and signs of hyper-reflexia. Tests for serum levels of thyroid-stimulating hormone and thyroxine are usually not routinely required [12].

Based on a study comparing the serum serotonin levels between 71 patients with PE and 64 controls, Yang et al. [13] reported that the mean serum serotonin levels were lower in the PE group, at 61.9 ng/mL, than the 120 ng/mL among the controls (P < 0.01). That report suggested that the serum serotonin level might be a useful diagnostic tool for PE based on its specificity and sensitivity.

Although penile hypersensitivity and the determination of penile thresholds have been evaluated as possible tools of evaluation in PE the current evidence does not support the use of these neurophysiological investigations in the clinical setting [14].

The current first-line pharmacological treatment for PE consists of oral selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants and topical anaesthetics. By blocking serotonin reuptake from synaptic clefts in serotonergic neurons, SSRIs provide an inhibitory signal to the ejaculatory reflex [15]. Commonly used SSRIs include sertraline, paroxetine, fluoxetine, citalopram and dapoxetine. Unlike the other SSRIs which are more effective when taken on a daily basis, dapoxetine was developed as a rapid and short-acting agent that can be taken on-demand 1–3 h before intercourse. Dapoxetine is approved for use in several European and Asian countries, but not in North America. The tricyclic antidepressant clomipramine is also used for PE, but it is not very effective [15].
For many years off-label local anaesthetics have been used to treat PE. The rationale was based on the correlation seen between the IELT and the penile sensory threshold [16]. Patients with PE have a heightened sensory response to penile stimulation. A topical eutectic mixture for PE (TEMPE), also known as PSD502, is a proprietary formulation of lidocaine and prilocaine which is delivered in the form of a metered-dose aerosol. The standard dose consists of three actuations, with each actuation delivering 7.5 mg lidocaine and 2.5 mg prilocaine [17]. Two double-blinded placebo-controlled multicentre phase III clinical trials, involving over 530 subjects with lifelong PE, have been completed [18,19]. The combined data show that when applied 5 min before intercourse, the mean IELT increased from a baseline of 0.58 to 3.17 min in the TEMPE group, and from 0.56 to 0.94 min in the placebo group, essentially delaying ejaculation by five to six times.

In the past year there have been increasing data supporting the use of tramadol for PE. This drug was developed in the 1970s and has a good safety record established from more than 30 years of human use. It was approved for use as an analgesic by the US Food and Drug Administration in 1995 [20].

Tramadol exerts its analgesic effect through its central effects as a weak μ-opioid receptor agonist. At the same time, it was shown to inhibit neuronal re-uptake of serotonin and noradrenaline [21], which is thought to be its likely mechanism of action in PE. Tramadol is rapidly absorbed when taken orally and can achieve peak plasma concentrations within 1.6–1.9 h, with a mean elimination half-life of 5–6 h [22]. These are ideal features for an on-demand treatment agent.

In a 28-week randomised cross-over study involving 300 patients with lifelong PE, Eassa et al. [23] subjected the patients to 4 weeks of placebo followed by 24 weeks of tramadol on-demand at either 25, 50 or 100 mg. There were 100 patients in each group and there was no significant difference in the baseline IELT. After treatment, the IELT improved in all three groups, increasing from 2.82 to 13.17 min (25 mg), 2.78 to 23.43 min (50 mg) and 2.99 to 36.49 min (P < 0.001). There was a correlation between the dose and response.

In a randomised double-blinded, placebo-controlled multicentre study consisting of an initial 3-week screening period (baseline), a 3-week single-blinded placebo lead-in-period, and a 12-week double-blinded treatment period, 604 patients with lifelong PE were given either placebo, 62 mg tramadol as an orally disintegrating tablet (ODT), or 89 mg tramadol ODT on-demand, 2–8 h before intercourse. Tramadol ODT resulted in significant increases in the median IELT (P < 0.01 for both doses vs. placebo) with a 2.4-fold (62 mg) and 2.5-fold (89 mg) increase in IELT compared to a 1.6-fold increase with placebo (P < 0.001 for all) [20].

Recent systematic reviews and meta-analyses also support the use of tramadol on-demand as an effective pharmacological treatment for PE [24,25] with increments in the IELT comparable to using chronic paroxetine [26]. Based on described safety data gathered from >21,000 trial patients, the most common adverse events associated with tramadol were nausea (6.1%), dizziness (4.6%), drowsiness (2.4%), tiredness/fatigue (2.3%), sweating (1.9%), vomiting (1.7%), and dry mouth (1.6%). For patients with PE treated with tramadol, the total incidence of adverse events varied from 0% to 28.1% [25], with somnolence and gastrointestinal discomfort being the most common symptoms. These effects are usually transient.

Although selective resection of the dorsal nerves (SRDN) of the penis has been described as a treatment for refractory PE, no randomised trial has been done to assess its efficacy. Zhang et al. [27] reported a randomised placebo-controlled trial whereby 101 patients with PE and undergoing circumcision were randomised to receive either circumcision or circumcision with SRDN. Through the circumcision wound, the deep dorsal fascia of the SRDN group was incised from the 10 to the 2 o’clock positions to expose the branches of the distal dorsal nerve. Alternate nerve segments near the level of the coronary ditch were then resected. There was no statistically significant difference in the preoperative mean IELT of both groups. After surgery no significant change was reported in the circumcision group. However, the mean IELT increased by 2.5 times, from 1.1 min (baseline) to 3.8 min in the SRDN group. Due to the level of invasiveness and the lack of reversibility, SRDN is not used as a primary treatment for PE in most centres.

CT-guided ablation of the pudendal nerve, the origin of the dorsal penile nerve (DPN), has been used successfully and safely to improve pain management in patients with intractable pelvic and perineal pain [28]. Polgo et al. [29] examined the effect of unilateral CT-guided percutaneous cryoaablation of the DPN in 24 patients with PE in whom conventional therapy had failed. While under sedation, a 17-G cryoaablation probe was advanced to the DPN on one side under CT guidance as it travelled through the sulci nervi dorsalis. This was followed by two freeze–thaw cycles with a 10-min freeze and 5-min thaw each.

At the follow-up the mean IELT increased from 54.7 s (baseline) to a maximum of 256 s at 7 days, before decreasing to 182.5 s at 90 days and 140.9 s by 1 year (P < 0.001). Four patients reported ED after the procedure, with two requiring treatment with phosphodiesterase-5 inhibitor (PDE5-I). Although novel, unilateral DPN ablation remains an experimental treatment for PE at this stage, and given its invasiveness it seems unlikely to gain widespread support.
ED

In the past 18 months new epidemiological studies have shown the varying perceptions of sexuality in different communities, and the relationship between ED and cardiovascular (CV) disease had been further defined.

The Global Online Sexuality Survey (GOSS) is a worldwide epidemiological study to evaluate the prevalence and perceptions of sexuality and sexual disorders in different communities. It is conducted online using validated questionnaires, and early reports from the Middle East were published in 2011 [30]. The online nature of the surveys minimised the embarrassment that can occur in face-to-face encounters and enforced privacy, which will encourage disclosure especially in more conservative communities. Of the 804 male respondents in the Middle East GOSS report, there was a collective ED prevalence rate of 47%, with a higher prevalence in patients with infertility and concerns over genital size, amongst other associated factors such as hypertension, diabetes, depression, subjective reports of severe penile deviation, interpersonal distress, PE and low libido. Of the men, 61.3% had never used PDE5-Is and 7.8% used PDE5-Is frequently or regularly. Moreover, 93.9% perceived PDE5-Is as harmful, with 75.5% believing that users might develop habituation/dependence, hypertension (36.3%), heart disease (32.2%), eye disease (9.8%), and death (14.8%).

In their report on the USA-based GOSS, Shaeer et al. [31] studied the responses from 1133 English-speaking men residing in USA. The collective prevalence of ED was 33.7%, with a higher prevalence in subjects with difficult micturition and concerns over genital size, amongst other associated factors such as hypertension, diabetes, depression, coronary heart disease, obesity, interpersonal distress, PE, low libido and irregular coitus. The GOSS findings from both territories identified concerns over genital size as a novel risk factor (35.4% in the USA and 30% in the Middle East) which might be a reversible cause of ED that can be addressed with counselling. In the Middle East, where infertility is a conservative communities. Of the 804 male respondents amongst other associated factors such as hypertension, diabetes, depression, subjective reports of severe penile deviation, interpersonal distress, PE and low libido. Of the men, 61.3% had never used PDE5-Is and 7.8% used PDE5-Is frequently or regularly. Moreover, 93.9% perceived PDE5-Is as harmful, with 75.5% believing that users might develop habituation/dependence, hypertension (36.3%), heart disease (32.2%), eye disease (9.8%), and death (14.8%).

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A meta-analysis to assess the overall risk of CV events in patients with ED and diabetes was reported by Yamada et al. [39]. In this meta-analysis, 3791 CV events in three cohorts and nine cross-sectional studies were included. The 12 studies covered a total of 22,586 subjects, including 2229 events in 9480 subjects with ED and 1562 events in 13,106 subjects with no ED. The relative risk of CV disease in men with diabetes and ED was 1.74, which was higher than the combined relative risk of ≥1.5 from two previous meta-analyses which were not limited to diabetic patients [40,35]. ED should be recognised as an independent risk factor for CV disease and screening for CAD in patients with severe vasculogenic or diabetes-associated ED might enhance the therapeutic outcome.

During the initial evaluation of a patient with ED, a clear medical and sexual history is essential. Although a physical examination does not usually reveal the cause of ED, its use is recommended to identify information of value such as Peyronie’s plaques, atrophic testes in hypogonadism, uncontrolled hypertension and neurological disorders [41]. Standardised questionnaires such as the International Index of Erectile Function (IIEF) [42] are useful for assessing the severity of ED, which affects the response to treatment.

Laboratory investigations are useful for uncovering potentially serious comorbidities. A fasting blood glucose test can reveal diabetes mellitus, which occurs in 20–25% of patients with ED, while a lipid profile can identify dyslipidaemia, which occurs in 40–70% of these patients. Additional tests such as serum testosterone, prolactin and thyroid function tests can be included at the physician’s discretion, based on the clinical scenario [43]. Hyperprolactinaemia can occur in 0.76% of patients with ED, with identifiable pituitary adenomas in 0.4% [44].

Dynamic colour duplex Doppler ultrasonography of the penis is not a mandatory test for all patients with ED. However, its role as an objective measurement of penile haemodynamics is useful in evaluating those not responding to PDE5-Is, where the cause for treatment failure is unclear, or in young men with primary or secondary ED and a history of pelvic trauma or drug abuse, or before surgical interventions for treating Peyronie’s disease, differentiating psychogenic and organic ED, and in medicolegal cases [45]. Also, among men with undiagnosed penile pain, occult penile septal scarring can be found in up to 7% of individuals and uncovering this pathology might alter the management in these men [46]. In exceptional cases, invasive diagnostic tools such as penile angiography and cavernosography/ cavernosometry can be used.

The association between ED severity and left ventricular diastolic dysfunction (LVDD) was reported by El-Sakka et al. [47]. In a study involving 230 patients with ED and no overt cardiac complaint, 77.4%, 74.8%, 80% and 66.1% had an abnormal transmural E/A ratio, deceleration time (DT), isovolumic relaxation time (IVRT), and mitral E velocity/tissue Doppler imaging E velocity (E/Em) ratio, respectively. Only the means of IVRT and E/Em ratio had significant associations with an increased severity of ED (P < 0.001 for each). There were significant associations between an increased severity of ED and the categorical echo variables of grades 1 and 2 of E/A ratio, DT, IVRT, and grades 1, 2, and 3 of the E/Em ratio (P < 0.05 for each), showing that LVDD is prevalent in patients with ED and ED-associated medical comorbidities but no overt cardiac complaint.

Chronic daily low-dose PDE5-I

Since sildenafil was approved for the treatment of ED in 1998, on-demand PDE5-I use has become the standard of care. Despite its drug efficacy, 30–35% of these patients fail to respond or are dissatisfied with PDE5-I treatment [48], and the voluntary discontinuation rate is fairly high, with up to 35% of users stopping the medication despite better erections [49]. The limited therapeutic window of an on-demand regimen can cause unnecessary anxiety in both patient and partner when performance is directly linked to use of a drug.

In 2007, the European Medicines Agency approved the use of once-daily low-dose tadalafil for treating ED, ushering in the age of chronic PDE5-I therapy, which allows users to attain a steady-state plasma concentration that can facilitate erectile function on an ongoing basis.

McMahon et al. [50] conducted a 26-week, open-label crossover study of 145 patients with ED using either on-demand 20 mg tadalafil or daily 10 mg tadalafil, and found that the improvement in the mean IIEF-EF score was significantly higher in the group receiving daily tadalafil (11.9 daily vs. 8.3 on-demand). Of the patients, 72% preferred taking tadalafil once a day, with the predominant reasons being superior sexual spontaneity (55.2%), superior efficacy (30.5%), and reduced incidence/severity of adverse events (11.4%).

Paduch et al. [51] reported a retrospective review to investigate the effects of tadalafil in patients with ED and coexisting ejaculatory disorders (EjD) and orgasmic disorders (OD), using the pooled data from 17 placebo-controlled 12-week trials. In all, 3581 subjects who had been randomised to placebo or treatment with tadalafil (5, 10 or 20 mg on-demand) were evaluated using the IIEF. Treatment with tadalafil showed a significant improvement in ejaculatory function (vs. placebo). Patients with severe EjD had a significant least-squares mean increase in IIEF-Q9, which was dose-related, at 1.6, 1.9 and 2.0 for tadalafil 5, 10 and 20 mg, respectively. The least-squares mean increase for orgasmic function (IIEF-Q10) was also significant (vs. placebo) and dose-related in patients with severe OD, at 1.3, 1.8 and 2.0 for tadalafil 5, 10 and 20 mg, respectively.
For patients with ED in whom treatment using on-demand PDE5-Is failed, chronic daily tadalafil is a salvage option that can be considered. Patients treated with tadalafil for mixed ED and EjD or OD can show improvements beyond that of better erections.

The prevalence of ED and LUTS associated with BPH increases with age and both conditions, which share similar age-related risk factors, such as neuropathies, atherosclerosis and ischaemia, often coexisting. Some 59–86% of men aged 40–60 years in the primary care setting, and 79–100% of men aged 50–70 years actively seeking treatment for LUTS, were found to have ED [52].

Currently, α1-adrenergic blockers and 5α-reductase inhibitors are the first-line treatment options for BPH-LUTS. Both agents are associated with unwanted side-effects that lead to sexual dysfunction. α1-adrenergic blockers can cause anejaculation/retrograde ejaculation, while 5α-reductase inhibitors can decrease ejaculate volumes, decrease libido and cause ED [53].

Clinical trials have supported the use of daily tadalafil in BPH-LUTS [54,55]. For such patients with coexisting ED or sexual dysfunction resulting from the use of α1-adrenergic blockers or 5α-reductase inhibitors, daily dosing of PDE5-I might offer them the relief from both ED and BPH symptoms, while maintaining the convenience of monotherapy. In a multinational phase III double-blinded study involving 406 patients with both ED and BPH-LUTS, Ergedie et al. [56] found that daily tadalafil 5 mg significantly improved both the IIEF-EF score and IPSS, whereas tadalafil 2.5 mg only improved the IIEF-EF with no significant effect on the IPSS.

**Low-intensity extracorporeal shock wave therapy (Li-ESWT)**

Many consider the pharmacological treatment of ED as palliative treatment because the underlying pathophysiology of the condition remains unaddressed. Although current animal and human studies suggest that chronic PDE5-I treatment can alter endothelial dysfunction [57,58], it has not been shown to reverse ED in a durable way. The novel idea of treating ED with Li-ESWT came about after research focusing on the biological effects of Li-ESWT in rabbit models showed that exposure to the acoustic Li-ESWT could stimulate neovascularisation by enhancing the expression of angiogenesis-related growth factors, such as endothelial nitric oxide synthase and vascular endothelial growth factor [59]. Similar findings were reported in porcine models of ischaemia-induced myocardial dysfunction, where the application of Li-ESWT to chronic ischaemics improved the regional myocardial blood flow [60]. The exact mechanism of how Li-SWT works remain to be elucidated.

In a randomised, double-blinded, controlled study investigating the effects of Li-ESWT in 25 patients with ischaemic heart disease, Yang et al. [61] reported that in patients who received nine ESWT treatments over 3 months the disease showed improvements as assessed by angina severity scores, a 6-min walking test and left ventricular ejection fraction.

In a proof-of-concept study to evaluate the feasibility, efficacy and safety of Li-ESWT in ED by Vardi et al. [62], 20 men with mild to moderate ED due to CV disease and responding to PDE5-I therapy were treated with Li-SWT at five different sites on the penile shaft and crural level. The men had two treatment sessions per week of Li-SWT for 3 weeks, with a repetition of the Li-SWT after a 3-week treatment-free interval. At 1 month after Li-SWT, 15 men showed an improvement, with significant increases in penile rigidity, duration of the erections and an increase in their IIEF-EF scores. At 6 months 10 men continued to have a durable response and erections sufficient for penetration with no need for PDE5-I.

In a prospective, randomised, double-blinded, sham-controlled study, Vardi et al. [63] recruited 60 men with ED and applied the same treatment protocol and study parameters after randomisation. The probe used for the sham group did not produce any SW energy but looked identical to the treatment probe and produced the same noise. At the 1-month follow-up, the mean IIEF-EF in the treated group increased by 6.7 points, whilst the score in the sham group increased by 3.0 points ($P = 0.032$); 26 (65%) men in the treated group and four (20%) in the sham group had a $\geq$5-point increase in the IIEF-EF score ($P < 0.001$).

These preliminary results suggest that Li-ESWT might have properties that can rehabilitate erectile tissue on a more permanent basis [64], although longer term and larger scale studies are required to validate that. The noninvasive and painless nature of this treatment will be favourable for patient compliance.

**Endovascular therapy**

During the 1980s, arterial inflow lesions were described in patients with ED, and there are several reports describing the feasibility of revascularisation using balloon angioplasty [65] in these patients. However, the initial enthusiasm for this technique decreased because of the high incidence of re-stenosis, causing the ED to recur. There was also a lack of small-vessel endovascular therapies at that time, because bare metal stents and first-generation drug-eluting stents have problems of late stent thrombosis from the inflammation-inducing nature of the polymers of which they are made [66].

The Pelvic Angiography in Non-Responders to Phosphodiesterase-5 Inhibitors study was the first to evaluate pelvic arterial disease in PDE5-I nonresponders with suspected CAD [67]. There was a high correlation between the presence of angiographic CAD and internal pudendal artery (IPA) disease.
In a report from the ZEN trial [68], 30 subjects had 45 stents placed, mainly in the distal IPA (24 lesions, 53%) and ostial IPA (six lesions, 13%). At 6 months the mean (SD) total IIEF score was 52.9 (15.8) vs. 40.4 (9.0) (baseline). The duplex ultrasonography-assessed mean (SD) peak systolic velocity of the cavernous arteries increased from 16.4 (8.1) to 42.0 (26.9) cm/s. Binary re-stenosis occurred in 11 (34%) of 32 lesions.

Unlike bare-metal and drug-eluting stents, the ‘Resolute Zotarolimus-Eluting Stent System’ (Medtronic, Santa Rosa, CA, USA) is made of a cobalt-chromium alloy platform coated with a biocompatible triopolymer (Biolinx) containing the antiproliferative agent zotarolimus (a tetrazole-containing macrocyclic immunosuppressant), that is eluted over 180 days, allowing gentle angiogenic potential of Li-ESWT, and further effect of chronic PDE5-I on endothelial dysfunction, and thus optimise the therapeutic outcomes. The long-term intervention for these conditions, which will undoubtedly comorbidities allows the early detection of and the invasive nature of these procedures seems unpalatable, cryoablative technologies might become viable treatment for these lesions and no veno-occlusive dysfunction.

Conclusion

Studies over the past 12 months have increased the understanding of male sexual dysfunction and provided new therapeutic possibilities. Tramadol, a well-known analgesic has a new role in the treatment of PE. A better understanding of the aetiology and pathophysiology of PE might allow the ejaculatory response to be more effectively modulated by pharmacotherapy. Super-selective targeting of the dorsal penile nerves by surgery or cryoablative technologies might become viable treatment options for refractory PE in the future, although the invasive nature of these procedures seems unpleasant to many. The role of ED as a harbinger of important comorbidities allows the early detection of and intervention for these conditions, which will undoubtedly optimise the therapeutic outcomes. The long-term effect of chronic PDE5-I on endothelial dysfunction, the angiogenic potential of Li-ESWT, and further advances in drug-eluting endovascular stents might in future allow clinicians to treat ED more definitively.

Conflict of interest

None.

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References

[1] Jannini EA, Maggi M, Lenzi A. Evaluation of premature ejaculation. J Sex Med 2011;8(Suppl. 4):328–34.
[2] Rosen R, Porst H, Montorsi F. The Premature Ejaculation Prevalence and Attitudes (PEPA) Survey: a Multi-National Survey [Abstract]. Proceedings of the 11th World Congress of the International Society of Sexual and Impotence Research 2004, 17–21 October 2004.
[3] Santtila P, Jern P, Westberg L, Walum H, Pedersen CT, Eriksson E, et al. The dopamine transporter gene (DAT1) polymorphism is associated with premature ejaculation. J Sex Med 2010;7:1538–46.
[4] Janssen PK, Bakker SC, Retheley J, Zwinderman AH, Touw DJ, Olivier B, et al. Serotonin transporter promoter region (5-HTTLPR) polymorphism is associated with the intravaginal ejaculation latency time in Dutch men with lifelong premature ejaculation. J Sex Med 2009;6:276–84.
[5] Jern P, Westberg L, Johansson A, Jonsson L, Corander J, Sandnabba NK, et al. Are single nucleotide polymorphisms in the oxytocin and vasopressin 1A/1B receptor genes likely candidates for variation in ejaculatory function? BJU Int 2012;110, E1173-80.
[6] 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 2007;51:304–14.
[7] Arafa M, Shamlou R. Development and evaluation of the arabic index of premature ejaculation (AIPE). J Sex Med 2007;4:1750–6.
[8] Patrick DL, Giuliano F, Ho KF, Gagnon DD, McNulty P, Rothman M. The premature ejaculation profile. Validation of self-reported outcome measures for research and practice. BJU Int 2009;103:358–64.
[9] Symonds T, Perelman MA, Althof S, Giuliano F, Martin M, May K, et al. Development and validation of a premature ejaculation diagnostic tool. Eur Urol 2007;52:565–73.
[10] Waldinger MD. Towards evidence-based drug treatment research on premature ejaculation: a critical evaluation of methodology. Int J Impot Res 2003;15:309–13.
[11] Isidori AM, Pozza C, Esposito K, Giuliano D, Morano S, Vignozzi L, et al. Development and validation of a 6-item version of the female sexual function index (FSFI) as a diagnostic tool for female sexual dysfunction. J Sex Med 2010;7:1139–46.
[12] Althof SE, Abdo CH, Dean J, Hackett G, McCabe M, McMahon CG, et al. International society for sexual medicine. International society for sexual medicine’s guidelines for the diagnosis and treatment of premature ejaculation. J Sex Med 2010;7:2947–69.
[13] Yang C, Tang K, Wang B. Clinical value of serum 5-HT level in diagnosis and treatment of premature ejaculation. Urol Int 2013;90:214–8.
[14] Giuliano F, Rowland DL. Standard operating procedures for neurophysiologic assessment of male sexual dysfunction. J Sex Med 2013;10:1205–11.
[15] Morales A. Evolving therapeutic strategies for premature ejaculation: The search for on-demand treatment – topical versus systemic. Can Urol Assoc J 2012;6:380–5.
[16] Wylie MG, Hellstrom WJ. The link between penile hypersensitivity and premature ejaculation. BJU Int 2011;107:452–7.
[17] Wylie MG, Powell JA. The role of local anaesthetics in premature ejaculation. BJU Int 2012;110, E943-8.
[18] Dinsmore WW, Wylie MG. PSD502 improves ejaculatory latency, control and sexual satisfaction when applied topically 5 min before intercourse in men with premature ejaculation: results of a phase III, multicentre, double-blind, placebo-controlled study. BJU Int 2009;103:940–9.
[19] Carson C, Wylie M. Improved ejaculatory latency, control and sexual satisfaction when applied topically in men with premature ejaculation: results of a phase III, double-blind, placebo-controlled study. J Sex Med 2010;7:3179–89.
[20] Bar-Or D, Salottolo KM, Orlando A, Winkler JV. Tramadol OD1 study group. A randomized double-blind, placebo-controlled multicenter study to evaluate the efficacy and safety of two doses of the tramadol orally disintegrating tablet for the
Sexual dysfunction in 2013: Advances in epidemiology, diagnosis and treatment

[21] Frink MC, Hennies HH, Englberger W, Haarmand M, Wilflert B. Influence of tramadol on neurotransmitter systems of the rat brain. Arzneimittelforshung 1996;46:1029–36.

[22] Safarinejad MR, Hosseini SY. Safety and efficacy of tramadol in the treatment of premature ejaculation a double-blind, placebo-controlled, fixed-dose, randomized study. J Clin Psychopharmacol 2006;26:27–31.

[23] Eassa BI, El-Shazly MA. Safety and efficacy of tramadol hydrochloride on treatment of premature ejaculation. Asian J Androl 2013;15:138–42.

[24] Wong BL, Malde S. The use of tramadol 'on-demand' for premature ejaculation: a systematic review. Urology 2013;81:98–103.

[25] Wu T, Yue X, Duan X, Luo D, Cheng Y, Tian Y, et al. Efficacy and safety of tramadol for treatment of premature ejaculation: a systematic review and meta-analysis. Urology 2012;80:618–24.

[26] Cossmann M, Kohlen C, Langford R, McCartney C. Tolerance and safety of tramadol use. Results of international studies and data from drug surveillance. Drugs 1997;53(Suppl. 2):50–62.

[27] Zhang GX, Xie L, Bai WJ, Wang XF. Selective resection of dorsal nerves of penis for premature ejaculation. Int J Androl 2012;35:873–9.

[28] Rhame EE, Levey KA, Gharibo CG. Successful treatment of refractory pudendal neuralgia with pulsed radiofrequency. Pain Phys 2009;12:633–8.

[29] David Prolojo J, Snyder LL., Cherullo E, Passalacqua M, Pirasteh A, Corn D, et al. guided cryoablation of the dorsal penile nerve for treatment of symptomatic premature ejaculation. J Vasc Inter Radiol 2013;24:214–9.

[30] Shaer O, Shaer K. The global online sexuality survey (GOSS): erectile dysfunction among arabic-speaking internet users in the Middle East. J Sex Med 2011;9:2152–63.

[31] Shaer O, Shaer K. The global online sexuality survey (GOSS). The United States of America in 2011. Chapter I. Erectile dysfunction among English-speakers. J Sex Med 2012;9:3018–27.

[32] Shaer O. The global online sexuality survey (GOSS). The United States of America in 2011 chapter II. Phosphodiesterase inhibitors utilization among English speakers. J Sex Med 2013;10:532–40.

[33] Glina S, Sharlip ID, Hellstrom WJG. Modifying risk factors to prevent and treat erectile dysfunction. J Sex Med 2013;10:115–9.

[34] Ahmed I, El-Sakka A. Erectile dysfunction in Arab countries. Part I prevalence and correlates. Arab J Urol 2012;10:97–103.

[35] Guo W, Liao C, Zou Y, Li F, Li T, Zhou Q, et al. Erectile dysfunction and risk of clinical cardiovascular events: a meta-analysis of seven cohort studies. J Sex Med 2010;7:2805–16.

[36] Araujo AB, Travison TG, Gonz P, Chiu GR, Kupelian V, Rosen RC, et al. Erectile dysfunction and mortality. J Sex Med 2009;6:2454–55.

[37] Hotaling JM, Walsh TJ, Macleod LC, Heckbert S, Pocobelli G, Wessells H, et al. Erectile dysfunction is not independently associated with cardiovascular death. Data from the vitamins and lifestyle (VITAL) study. J Sex Med 2012;9:2104–10.

[38] Banks E, Joshy G, Abhayaratna WP, Kritharides L, Macdonald RJ, Korda RJ, et al. Erectile dysfunction severity as a risk marker for cardiovascular disease hospitalisation and all-cause mortality: a prospective cohort study. Plos Med 2013;10:e1001372.

[39] Yamada T, Hara K, Umematsu H, Suzuki R, Kadowaki T. Erectile dysfunction and cardiovascular events in diabetic men: a meta-analysis of observational studies. Plos One 2012;7:e43673.

[40] Dong JY, Zhang YH, Qin LQ. Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. J Am Coll Cardiol 2011;58:1378–85.

[41] Ghanem HM, Salonia A, Martin-Morales AS. Physical examination and laboratory testing for men with erectile dysfunction. J Sex Med 2013;10:108–10.

[42] Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile dysfunction (IIEF), a multidimensional scale for assessment of erectile dysfunction. Urology 1997;49:822–30.

[43] Hatzichristou D, Rosen RC, Derogatis LR, Low WY, Meuleman R, Sadovsky R, et al. Recommendations for the clinical evaluation of men and women with sexual dysfunction. J Sex Med 2011;7:337–48.

[44] Buvat J. Hyperprolactinemia and sexual function in men: a short review. Int J Impot Res 2003;15:373–7.

[45] Sikka SC, Hellstrom WJG, Brock G, Morales AM. Standardization of vascular assessment of erectile dysfunction. J Sex Med 2013;10:120–9.

[46] Bella AJ, Sener A, Foell K, Brock GB. Nonpalpable scarring of the penile septum as a cause of erectile dysfunction: an atypical form of Peyronie’s disease. J Sex Med 2007;4:226–30.

[47] El-Sakka AI, Morsey AM, Fagih BI. Severity of erectile dysfunction could predict left ventricular diastolic dysfunction in patients without overt cardiac complaint. J Sex Med 2011;8:2590–7.

[48] McMahon CN, Smith CJ, Shabasgh R. Treating erectile dysfunction when PD5 inhibitors fail. BJU Int 2006;53:226–7.

[49] Son H, Park K, Kim SW, Paick JS. Reasons for discontinuation of sildenafil citrate after successful restoration of erectile function. Asian J Androl 2004;6:117–20.

[50] McMahon CG. Comparison, efficacy, and tolerability of on-demand tadalafil and daily dosed tadalafil for the treatment of erectile dysfunction. J Sex Med 2005;2:415–25.

[51] Paduch DA, Bolyakov A, Polzer PK, Watts SD. Effects of 12 weeks of tadalafil treatment on ejaculatory and orgasmic dysfunction and sexual satisfaction in patients with mild to severe erectile dysfunction: integrated analysis of 17 placebo-controlled studies. BJU Int 2013;111:334–43.

[52] Seifel AD, de la Rosette J, Birt J, Porter V, Zarotsky V, Viktrup L. Coexisting lower urinary tract symptoms and erectile dysfunction: a systematic review of epidemiological data. Int J Clin Pract 2013;67:32–45.

[53] Broderick GA, Brock GB, Roehrborn CG, Watts SD, Elion-Mboussa A, Viktrup L. Effects of tadalafil on lower urinary tract symptoms secondary to benign prostatic hyperplasia in men with or without erectile dysfunction. Urology 2010;75:1452–9.

[54] Roehrborn CG, Kaminetsky JC, Auerbach SM, Montelongo A, Elion-Mboussa A, Viktrup L. Changes in peak urinary flow and voiding efficiency in men with signs and symptoms of benign prostatic hyperplasia during once daily tadalafil treatment. BJU Int 2009;105:502–7.

[55] Oelke M, Giuliani F, Mirono V, Xu L, Cox D, Viktrup L. Monotherapy with tadalafil or tamsulosin similarly improved lower urinary tract symptoms suggestive of benign prostatic hyperplasia in an international, randomised, parallel, placebo-controlled clinical trial. Eur Urol 2012;61:917–25.

[56] Egerdie RB, Auerbach S, Roehrborn CG, Costa P, Garza MS, Esler AL, et al. Tadalafil 2.5 or 5 mg administered once daily for the treatment of erectile dysfunction: integrated analysis of 17 placebo-controlled studies. BJU Int 2008;102:213–20.

[57] Aversa A, Vitale C, Volterrani M, Fabbri A, Spera G, Fini M, et al. Chronic administration of Sildenafil improves markers of endothelial function in men with Type 2 diabetes. Diabet Med 2008;25:437–44.

[58] Wang CJ, Yang KD, Weng LH, Hsu CC, Huang CS, et al. Shock wave therapy induces neovascularization at the tendon-bone junction. A study in rabbits. J Orthop Res 2003;21:984–9.
[60] Nishida T, Shimokawa H, Oi K, Tatewaki H, Uwatoku T, Abe K, et al. Extracorporeal cardiac shock wave therapy markedly ameliorates ischemia-induced myocardial dysfunction in pigs in vivo. *Circulation* 2004;110:3055–61.

[61] Yang P, Guo T, Wang W, Peng YZ, Wang Y, Zhou P, et al. Randomized and double-blind controlled clinical trial of extracorporeal cardiac shock wave therapy for coronary heart disease. *Heart Vessels* 2013;28:284–91.

[62] Vardi Y, Appel B, Jacob G, Massarwi O, Gruenwald I. Can low-intensity extracorporeal shockwave therapy improve erectile function? A 6-month follow-up pilot study in patients with organic erectile dysfunction. *Eur Urol* 2010;58:243–8.

[63] Vardi Y, Appel B, Kilchevsky A, Gruenwald I. Does low intensity extracorporeal shock wave therapy have a physiological effect on erectile function? Short-term results of a randomized, double-blind, sham controlled study. *J Urol* 2012;187:1769–75.

[64] Gruenwald I, Appel B, Kitrey ND, Vardi Y. Shockwave treatment of erectile dysfunction. *Ther Adv Urol* 2013;5:95–9.

[65] Rogers JH, Rocha-Singh KJ. Endovascular therapy for vasculogenic erectile dysfunction. *Curr Treat Options Cardiovasc Med* 2012;14:193–202.

[66] Kutcher MA. The ‘Final Voyage’ of the endeavor stent. *JACC Cardiovasc Interv* 2013;6:513–5.

[67] Rogers JH, Karimi H, Kao J, Link D, Javidan J, Yamasaki DS, et al. Internal pudendal artery stenoses and erectile dysfunction: correlation with angiographic coronary artery disease. *Catheter Cardiovasc Interv* 2010;76:882–7.

[68] Rogers JH, Goldstein I, Kandzari DE, Köhler TS, Stinis CT, Wagner PJ, et al. Zotarolimus-eluting peripheral stents for the treatment of erectile dysfunction in subjects with suboptimal response to phosphodiesterase-5 inhibitors. *J Am Coll Cardiol* 2012;60:2618–27.