



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

King Chien Joe Lee, Nader Fahmy & Gerald B. Brock

To cite this article: King Chien Joe Lee, Nader Fahmy & Gerald B. Brock (2013) Sexual dysfunction in 2013: Advances in epidemiology, diagnosis and treatment, Arab Journal of Urology, 11:3, 194-202, DOI: [10.1016/j.aju.2013.06.002](https://doi.org/10.1016/j.aju.2013.06.002)

To link to this article: <https://doi.org/10.1016/j.aju.2013.06.002>



© 2013 Arab Association of Urology



Published online: 05 Apr 2019.



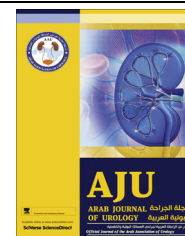
Submit your article to this journal [↗](#)



Article views: 451



View related articles [↗](#)



REVIEW

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



King Chien Joe Lee ^{a,*}, Nader Fahmy ^b, Gerald B. Brock ^{b,*}

^a Department of Urology, National University Hospital, Singapore

^b Division of Urology, St Joseph's Health Care, University of Western Ontario, London, Ontario, Canada

Received 3 May 2013, Received in revised form 5 June 2013, Accepted 9 June 2013

Available online 23 July 2013

KEYWORDS

Sexual dysfunction;
Erectile;
Premature ejaculation;
Endovascular therapy;
Cryoablation;
Epidemiology

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.

© 2013 Production and hosting by Elsevier B.V. on behalf of Arab Association of Urology.

* Corresponding authors. Address: St Joseph's Hospital, Division of Urology, 268 Grosvenor Street, London, ON N6A 4V2, Canada. Tel.: +1 519 646 6042; fax: +1 519 646 6102.

E-mail addresses: joe_kc_lee@nuhs.edu.sg (K.C.J. Lee), gebrock@sympatico.ca (G.B. Brock).

Peer review under responsibility of Arab Association of Urology.



Production and hosting by Elsevier

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

efficacy of cost. Male sexual dysfunction can be broadly classified into two main categories, i.e. erectile dysfunction (ED)¹ and ejaculatory disorders such as premature ejaculation (PE) [1]. Based on a Pubmed/Medline search, more than 700 scientific articles on these subjects were published in the last 12 months. In this review we provide an update on some of the interesting advances in the epidemiology, diagnosis and treatment of male sexual dysfunction (Table 1).

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 neurones, 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].

¹ Abbreviations: PE, premature ejaculation; ED, erectile dysfunction; IELT, intravaginal ejaculatory latency time; SSRIs, selective serotonin reuptake inhibitors; TEMPE, topical eutectic mixture for PE; ODT, orally disintegrating tablet; SRDN, selective resection of the dorsal nerves; DPN, dorsal penile nerve; PDE5-I, phosphodiesterase-5 inhibitor; CV, cardiovascular; GOSS, global online sexuality survey; CAD, coronary artery disease; IIEF, International Index of Erectile Function; LVDD, left ventricular diastolic dysfunction; DT, deceleration time; IVRT, isovolumic relaxation time; E/Em, mitral E velocity/ tissue Doppler imaging E velocity; EjD, ejaculatory disorders; OD, orgasmic disorders; LI-ESWT, low-intensity extracorporeal shock wave therapy; IPA, internal pudendal artery.

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 circumcisional 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]. Pologo et al. [29] examined the effect of unilateral CT-guided percutaneous cryoablation of the DPN in 24 patients with PE in whom conventional therapy had failed. While under sedation, a 17-G cryoablation 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, Shaer 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 more significant social stigma, there was a closer association with ED, whereas it was not a major concern amongst the USA respondents. This highlighted the cultural differences that clinicians need to consider when managing ED.

From the 603 subjects who answered the section on ED treatment, public attitudes on the use of PDE5-Is were studied. PDE5-Is were used regularly by 23.7% of subjects. This comprised 37.5% of subjects with ED and 15.6% of subjects without ED (recreational users) [32]. Of PDE5-I users, 79.6% obtained their medications through prescriptions by medical practitioners, while 20.4% used PDE5-Is with no formal prescription. Of those using PDE-Is with no prescription, 9.6% had coronary heart disease. Of the PDE5-Is, 16.5% were

purchased over the Internet and 68% of these online buyers did so with no prescription. Of the subjects who were using PDE5-Is on prescription, sildenafil comprised 44.8%, tadalafil 38.4% and vardenafil 16.8% of the drugs. For users with no ED, where PDE5-Is are consumed recreationally and with no prescriptions, 75% opted for sildenafil, 12.5% for tadalafil and 12.5% for vardenafil. Subjects with coronary heart diseases and using PDE5-Is with no prescription, comprised 1.96% of the respondents.

Comorbidities such as hypertension, diabetes mellitus, dyslipidaemia, coronary artery disease (CAD) and depression have been described as primary risk factors for the development of ED [33]. Several studies in the Middle East showed that the prevalence of ED was > 40% in Arab men, which is higher than in other parts of the world. At least five Arab countries are included in the top 10 countries worldwide with a high prevalence of diabetes mellitus [34]. The independent association between ED and CV events like angina, myocardial infarction and stroke had been well established in earlier epidemiological studies [35]. However, the relationship between ED and CV deaths as a result of the CV events remains unclear.

In the Massachusetts Male Aging Study, where a prospective population-based cohort of 1709 men were followed up, ED was associated with all-cause mortality. Although there was no formal significance detected between ED and CV deaths in this study, the trend suggested that CV deaths were a significant part of the all-cause mortality [36]. Hotaling et al. [37] followed up on the data from 31,296 men in Washington aged 50–76 years who completed a questionnaire in 2000–2002 on supplements, diet, exercise, personal health, and ED, as part of the Vitamins and Lifestyle Study. About 7762 men had ED and there were 486 CV deaths over a mean 7.8-year follow-up. ED was not independently associated with an increased risk of CV deaths, suggesting that CV events might cause CV deaths through other factors that are not related to ED.

In a prospective population-based Australian study called 'The 45 and Up Study', data collected from questionnaires administered to 95,038 men (aged > 45 years) between 2006 and 2009 were linked with hospitalisation data up to 30 June 2010 and death records up to 31 December 2010 [38]. Over a mean follow-up of 2.2 years, there were 7855 CV disease-related hospitalisations, and over a mean follow-up of 2.8 years there were 2304 deaths. The age-standardised incidences of all-cause mortality and of hospitalisation for ischaemic heart disease, heart failure, and other CV diseases increased with the increasing severity of ED. Men with severe ED had double the risk of death during the follow-up than men with no ED. That study reinforced ED as a risk marker in men with and with no known CV disease.

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 transmitral 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, α 1-adrenergic blockers and 5 α -reductase inhibitors are the first-line treatment options for BPH-LUTS. Both agents are associated with unwanted side-effects that lead to sexual dysfunction. α 1-adrenergic blockers can cause anejaculation/retrograde ejaculation, while 5 α -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 α 1-adrenergic blockers or 5 α -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 ≥ 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 tripolymer (Biolinx) containing the antiproliferative agent zotarolimus (a tetrazole-containing macrocyclic immunosuppressant), that is eluted over 180 days, allowing gentle anti-proliferation and better endothelialisation of the stent, with a lower risk of late stent thrombosis [68].

With future advances, endovascular therapy could be a potential salvage therapy for refractory patients with discrete IPA 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 unpalatable 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.

Funding

None.

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, Réthelyi 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* 2010;**57**:804–14.
- [7] Arafa M, Shamloul R. Development and evaluation of the arabic index of premature ejaculation (AIEPE). *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, Giugliano 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] Wyllie MG, Hellstrom WJ. The link between penile hypersensitivity and premature ejaculation. *BJU Int* 2011;**107**:452–7.
- [17] Wyllie MG, Powell JA. The role of local anaesthetics in premature ejaculation. *BJU Int* 2012;**110**, E943–8.
- [18] Dinsmore WW, Wyllie 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, Wyllie M. Improved ejaculatory latency, control and sexual satisfaction when PSD502 is 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 ODT 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

- treatment of premature ejaculation within less than 2 min. *Eur Urol* 2012;**61**:736–43.
- [21] Frink MC, Hennies HH, Englberger W, Haurand M, Wilffert B. Influence of tramadol on neurotransmitter systems of the rat brain. *Arzneimittelforschung* 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 premature ejaculation: a systematic review and meta-analysis. *Urology* 2012;**80**:618–24.
- [26] Cossmann M, Kohnen 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, Yu LP, 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 Prologo 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 Interv 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, Ganz P, Chiu GR, Kupelian V, Rosen RC, et al. Erectile dysfunction and mortality. *J Sex Med* 2009;**6**:2445–54.
- [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* 2010;**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, Morsy 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, Shabsigh R. Treating erectile dysfunction when PDE5 inhibitors fail. *BMJ* 2006;**332**:589–92.
- [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] Seftel 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, Giuliano F, Mirone 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 12 weeks in men with both erectile dysfunction and signs and symptoms of benign prostatic hyperplasia: results of a randomized, placebo-controlled, double-blind study. *J Sex Med* 2012;**9**:271–81.
- [57] De Young LX, Domes T, Lim K, Carson J, Brock GB. Endothelial rehabilitation. The impact of chronic PDE5 inhibitors on erectile function and protein alterations in cavernous tissue of diabetic rats. *Eur Urol* 2008;**54**:213–20.
- [58] 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**:37–44.
- [59] Wang CJ, Wang FS, 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.