Introduction

Rapid or premature ejaculation (PE) was first described in the medical literature in 1887 (1) and is widely accepted to be the most common sexual complaint in males (2). Among the multiple definitions and criteria for the diagnosis of PE, the most frequently cited are short time to ejaculation, inability to delay or control ejaculation and negative personal consequences (3-6).

PE can be subdivided into lifelong and acquired PE (7). Lifelong PE is defined by the International Society of Sexual Medicine (ISSM) as a male sexual dysfunction characterized by ejaculation that always or nearly always occurs before or within approximately one minute of vaginal penetration, the inability to delay ejaculation on all or nearly all vaginal penetrations, and negative personal consequences such as distress, bother, frustration and/or the avoidance of sexual intimacy (6). This definition is based on evidence that 80-90% of men with lifelong PE ejaculate within 60 seconds (8). Acquired PE characteristically develops later in life after a history of normal sexual function and ejaculatory control (9). Acquired PE is usually associated with urologic or psychological problems (10). This form of PE can often be remedied by treating the underlying etiology (10).

In 2006, two more PE subtypes, natural variable PE and premature-like ejaculatory dysfunction, were proposed (11). Natural variable PE is regarded as a normal variant of sexual performance, whereas premature-like ejaculatory dysfunction is defined as a complaint of PE superimposed on ejaculation time in the normal range (10). These new subtypes help physicians more precisely stratify patients and set treatment algorithms. Pharmacotherapy remains the basis of management of lifelong and acquired PE, whereas psychotherapy should be considered for patients with natural variable PE and premature-like ejaculatory dysfunction (12).

Methods

A PubMed search was conducted on articles reporting data on dapoxetine for the treatment of PE. Articles describing the pathophysiology and treatment options for PE were additionally included for review.

Results

The etiology of PE is multi-factorial in nature. There are many treatment options for PE such as psychological/behavioral therapy, topical anesthetic agents, phosphodiesterase type 5 (PDE-5) inhibitors, and tramadol hydrochloride. SSRIs play a major role in PE treatment. Animal and clinical studies in addition to its pharmacokinetic document dapoxetine’s clinical efficacy and safety for on-demand treatment of PE.

Conclusions

Dapoxetine demonstrates clinical efficacy and a favorable side effect profile. Dapoxetine is currently the oral drug of choice for on-demand treatment of PE.

Keywords: Dapoxetine; premature ejaculation (PE); selective serotonin reuptake inhibitor (SSRI)
Pathophysiology of PE

Ejaculation is comprised of two phases: emission and expulsion (13). The ejaculatory reflex requires the coordination of sympathetic, parasympathetic and somatic pathways, interlaced with central serotonergic and dopaminergic neuronal pathways (5,13). Emission is the deposition of sperm and seminal fluid into the posterior urethra by contraction of the seminal vesicles and the prostate gland and is mediated by the sympathetic nervous system (T10-L2) (13,14). The epididymis, vas deferens, seminal vesicles, prostate gland, prostatic urethra as well as the bladder neck are involved in the emission phase (13). Expulsion is the forceful antegrade ejection of sperm from the urethra and is controlled by somatic nerves (S2-4) (14). The external urethral sphincter relaxes and the ischio cavernous, bulbocavernous and other pelvic floor muscle undergo rhythmic synchronous contractions to allow antegrade flow of sperm out of the urethra. Concurrently, the smooth muscle of the bladder neck contracts to prevent retrograde flow (13).

A large body of research indicates that serotonin acting on the brain’s post-synaptic receptors exerts an overall inhibitory control on the ejaculatory process. As far back as 1976, administration of the serotonin (5-Hydroxytryptamine, 5-HT) precursor 5-Hydroxytryptophan was shown to inhibit male rat sexual behavior (15). 5-HT1A receptors have been demonstrated to exert a pro-ejaculatory effect on male sexual behavior. These receptors act on serotonergic neuronal cell bodies as a means of down regulating the release of 5-HT into the synaptic cleft. Hence, microinjections and a systemic delivery of 8-hydroxy-2-(di-n-propyl-amino) tetralin hydrobromide (8-OH-DPAT), a selective agonist of 5-HT1A receptors, elicits a diminished ejaculatory latency time in rats. There is limited evidence on the function of 5-HT1B and 5-HT2C receptors on ejaculation; however, the studies conducted implicate inhibitory activity for 5-HT1B and 5-HT2C (16,17). Both 5-HT2C and 5-HT1B receptors are distributed within the hypothalamus and in the lumbosacral areas of the spinal cord, along with 5-HT1A receptors (18).

The etiology of PE is multi-factorial in nature. Clinical evidence is limited and contradictory for many purported mechanisms. PE has been associated with both inherited and non-inherited neurobiological etiologies, pharmacological factors, urological pathology, endocrine disorders, and psychological/psychosocial mechanisms. Inherited defects in serotonergic control have been proposed to underlie a genetic basis of PE, possibly due to hyposensitive 5-HT2C and/or hypersensitive 5-HT1A receptors or increased expression of the serotonin transporter (1,18,19).

Acquired neurological diseases such as multiple sclerosis, peripheral neuropathies, spinal cord tumors, and a hypothetical hypersensitivity of the glans penis have been associated with PE; however, much of this evidence is limited and conflicting (20). Possible pharmacological causes of PE include bupropion intake and withdrawal of opioid/SSRI drug use (21-23). Urological factors include a short frenula, with one study reporting 43% of its lifetime PE patients having short frenula and improvement with frenulectomy (24). Researchers have linked hyperthyroidism to PE (25-28). As many as 72% of untreated hyperthyroid men were found to have PE according to one study and the mean IELTs increased dramatically after treatment (28). Some studies have noted a strong association between chronic prostatitis and PE. Improvements in PE and IELTs following antimicrobial therapy were reported (29-32). PE is strongly associated with psychosocial factors such as immature techniques for controlling ejaculation, conditioned from early hurried sexual experiences, alexithymia, anxiety, social phobias, and distressed emotions (33-36). Conversely, men with psychosocial burden have often leads to PE, leading to the question of which came first and making it difficult to scientifically establish causality (20).

Treatment of PE

There are multiple psychological/behavioral treatments for PE, which may be used as a single therapy for natural variable PE or premature-like ejaculatory dysfunction or in combination with pharmacologic therapy for other subtypes of PE (10,37). Psychotherapy and sexual education can reduce patient anxiety, increase communication between a man and his partner, give patients more confidence, and modify many maladaptive sexual scripts (10,14,38). Behavioral therapy is primarily comprised of the “stop and start” technique, established by Semans (39) and a variation/modification of this technique, the ‘squeeze’ technique, proposed by Masters and Johnson (40). The aim of these methodologies is to help a patient maintain his sexual excitement just below the threshold for triggering ejaculation, by either stopping sexual activity or squeezing the head of the penis until the urge to ejaculate subsides (41). Desensitization of the penis via masturbation before sexual intercourse is a practice used by younger men and has proved
effective in prolonging the ejaculatory period (42). These psychological/behavioral practices can lead to short-term improvement with overall success rates of 50-60% (43,44). However, as these methods require patient/partner commitment and practice to maintain viability, their efficacy decreases over time (45).

Topical local anesthetics such as lidocaine and/or prilocaine are the oldest drugs used for PE treatment. These are available in cream, gel and aerosol formulations (46,47). These agents delay ejaculation in theory by reducing the sensitivity of the glans penis. The use of topical anesthetics is a relatively efficacious, user friendly, and inexpensive modality for PE treatment (48). However, they can cause penile glans numbness and condom use or prior washing off before sexual activity is required to prevent transference of the drug to the vaginal mucosa (14).

Another potential medical treatment option for PE is the phosphodiesterase type 5 (PDE-5) inhibitors. PDE-5 inhibitors have traditionally been used to treat ED. Theoretically, a man trying to decrease his level of excitation to prevent PE may lead to ED, and conversely a man trying to excite himself to remedy his ED may experience PE. In theory, these are two sides of the same coin and may be superimposed upon each other (49). PE is observed in about 1/3 of patients complaining of ED (50). The efficacy of PE treatment with PDE-5 inhibitors reveals conflicting results. Several authors report better IELT with PDE-5 inhibitors administration for PE (51-53). However, in one well designed, randomized, double blind, placebo-controlled study, IELT was not significantly improved in the sildenafil group compared to placebo (54). A systematic review of PDE-5 inhibitors used in this context failed to provide strong evidence to support a role for PDE-5 inhibitors in the treatment of men with lifelong PE who maintain normal erectile function (55,56). Despite these results, sildenafil reduces anxiety, increase confidence, and gives a perception of ejaculatory control (54). There is some evidence to support the efficacy and safety of off-label on-demand or daily dosing of PDE-5 inhibitors in the treatment of lifelong PE in men with normal erectile function (51-53). However, treatment of lifelong PE with PDE5-inhibitors in such situations is not recommended (level of evidence 4) and further evidence-based research is encouraged to understand these conflicting data (14).

Tramadol hydrochloride is a synthetic opioid analgesic developed in the late 1970s (57). It is a centrally acting analgesic, which binds to both μ-opioid and gamma-aminobutyric acid (GABA) receptors. Secondarily, it inhibits the reuptake of norepinephrine and serotonin (14,57). Systematic reviews and recent published data support the efficacy and safety of on-demand use of tramadol as an alternative treatment for PE (58-61). Meta-analysis reveals that tramadol increases IELT by three minutes (58). However, long-term clinical efficacy, safety issues, and the potential for addiction need to be clarified before tramadol can be routinely used in clinical practice for the treatment of PE (14,59).

Selective serotonin reuptake inhibitors (SSRIs) are the most commonly prescribed medications for the treatment of a variety of mood disorders such as depression (62). The use of SSRIs to treat PE is based on the observation that delayed ejaculation and anorgasmia are common side effects of this class of drugs (41,63). SSRIs, either alone at low doses or in combination with psychosexual counseling are widely accepted as first line treatments for lifelong PE (14). Men with acquired PE generally receive targeted therapy aimed at resolving the underlying etiology of their PE, either with or without the addition of SSRIs (10). SSRIs act to block the axonal reuptake of serotonin from the synaptic cleft of central serotonergic neurons by 5-HT transporters, which desensitize the 5-HT1A and 5-HT1B receptors (64). The delay in ejaculation can occur within a few days; however, chronic administration for at least 2-3 weeks is necessary to maximize the drugs therapeutic effects (10). With the exception of fluvoxamine, most SSRIs have been shown to clinically delay ejaculatory time (Table 1) (75). Daily use of SSRIs increases geometric mean IELT by 2.6 to 13.2 fold (75).

Although daily administration of these drugs improves ejaculatory latency, chronic use of SSRIs also increases the likelihood of unwanted adverse events. Common adverse effects include fatigue, yawning, nausea, diarrhea and perspiration, which are usually mild and gradually improve within a few weeks (48). This class of drugs is also associated with unwanted sexual adverse events. Decreased libido (41-64%), anorgasmia (31-53%), and impotence/erectile dysfunction (10-41%) have been observed following treatment with fluoxetine, paroxetine, fluvoxamine, sertraline, and citalopram (76,77). The sudden discontinuation of these medications or rapid dose reduction may lead to SSRI-withdrawal syndrome; a cluster of psychological and vegetative clinical symptoms occurring 3-4 days after drug withdrawal and lasting for longer than one week and sometimes accompanied by suicidal thoughts and actions (48,78). The ideal SSRI for treatment of PE should have rapid onset and clearance, good tolerability,
fewer adverse effects, and be formulated for use as on-demand treatment (63). Dapoxetine is a short acting SSRI that fits the treatment requirements of PE by exhibiting these ideal parameters.

In this review, we further examine the pharmacokinetics, animal and clinical studies and the adverse events associated with the use of dapoxetine for the treatment of PE.

### Table 1 Medical treatment options for premature ejaculation (65)

| Drug          | Trade name | Dose                                      | IELT fold increase |
|---------------|------------|-------------------------------------------|--------------------|
| Oral therapy  |            |                                           |                    |
| Clomipramine (65-68) | Anafranil® | 12.5-50 mg/day or 12.5-50 mg on demand | 6; 4               |
| Fluoxetine (69) | Prozac®, Sarafem® | 20-40 mg/day | 5                  |
| Paroxetine (66,70) | Paxil®, Seroxat® | 10-40 mg/day or 10-40 mg/day on demand | 8; 1.4             |
| Sertraline (71) | Zoloft® | 50-200 mg/day | 5                  |
| Citalopram (72) | Celexa®, Cipramil® | 20-40 mg/day | 2                  |
| Tramadol (73) | Zertane® | 62 mg ODT on demand or 89 mg ODT on demand | 2.4; 2.5          |
| Topical therapy |            |                                           |                    |
| Lidocaine/prilocaine cream (74) | EMLA® cream | 25 mg/gm lidocaine, 25 mg/gm prilocaine | 4-6               |

Abbreviations: IELT, intravaginal ejaculatory latency time; ODT, orally disintegrating tablet.

### Table 2 Pharmacokinetics of dapoxetine 30 and 60 mg (80,81)

|                      | Dapoxetine 30 mg | Dapoxetine 60 mg |
|----------------------|------------------|------------------|
| C_{max} (ng/mL)      | 297              | 498              |
| T_{max} (h)          | 1.01             | 1.27             |
| T1/2 (h)             | 17.2             | 18.2             |
| Initial T1/2 (h)     | 1.31             | 1.42             |
| Terminal T1/2 (h)    | 18.7             | 21.9             |
| T50% C_{max} (h)     | 1.92             | 2.14             |
| AUC 0-24 h (ng·h/mL) | 1,110            | 2,070            |
| AUC∞ (ng·h/mL)       | 1,390            | 2,640            |

Effect of high fat meal

|                      | Dapoxetine 30 mg | Dapoxetine 60 mg |
|----------------------|------------------|------------------|
| C_{max} (ng/mL) (fasted) | –                | 443              |
| C_{max} (ng/mL) (high-fat meal) | –                | 398              |
| T_{max} (h) (fasted) | –                | 1.30             |
| T_{max} (h) (high-fat meal) | –                | 1.83             |
| T1/2 (h) (fasted) | –                | 16.3             |
| T1/2 (h) (high-fat meal) | –                | 17.8             |
| AUC∞ (ng·h/mL) (fasted) | –                | 2,190            |
| AUC∞ (ng·h/mL) (high-fat meal) | –                | 2,450            |

Abbreviations: C_{max}, maximum plasma concentration; T_{max}, time to peak concentration; T1/2, half-life; AUC, area under the curve.

### Dapoxetine

#### Structure and pharmacokinetics

Dapoxetine (Priligy, Menarini, Italy) shares a similar mode of action with other SSRIs. Dapoxetine inhibits the serotonin reuptake transporter, with minimal inhibitory effects at the norepinephrine and dopamine reuptake transporters (41). The chemical name is (+)-(S)-(N), N-dimethyl-(a)-[2-(1-napthalenyloxy)ethyl]-benzenemethanamine hydrochloride. Its structure is similar to fluoxetine (79). The molecular weight of dapoxetine is 341.88 and is a water-soluble compound (38). The pKa is 8.6 and it is charged at a physiological pH of 5.87 (38). After administration, dapoxetine is rapidly absorbed (80). Rate of absorption of dapoxetine is slightly decreased by food as shown in Table 2. Elimination of dapoxetine is biphasic. The initial half-life for 30 and 60 mg doses of dapoxetine is approximately 1.31 and 1.42 hours respectively and 18.7 and 21.9 hours for the terminal half-life, respectively (80). Longer-acting SSRIs such as fluoxetine and paroxetine are absorbed much slower than dapoxetine (80). The half-lives of fluoxetine, paroxetine and sertraline range from 16 to 96 hours (82). On account of its short half-life, the steady state plasma concentrations of dapoxetine are reached within four days compared to 1-22 months for fluoxetine (83,84). Dapoxetine is extensively metabolized in the liver by cytochrome P450 isoenzymes CYP3A4 and CYP2D6 and is excreted primarily in the urine (38,83). Dapoxetine has no inhibitory or inductive effects on cytochrome P450 enzymes (38).

The metabolites of dapoxetine include dapoxetine-N-oxide, desmethylapoxetine and didesmethyldapoxetine.
Dapoxetine-N-oxide does not have any clinical efficacy, while desmethyl dapoxetine and didesmethyldapoxetine have similar efficacy to dapoxetine, but as they comprise far smaller percentages of circulating dapoxetine species (less than 3%) their clinical effects are limited (80). At 24 hours, plasma dapoxetine concentrations drop to 3.5% and 3.9% of peak concentrations for 30 and 60 mg doses, respectively (80). The pharmacokinetics of dapoxetine are unaffected by multiple dosing with minimal apparent accumulation (80). In contrast, chronic use of paroxetine and sertraline has a 8- and 2-fold increases in plasma concentrations, respectively (85,86). Elimination of multiple doses is rapid. At 24 hours following the last dose on day 9, there is 5.5% and 6.6% of peak plasma dapoxetine concentrations left in the blood circulation for the 30 and 60 mg doses, respectively (80). Moreover, co-administration of PDE-5 inhibitors with dapoxetine has no effect on the pharmacokinetics of dapoxetine (81). This favorable pharmacokinetic profile makes dapoxetine the drug of choice for on-demand treatment of PE.

**Animal studies of dapoxetine**

The long acting SSRIs, clomipramine, serotonin, fluoxetine and sertraline, inhibit increases in seminal vesicle pressure and the contractile responses induced by hypogastric nerve stimulation in the animal model of PE (87). However, dapoxetine appears to inhibit the ejaculatory reflex at a supraspinal level. Giuliano et al. studied the effect of dapoxetine on pudendal motoneuron reflex discharges (PMRD) elicited by bilateral stimulation of the dorsal nerve of the penis in the rat model (88). The results revealed that dapoxetine significantly increased PMRD latency and was more efficient than paroxetine in inhibiting PMRD (88). At the supraspinal level, there are 5-HT neurons in the lateral paragigantocellular nucleus (LPGi), which is located in the ventral portion of the rostral medulla in the rat brain (89). Microstimulation of the medullary reticular formation decreases the amplitude and increases the latency of PMRD (90). Intrathecal and intravenous injection of dapoxetine in rats with LPGi lesions did not alter either PMRD latency or amplitude, whereas rats with intact LPGi experienced significant increases in latency and decreases in amplitude of PMRD. Hence, dapoxetine was shown to inhibit the ejaculatory expulsion reflex by modulating activity at a supraspinal level and it is now established that LPGi is a requisite brain structure for this effect (91). Clément’s behavioral study using Fos protein expression in the male rat as a marker of neuronal activity led to the identification of brain areas specifically involved in ejaculation (92). In rapidly ejaculating rats, the density of Fos expressing cells in the hypothalamus, amygdala, and LPGi were significantly higher than in the normal and sluggish categories (92,93). These results demonstrate that acute oral dapoxetine significantly prolongs latency and decreases the number of ejaculations in the rapid ejaculation rat model of PE when compared to controls (vehicle) (92). Fos expression levels in the hypothalamus, thalamus and amygdala were significantly lower in dapoxetine-treated rapid rats compared to vehicle-treated rapid rats (92). The rat model of PE clearly shows that dapoxetine significantly delays ejaculation by reducing neuronal activity in the excitatory thalamic and hypothalamic areas of the ejaculatory circuit.

**Clinical studies of dapoxetine**

Because of its rapid action and short half-life, the on-demand use of dapoxetine makes it a popular alternative for treating PE (94-97). Currently, dapoxetine is approved for the treatment of PE in over 50 countries. Several randomized controlled trials (RCTs) demonstrated the efficacy and safety of dapoxetine on more than 6,000 men with PE in over 25 countries (95,97-99) (Table 3). Integrated analysis of these phase III trials of dapoxetine demonstrate a significant increase in geometric mean IELT, from baseline (0.8 min) with 30 mg (2.0 min) and 60 mg (2.3 min) vs. placebo (1.3 min) at 12 weeks (96). In addition to IELT, both doses of dapoxetine improved patient reported outcome measures compared to placebo (96). Dapoxetine was comparably effective both in men with lifelong and acquired PE (96,101,102).

Despite these favorable outcomes, the results of the integrated analysis of the clinical dapoxetine trials revealed that 30.4% of the subjects included into the study discontinued, mostly due to lack of efficacy and personal reasons (96). These findings were in accordance with those of a recent report that demonstrated 20% of lifelong PE patients decided not to start dapoxetine treatment and almost 90% of the ones who initiated this therapy discontinued within one year because the beneficial effect were below expectations (24.4%), cost (22.1%), side effects (19.8%), loss of interest in sex 19.8%, and lack of efficacy 13.9% (103).

Adverse events related to dapoxetine therapy were more common than placebo (56.1% vs. 35.1%) (96). Although
these events were usually mild to moderate in severity, they still resulted in discontinuation from treatment, especially among patients who were treated with dapoxetine 60 mg (1.0%, 3.5%, 8.8%, and 10.0% of subjects with placebo, dapoxetine 30 mg prn, dapoxetine 60 mg prn, and dapoxetine 60 mg qd, respectively) (96). The adverse events included nausea (17.3%), dizziness (9.4%), headache (7.9%), diarrhea (5.9%), somnolence (3.9%), fatigue (3.9%), insomnia (3.8%) and nasopharyngitis (3.1%). A recent dapoxetine postmarketing observational study confirmed its safety profile and low prevalence of adverse events, which were noted to be more common in patients aged >65 yr (21.4%) (104).

No drug-drug interactions associated with dapoxetine

Table 3 Randomized controlled trials of dapoxetine (96, 100)

| Study (clinical registration number) | Study description | Treatment duration | Randomized subjects | Inclusion criteria | Results |
|-------------------------------------|-------------------|--------------------|---------------------|--------------------|---------|
| U.S. study (NCT00211094) (97)       | Multicenter, double-blind, randomized, placebo-controlled, parallel-group | 12 weeks | 1,294 | • ≥18 years of age | Mean IELT increased from 0.9, 0.92 and 0.91 minutes to 1.75, 2.78 and 3.32 minutes for placebo, 30 and 60 mg dapoxetine respectively |
| U.S. study (NCT00211107) (97)       | Multicenter, double-blind, randomized, placebo-controlled, parallel-group | 12 weeks | 1,320 | • Same as above | Same as above |
| International study (NCT00229073) (98) | Multi-center, double-blind, randomized, placebo-controlled, parallel-group study conducted in 22 countries, primarily in Europe and South America | 24 weeks | 1,162 | • Same as above except: • IELT of ≤2 minutes in ≥75% of intercourse episodes during a 4-week baseline period | Mean geometric IELT increased from 0.7 minutes to 1.1, 1.8 and 2.3 minutes for placebo, 30 and 60 mg dapoxetine respectively |
| Asia-Pacific study (NCT00210704) (95) | Multicenter, double-blind, randomized, placebo-controlled, parallel-group | 12 weeks | 1,067 | • Same as International study | Mean geometric IELT increased from 0.9 minutes to 1.8, 2.7, and 3.1 minutes for placebo, 30 and 60 mg dapoxetine respectively |
| North American study (NCT00210613) (99) | Multicenter, double-blind, randomized, placebo-controlled, parallel-group | 9 weeks | 1,238 | • Same as International study except no IELT Criterion | Dapoxetine reduced the personal distress and interpersonal difficulty associated with PE |

Abbreviations: DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision; IELT, intravaginal ejaculatory latency time; MADRS, Montgomery-Åsberg Depression Rating Scale; PE, premature ejaculation.
have been reported (105). In men with PE and comorbid ED, who were on a stable regimen of a PDE5 inhibitor, dapoxetine provided meaningful treatment benefit and was generally well tolerated (106).

Conclusions

There are a number of treatment options available for men who suffer from PE. These include psychological/behavioral therapy, topical anesthetic agents, PDE-5 inhibitors and tramadol hydrochloride. Off-label oral SSRIs are commonly prescribed for PE treatment; however, despite their efficacy, daily use of SSRIs comes with unwanted adverse events. Dapoxetine is a short-acting SSRI, designed specifically for the treatment of PE. Dapoxetine has demonstrated clinical efficacy and safety in five large, randomized, placebo-controlled phase III clinical trials. The postmarketing observational studies confirm its reliable safety profile and low prevalence of adverse events associated with its use. Dapoxetine is currently the oral drug of choice for on demand therapy of PE.

Acknowledgements

None.

Footnote

Conflict of Interest: Ege Can Serefoglu is consultant for Allergan Inc. Irwine, CA, USA. Wayne J.G. Hellstrom: American Medical Systems—Consultant or Advisor; Andromedical—Consultant or Advisor; Auxilium—Meeting Participant or Lecturer, Consultant or Advisor, Investigator; Allergan—Consultant or Advisor, Scientific Study or Trial; Coloplast—Consultant or Advisor, Investigator; Cook—Consultant or Advisor, Lecturer; Endo—Consultant or Advisor, Investigator, Lecturer; Johnson & Johnson—Consultant or Advisor, Meeting Participant or Lecturer, Investigator; Lilly, USA—Consultant or Advisor, Lecturer; NIH—Board Member, Officer, Trustee; Slate Pharmaceutical—Lecturer, Advisor, and Investigator Theralogix—Board Member, Officer, Trustee; VIVUS—Advisor/Consultant, Investigator, Lecturer. Premphants Sangkum and Rhaam Badr do not have conflict of interest.

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Cite this article as: Sangkum P, Badr R, Serefoglu EC, Hellstrom WJ. Dapoxetine and the treatment of premature ejaculation. Transl Androl Urol 2013;2(4):301-311. doi: 10.3978/j.issn.2223-4683.2013.12.01