Dapoxetine: an evidence-based review of its effectiveness in treatment of premature ejaculation

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Abstract: Premature ejaculation (PE) is a major issue in male sexual health. The global prevalence of PE is estimated to be between 20% and 40%, making it the most common sexual dysfunction in men. PE causes distress and reduced quality of life for patients and has a negative impact on interpersonal relationships. Historically, it has been treated with cognitive therapy, behavioral methods, and off-label use of selective serotonin reuptake inhibitors usually used to treat depression and other psychological disorders. Dapoxetine is a selective serotonin reuptake inhibitor specifically designed to treat PE. This paper reviews the current evidence for use of dapoxetine in the treatment of PE in adult men. There is substantial evidence that dapoxetine 30 mg or 60 mg taken “on-demand” results in a significant increase in intravaginal ejaculatory latency time when compared with placebo. Patient-reported outcomes are clearly improved relative to placebo following dapoxetine therapy, indicating greater control over ejaculation, more satisfaction with intercourse, less ejaculation-related distress, and, importantly, significantly reduced interpersonal difficulty. These data were supported by consistent reports of improvement in Clinical Global Impression of change in PE following treatment with dapoxetine. Further studies are needed to evaluate long-term efficacy and health economics. The unique pharmacology of dapoxetine makes it ideal for on-demand dosing, and the clinical evidence shows dapoxetine to be an efficacious and tolerable treatment for lifelong and acquired PE.

Keywords: dapoxetine, intravaginal ejaculatory latency time, patient-reported outcomes, premature ejaculation

Scope, aims, and objectives

Dapoxetine (Priligy™, Johnson and Johnson, Raritan, NJ) is the first and only product licensed for the treatment of premature ejaculation (PE) in men aged 18–64 years. At present, dapoxetine is licensed in ten countries, including several countries in Europe, and Mexico, South Korea, and New Zealand.1,2 PE is the most common sexual dysfunction in men, with a global prevalence estimated to be between 20% and 40%.3–5 The uncertainty about prevalence figures is due to the intimate nature of the condition and, until recently, the lack of a universal evidence-based definition. It is probable that many men do not admit to having the condition and do not seek medical advice.

PE is characterized by ejaculation prior to, or soon after, vaginal penetration with minimal stimulation, with the male having no control over ejaculation. Definitions have been published by the International Society for Sexual Medicine and in the Diagnostic Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR), with the key point being the uncontrolled brevity of sexual intercourse.6–8 The negative consequences of PE are significant, and affect both the male and female partner.
As well as obvious sexual dissatisfaction, the condition can cause personal distress, low self-esteem, and interpersonal difficulty.5,9–11

Dapoxetine belongs to a class of drugs called selective serotonin reuptake inhibitors (SSRIs) which are frequently used to treat depression. Prior to the availability of dapoxetine, psychotherapy (eg, cognitive behavior therapy) was widely used to treat PE. More recently, several SSRIs (other than dapoxetine) have been used off-label to treat PE.12,13 These SSRIs were not developed to treat PE,12 in contrast with dapoxetine which was specifically developed for this purpose and has a different pharmacological profile to the other SSRIs,14–17 with properties making it suitable for on-demand dosing.1

The aims of this article are to review the current evidence for use of dapoxetine in the treatment of PE, including the ability of the drug to not only increase time to ejaculation post-penetration, termed intravaginal ejaculatory latency time (IELT), but also to improve patient self-esteem, satisfaction with sexual intercourse, and perceived control over ejaculation.

Methods

Literature searches were carried out in August 2011 using PubMed (http://www.ncbi.nlm.nih.gov/pubmed), the Cochrane Database of Systematic Reviews (http://www.thecochranelibrary.com/view/0/AboutTheCochraneLibrary.html#CDSR), NHS Evidence (http://www.evidence.nhs.uk/search?q=dapoxetine&pa=2), and the National Institute for Health and Clinical Excellence (NICE, http://www.nice.org.uk). These databases were searched using the terms “dapoxetine” or “dapoxetine AND premature ejaculation”.

Articles involving dapoxetine for the treatment of PE were identified, with priority given to systematic reviews, meta-analyses and integrated analyses, double-blind, randomized, placebo-controlled clinical trials (RCTs), and nonrandomized observational studies. Only articles published in English were selected for inclusion. The references listed in identified articles were used as a further source of relevant studies.

Overview of premature ejaculation

PE is highly prevalent and, due to the nature of the disorder, is likely to be under-reported and undertreated.5,18 Reported prevalence has also been variable due to the previous lack of an evidence-based definition. In the past, physicians generally considered PE to have a psychological element, hence the historical use of psychotherapy to treat the condition. However, in recent years, the biological component has become more widely understood, and pharmacotherapy is the new focus for the treatment of PE.

Two types of PE have been widely recognized, ie, lifelong (primary) and acquired (secondary) PE. Lifelong PE is present from the first sexual experience onwards, occurs in almost all attempts at intercourse, and is considered to have a neurobiological etiology. Secondary PE occurs later in life after a period of perceived normal ejaculatory control, and may have a psychological and neurobiological etiology. This type of PE may be triggered by stress or linked to adverse events associated with medications.19,20 Waldinger et al suggested that, in addition to these well known types of PE, there are two other subtypes, ie, natural variable PE and premature-like ejaculatory dysfunction.21 Natural variable PE refers to those men reporting occasional early ejaculation in the course of normal events, whilst with the latter, men experience or complain of PE while having normal or prolonged IELT.22,23

Despite the above classifications, features common to all PE are an inability to control ejaculation, ejaculation prior to/soon after vaginal penetration, embarrassment, low self-esteem, personal distress, and often interpersonal difficulty and relationship problems as a result of the lack of sexual satisfaction for both the man and his partner.6,7 The first evidence-based definition of lifelong PE has recently been published by the International Society for Sexual Medicine, and includes the criterion of “ejaculation which always or nearly always occurs prior to or within about 1 minute of vaginal penetration”, ie, an IELT of 1 minute or less. Other specified criteria are “… 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”.8 Prior to this, researchers recruiting patients for clinical studies of PE tended to use the definition given in the DSM-IV-TR, which is similar to that of the International Society for Sexual Medicine, but does not specify an IELT threshold.6

The etiology of PE is multifactorial, and associations with psychological, environmental, endocrine, and neurobiological factors have been made. Control of ejaculation is under neuronal control from the supraspinal level and involves various neurotransmitters, the most widely studied of which is serotonin (5-hydroxytryptamine, 5-HT). The role of 5-HT in the pathophysiology of PE is complex, with at least three receptor subtypes (5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C}) being known to play a role.24 Recently, there has been interest in investigating a potential genetic basis for PE.25 It is postulated that a polymorphism of the serotonin transporter...
gene (5-HTT) may be associated with the response to treatment with SSRIs.26

**Current therapeutic options**

Due to a perceived psychosomatic aspect of PE, psychotherapy, such as sex therapy or cognitive therapy, has been widely used historically to treat PE.12 The aim of such treatment is to encourage self-confidence and improve communication and intimacy between PE patients and their partners, in the hope of improving performance and reducing the anxiety associated with intercourse. Behavioral methods are also used to reduce the urgency to ejaculate, including squeezing the glans of the penis or intermittent penetration, although the latter may actually lead to prolonged sexual frustration rather than greater penetrative time.27 Despite some reported short-term efficacy, there is little evidence of any long-term benefit associated with these treatment methods.1,9,28,29

The use of topical anesthetic creams was first described by Schapiro in 1943, the rationale being that reduced penile sensitivity would result in prolongation of sexual intercourse without adversely affecting the sensation of ejaculation.30,31 Prilocaine/lidocaine cream (EMLA®) has commonly been used off-license in the first-line management of PE. A novel metered-dose aerosol spray of lidocaine/prilocaine (TEMPE®) was found to increase IELT significantly compared with placebo (up to an eight-fold increase in one study) but is awaiting licensing.30,32–34 On face value, these topical treatments may appear ideal for on-demand use in PE, but they have several disadvantages, including genital numbness for both the patient and partner, reduced ability to maintain an erection, and messy application.12 As a result, these topical therapies have never achieved widespread acceptability.

The phosphodiesterase type 5 inhibitors, which are licensed for the treatment of erectile dysfunction, have been evaluated for use in PE. Despite their success in treating erectile dysfunction, there are limited data to support their use in PE alone. The only randomized, placebo-controlled, double-blind multicenter study evaluating sildenafil showed a 2.6-fold increase in IELT, but this was not statistically significant from placebo.35 However, it did show an improvement in ejaculatory control, confidence, and satisfaction in patient-derived questionnaires. A systematic review of 14 clinical trials assessing the efficacy of phosphodiesterase type 5 inhibitors and on-demand SSRIs concluded that wide ranges of IELT changes were due to inconsistencies in study designs and therefore are difficult to interpret reliably.36

Several years ago, the observation that one of the adverse effects of SSRIs when used to treat depression and other psychological disorders, ie, anorgasmia or delayed ejaculation, suggested SSRIs as a possible pharmacotherapy for PE.8,9 Subsequent research on the central and presynaptic involvement of 5-HT in ejaculation confirmed the mechanism of action of SSRIs in PE and marked a new era in pharmacotherapy for the condition.24

A number of SSRIs are currently used off-label in long-term daily dosing regimens for treatment of PE, including paroxetine, fluoxetine, fluvoxamine, sertraline, and citalopram.2 Paroxetine appears to be particularly effective at improving IELT; in one study, paroxetine 20–40 mg per day over a 6-week period was found to increase median IELT by 9.5 minutes, while placebo provided no change in IELT ($P = 0.002$).37,38 Significantly increased IELT comes at a cost, because several adverse effects are commonly experienced with these SSRIs, including erectile dysfunction, loss of libido, mood changes, and discontinuation syndrome.12 Discontinuation syndrome consists of a cluster of psychological and somatic symptoms, including dizziness, headache, agitation, and insomnia, which may occur 1–3 days after stopping an SSRI and last for longer than 1 week, but subside on reintroduction of an SSRI.

A recent report by Koyunchu et al suggested that the use of escitalopram in the treatment of lifelong PE resulted in reduced semen parameters (specifically concentration, motility, and morphology) and could therefore have a negative effect on male fertility.39 Further studies need to be done to establish a possible mechanism and determine if this observation is similar with other SSRIs.

Unlike the SSRIs mentioned above, dapoxetine was developed specifically for treatment of PE and is the only SSRI approved for treatment of the condition. What sets dapoxetine apart from other SSRIs currently used off-label to treat PE is its pharmacokinetic profile.15,16 Briefly, the pharmacology of dapoxetine may be summarized as follows:

- **Dapoxetine** is rapidly absorbed following oral administration, whereas other SSRIs take several days or even weeks to reach steady-state concentrations.14
- Peak plasma levels of dapoxetine are reached in approximately 1 hour following a dose of 30 mg or 60 mg.15,16
- Dapoxetine is rapidly eliminated; its initial half-life is approximately 1.4 hours for both doses, compared with 21 hours to 4 days for other SSRIs.14
- Dapoxetine has a terminal half-life of 18.7 hours for the 30 mg dose and 21.9 hours for the 60 mg dose.15
- Even with multiple dosing, the pharmacokinetics of dapoxetine are unchanged, and it does not appear to accumulate significantly.15
These pharmacokinetic characteristics make dapoxetine ideal for on-demand dosing, which reduces the probability of unwanted side effects.\textsuperscript{15,40} Previous Phase II studies identified the optimal dose to be 30 mg initially, with an increase to 60 mg (the maximum recommended dose) if required. Pharmacodynamic studies identified the optimal dose administration time to be 1–3 hours before sexual intercourse.\textsuperscript{41}

**Clinical evidence for dapoxetine**

From the literature searches, nine publications were identified for inclusion in the following evaluation of the clinical evidence for dapoxetine in the treatment of PE. These comprised three integrated analyses, six randomized placebo-controlled studies (two studies of identical design are only available as an integrated analysis), one subanalysis of two studies, and one long-term extension study.

In the following discussion, to aid critical analysis of the studies included for assessment, each publication has been assigned a “quality of evidence” rating based on the criteria shown in Table 1.

### Increase in IELT

Due to the nature of PE, a change in IELT is the only disease-orientated outcome that is regularly measured and reported. Other frequently reported outcomes are necessarily patient-reported outcomes, and these are discussed later. Table 2 provides a summary of the identified studies reporting changes in IELT with dapoxetine and the quality of evidence supporting these changes. All of these studies were carried out before the recent definition of lifelong PE was published by the International Society for Sexual Medicine,\textsuperscript{4} so the recruitment criteria are based on the definition given by the DSM-IV-TR,\textsuperscript{6} with the added criterion of IELT ≤2 minutes in at least 75% of sexual events (at least 90% of sexual events in Safarinejad\textsuperscript{43}). In the studies listed in Table 2, IELT was measured using a stopwatch held by the partner during episodes of sexual intercourse and averaged over the specified baseline and treatment periods.

Stopwatch-measured IELT was reported in seven publications listed in Table 2, with the duration of these studies ranging from 9 to 24 weeks. Mean average IELT was significantly increased in all cases following treatment with dapoxetine 30 mg or 60 mg, with end-of-study values being significantly greater than those for placebo, indicating an improvement in PE. The RCT by McMahon et al demonstrated significant increases from baseline in mean (± standard deviation) IELT after just one dose of dapoxetine, ie, 30 mg (1.1 [0.45]–2.7 [2.68] minutes), 60 mg (1.1 [0.48]–3.0 [3.19] minutes), and placebo (1.0 [0.47]–1.8 [1.71]; \(P < 0.001\)) for both doses of dapoxetine vs placebo.\textsuperscript{44} This significant difference from placebo was evident at all time points to the end of the study.

Of the seven studies in Table 2, four reported arithmetic and geometric means of average IELT, while three reported only one or the other. Geometric means give more conservative results that are less affected by data outliers, thus the values tend to be lower than those for arithmetic means. Where both geometric and arithmetic means were presented, the results for average IELT were similar for both methods. For example, in the integrated analysis of five Phase III studies, geometric mean IELT increased from 0.8 minutes at baseline in all groups to 2.0 and 2.3 minutes in those taking dapoxetine 30 mg and 60 mg, respectively, compared with 1.3 minutes for those taking placebo (both \(P < 0.001\)).\textsuperscript{45} The corresponding arithmetic means increased from 0.9 minutes at baseline to 3.1, 3.6, and 1.9 minutes, respectively (both \(P < 0.001\) vs placebo, Table 2).

Even in more extreme cases of PE, in which baseline IELT was very short, treatment with dapoxetine effectively increased IELT. In the integrated analysis of two Phase III studies by Pryor et al,\textsuperscript{46} increases from baseline in average IELT at 12 weeks were significantly greater for either dose of dapoxetine (30 mg or 60 mg) than for placebo in the subgroups of patients with baseline average IELTs ≤1 minute and ≤30 seconds. The subanalysis of

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**Table 1** Levels of evidence applied to studies included in this review

<table>
<thead>
<tr>
<th>Strength of evidence</th>
<th>Criteria</th>
<th>Number of studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level 1</td>
<td>Strong evidence from at least one systematic review, meta-analysis, or integrated analysis</td>
<td>3</td>
</tr>
<tr>
<td>Level 2</td>
<td>Evidence from randomized controlled trials</td>
<td>7\textsuperscript{*}</td>
</tr>
<tr>
<td>Level 3</td>
<td>Evidence from nonrandomized well designed trials, single-group pre/post intervention, cohort, time series, or matched-case control studies</td>
<td>1</td>
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<tr>
<td>Level 4</td>
<td>Evidence from well designed, nonexperimental, observational studies from more than one center or research group</td>
<td>0</td>
</tr>
<tr>
<td>Level 5</td>
<td>Opinions of respected authorities, based on clinical experience, descriptive studies, and reports of expert committees</td>
<td>0</td>
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</tbody>
</table>

Note: \*Two trials of identical design are only available as an integrated analysis and are included in the level 1 category.\textsuperscript{48} Adapted from Clark and Mucklow.\textsuperscript{49}
Table 2 Summary of evidence for end-of-study changes in intravaginal ejaculation latency time following treatment of premature ejaculation with dapoxetine

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Design</th>
<th>Treatment and dose</th>
<th>Intravaginal ejaculatory latency time (minutes)</th>
<th>P value (vs placebo)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Integrated analysis of five studies</td>
<td>DPX 30 mg or 60 mg, or PBO</td>
<td>Baseline 0.8 (1.02) Geometric mean (SE) 2.0 (1.03) Arithmetic mean (SD) 1.3 (1.02)</td>
<td>&lt;0.001</td>
<td>McMahon et al45</td>
</tr>
<tr>
<td>1</td>
<td>Integrated analysis of two studies</td>
<td>DPX 30 mg or 60 mg, or PBO</td>
<td>Baseline 0.9 (0.49) Geometric mean (SE) 3.1 (3.91) Arithmetic mean (SD) 1.9 (2.43)</td>
<td>&lt;0.001</td>
<td>Pryor et al46</td>
</tr>
<tr>
<td>1</td>
<td>Integrated analysis of two studies</td>
<td>DPX 30 mg or 60 mg, or PBO</td>
<td>Acquired PE Baseline Geometric mean (SE) 0.9 (1.03) Arithmetic mean (SD) 1.08 (0.48) Lifelong PE Geometric mean (SE) 0.8 (1.02) Arithmetic mean (SD) 0.92 (0.48)</td>
<td>&lt;0.001</td>
<td>Porst et al47</td>
</tr>
<tr>
<td>2</td>
<td>Double-blind RCT, 12 week n = 1067</td>
<td>DPX 30 mg or 60 mg, or PBO</td>
<td>Baseline DPX 30 1.0 (1.03) Geometric mean (SE) 2.7 (1.05) Arithmetic mean (SD) 2.5; 2.9; 1.7</td>
<td>&lt;0.001</td>
<td>McMahon et al48</td>
</tr>
<tr>
<td>2</td>
<td>Double-blind RCT, 24 weeks, n = 1162</td>
<td>DPX 30 mg or 60 mg, or PBO</td>
<td>Baseline DPX 30 0.9 (1.04) Geometric mean (SE) 3.1 (1.05) Arithmetic mean (SD) 3.3; 3.6; 1.9</td>
<td>&lt;0.001</td>
<td>Buvat et al49</td>
</tr>
<tr>
<td>2</td>
<td>Double-blind RCT, 12 weeks, n = 212</td>
<td>DPX 60 mg (30 mg twice-daily), or PBO</td>
<td>Baseline DPX 60 0.47 Geometric mean (SE) 3.22 Arithmetic mean (SD) 1.9 (1.90)</td>
<td>0.001</td>
<td>Safarinejad et al41</td>
</tr>
<tr>
<td>2</td>
<td>Subanalysis of integrated analysis by Pryor et al46</td>
<td>DPX 30 mg or 60 mg, or PBO</td>
<td>Baseline DPX 60 Patients with at least a 2-category increase in control 0.9 (0.47) Geometric mean (SE) 4.7 (4.41) Arithmetic mean (SD) 4.0; 4.1; 2.5</td>
<td>Not reported</td>
<td>Shabsigh et al49</td>
</tr>
</tbody>
</table>

Notes: *Only data for patients without erectile dysfunction are shown for consistency with other studies; 1P < 0.0001 vs 30 mg dapoxetine; P value is based on fold-increase from baseline, not difference from placebo as stated for the other studies.

Abbreviations: RCT, randomized controlled trial; SE, standard error; SD, standard deviation; PBO, placebo; DPX, dapoxetine; PE, premature ejaculation.

these studies by Shabsigh et al46 highlighted the importance of perceived control over ejaculation for achieving increases in IELT. Patients who reported at least a two-category improvement in control after 12 weeks of dapoxetine therapy recorded a mean change in IELT of 3.8 (0.9–4.7) minutes, whereas those who reported less than a two-category improvement in control recorded a mean change in IELT of 0.8 (0.9–1.7) minutes (Table 2). Overall, the consistent nature of the results from the studies identified indicates substantial evidence for a significant increase in IELT with dapoxetine 30 mg and 60 mg, compared with placebo, in adult patients with PE.

Patient-reported outcomes

In studies of PE, patient-reported outcomes form an important part of the evidence base because of the many ways in which PE can affect psychological wellbeing and quality of life, both for the patient and their sexual partner. The most
Significant improvement in ejaculatory control with dapoxetine 30 mg or 60 mg, as compared with placebo, was found in all RCTs in Table 3. These improvements were noted not only at the end-of-study but at all time points in between.44,47,52

The long-term use of on-demand dapoxetine has been addressed in just one study (see Table 3), ie, a 9-month extension study of the two 12-week trials described by Pryor et al.47 All of the 1774 men enrolled in the extension study received on-demand dapoxetine 60 mg, regardless of prior treatment group in the original studies (dapoxetine 30 mg, 60 mg, or placebo). At 9 months, approximately 70% of patients reported “fair”, “good”, or “very good” control over ejaculation.53 These data represent clear evidence of a significant improvement over placebo in perceived control over ejaculation in adult patients with PE taking dapoxetine 30 mg or 60 mg on-demand.

**Satisfaction with sexual intercourse**

Changes from baseline in satisfaction with sexual intercourse were reported in eight studies (Table 3). All three integrated analyses found significant improvements in satisfaction with sexual intercourse at study endpoint. In the analysis of two 12-week studies by Pryor et al, the proportion of patients receiving dapoxetine who reported at least “fair” satisfaction increased from approximately 50% at baseline to approximately 75% (dapoxetine 30 mg) and 80% (dapoxetine 60 mg) at end-of-study, compared with approximately 55% with placebo ($P < 0.001$ for both dapoxetine doses vs placebo; data estimated from Pryor et al).47 Furthermore, significant differences from baseline were seen at every time point for both doses of dapoxetine vs placebo (weeks 4, 8, and 12). Importantly, the partners of subjects in these trials also reported significant improvements in satisfaction with sexual intercourse at every time point, suggesting possible associated reductions in interpersonal difficulty (not measured in these studies). This integrated analysis also found a dose-dependent effect of dapoxetine, with significantly more patients on dapoxetine 60 mg reporting at least “fair” satisfaction at every time point compared with those on dapoxetine 30 mg.47 Subanalysis of the trials published by Shabsigh et al highlighted the impact of greater perceived control over ejaculation on other aspects of sexual experience, with 74% of patients having at least a two-category increase in control-rated satisfaction with intercourse of “good” or “very good” at end-of-study.49

The integrated analysis of two studies by Porst et al showed no differences in satisfaction with intercourse
<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Design and dose</th>
<th>Patient-reported outcome</th>
<th>Satisfaction with intercourse</th>
<th>Personal distress related to ejaculation</th>
<th>Interpersonal difficulty related to ejaculation</th>
<th>CGI of change in PE</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Integrated analysis of five studies</td>
<td>DPX 30 mg or 60 mg, or PBO</td>
<td>Improvement over placebo for both doses of DPX (both P &lt; 0.001)</td>
<td>Improvement over placebo for both doses of DPX (both P &lt; 0.001)</td>
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<td>1</td>
<td>Integrated analysis of two studies</td>
<td>DPX 30 mg or 60 mg, or PBO</td>
<td>Improvement over placebo for both doses of DPX (both P &lt; 0.05). Similar results for acquired/lifelong PE</td>
<td>Improvement over placebo for both doses of DPX (both P &lt; 0.05). Similar results for acquired/lifelong PE</td>
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<td>Porst et al47</td>
</tr>
<tr>
<td>2</td>
<td>Double-blind RCT, 12 weeks, n = 1067</td>
<td>DPX 30 mg or 60 mg, or PBO</td>
<td>% patients with ≥ one category increase: DPX 30: 69.3%, DPX 60: 75.9%, PBO: 57.8% (both P &lt; 0.001 vs PBO)</td>
<td>% patients with ≥ one category increase: DPX 30: 66.6%, DPX 60: 72.7%, PBO: 56.0% (both P &lt; 0.001 vs PBO)</td>
<td>% patients rating CGI “better” or “much better”: DPX 30: 17.9%, DPX 60: 13.4%, PBO: 27.3% (both P &lt; 0.005 vs PBO)</td>
<td>% patients rating CGI “better” or “much better”: DPX 30: 17.9%, DPX 60: 13.4%, PBO: 27.3% (both P &lt; 0.005 vs PBO)</td>
<td>McMahon et al44</td>
</tr>
<tr>
<td>2</td>
<td>Double-blind RCT, 24 weeks, n = 1162</td>
<td>DPX 30 mg or 60 mg, or PBO</td>
<td>% patients with ≥ one category increase: DPX 30: 48.5%, DPX 60: 55.8%, PBO: 35.7% (both P &lt; 0.001 vs PBO)</td>
<td>% patients with ≥ one category increase: DPX 30: 60.0%, DPX 60: 68.6%, PBO: 47.8% (both P &lt; 0.001 vs PBO)</td>
<td>% patients rating CGI “better” or “much better”: DPX 30: 30.6%, DPX 60: 39.2%, PBO: 15.6% (both P &lt; 0.001 vs PBO)</td>
<td>% patients rating CGI “better” or “much better”: DPX 30: 30.6%, DPX 60: 39.2%, PBO: 15.6% (both P &lt; 0.001 vs PBO)</td>
<td>Buvat et al48</td>
</tr>
<tr>
<td>2</td>
<td>Double-blind RCT, 9 weeks, n = 1238</td>
<td>DPX 60 mg or PBO</td>
<td>Baseline to end of study scores: DPX: 1.4–2.5, PBO: 1.5–2.0 (P &lt; 0.001 vs PBO)</td>
<td>Baseline to end of study scores: DPX: 2.8–1.5, PBO: 2.5–1.5 (P &lt; 0.001 vs PBO)</td>
<td>Baseline to end of study scores: DPX: 1.7–0.8, PBO: 1.8–1.1 (P &lt; 0.001 vs PBO)</td>
<td>% patients rating CGI “better” or “much better”: DPX: 41.3%, PBO: 20.8% (P &lt; 0.001 vs PBO)</td>
<td>Kaufman et al42</td>
</tr>
</tbody>
</table>
between those with lifelong or acquired PE (no erectile dysfunction), indicating that the two forms potentially share some pathophysiological elements. The proportions of patients reporting at least “good” satisfaction with intercourse at baseline and end-of-study (pooled 12-week data from a 12-week and a 24-week study) were as follows:

- Acquired PE, 7% at baseline to 38% at end-of-study (dapoxetine 30 mg); 7% to 42% (dapoxetine 60 mg) and 7% to 29% (placebo)
- Life-long PE, 10% at baseline to 40% at end-of-study (dapoxetine 30 mg); 10% to 38% (dapoxetine 60 mg) and 10% to 23% (placebo)

All three of the RCTs in Table 3 found significant improvements from baseline in satisfaction with intercourse compared with placebo at end-of-study and at all time points in between. For example, at end of the McMahon et al study, the proportions of patients who reported “good” or “very good” satisfaction with intercourse were 41.3% for dapoxetine 30 mg, 40.9% for dapoxetine 60 mg, and 29.0% for placebo (P < 0.001 for both doses of dapoxetine vs placebo).

The effect of long-term dapoxetine treatment on satisfaction with sexual intercourse was examined in the non-randomized extension study by Steidle et al (see Table 3). Irrespective of prior treatment (dapoxetine 30 mg, 60 mg, or placebo), long-term on-demand use of dapoxetine 60 mg resulted in more than 80% of patients reporting at least “fair” satisfaction with intercourse after 9 months. There is clear evidence from these studies that dapoxetine therapy in adult males with PE improves satisfaction with sexual intercourse in comparison with placebo.

**Personal distress related to ejaculation**

Five studies in Table 2 report changes from baseline in personal distress related to ejaculation, ie, two integrated analyses and three RCTs. Both integrated analyses found significant reductions in distress related to ejaculation at study endpoint following dapoxetine treatment. In the integrated analysis by McMahon et al, the proportions of patients who reported “quite a bit” or “extreme” personal distress decreased from 71.3% at baseline to 28.2% for dapoxetine 30 mg, and from 69.7% to 22.2% for dapoxetine 60 mg, compared with 73.5% to 41.9% with placebo (P < 0.001 for both dapoxetine doses vs placebo).

As with the measures of ejaculatory control and sexual satisfaction, the integrated analysis of two studies by Porst et al found no differences in distress related to ejaculation between those with lifelong or acquired PE (and no erectile dysfunction), indicating that the two forms potentially share some pathophysiological elements.
The proportion of patients reporting “quite a bit” or “extreme” personal distress at baseline and end-of-study were as follows:

- Acquired PE, 73% at baseline to 23% at end-of-study (dapoxetine 30 mg), 73% to 20% (dapoxetine 60 mg), and 73% to 41% (placebo)
- Lifelong PE, 71% at baseline to 28% at end-of-study (dapoxetine 30 mg), 71% to 22% (dapoxetine 60 mg), and 71% to 44% (placebo).

All three of the RCTs in Table 2 reporting changes in personal distress related to ejaculation found significant improvements with dapoxetine therapy from baseline compared with placebo at end-of-study. Furthermore, one of these studies also found significant differences between dapoxetine (both 30 mg and 60 mg) and placebo at all time points between baseline and end-of-study. In the RCT by Kaufman et al, the proportion of patients who reported being “not at all” or “a little bit” distressed by their ejaculation timing increased from approximately 5% at baseline to 54.3% at end-of-study for those who received dapoxetine 60 mg, compared with 35.3% for those who received placebo. Thus, there is clear evidence that personal distress related to the timing of ejaculation is significantly reduced with dapoxetine treatment, compared with placebo, in adults with PE.

Interpersonal difficulty related to ejaculation

Changes from baseline in interpersonal difficulty related to ejaculation following dapoxetine therapy were reported in five studies (Table 3). Two integrated analyses reporting this outcome found significant reductions in interpersonal difficulty related to ejaculation compared with placebo at study endpoint, ie, McMahon et al (integrated results from five studies) and Porst et al (integrated results from two studies). In the McMahon analysis, the proportions of patients who reported “quite a bit” or “extreme” interpersonal difficulty decreased from 36.1% at baseline to 12.3% for dapoxetine 60 mg (there is an error in the publication for the dapoxetine 30 mg results), compared with 38.5% to 23.8% with placebo ($P < 0.001$ for dapoxetine 60 mg vs placebo).

The integrated analysis by Porst et al showed no differences in interpersonal difficulty related to ejaculation between those with lifelong or acquired PE (and no erectile dysfunction), adding further weight to the argument that lifelong and acquired PE have some shared etiology. The proportions of patients reporting “quite a bit” or “extreme” interpersonal difficulty at baseline and end-of-study were as follows:

- Acquired PE, 40% at baseline to 11% at the 12-week end-of-study (dapoxetine 30 mg and 60 mg) and 40% to 24% (placebo)
- Lifelong PE, 34% at baseline to 14% at end-of-study (dapoxetine 30 mg), 34% to 11% (dapoxetine 60 mg), and 34% to 26% (placebo)

All three of the RCTs in Table 2 reporting this outcome found significant improvements from baseline in interpersonal difficulty related to ejaculation compared with placebo at the study endpoint following dapoxetine treatment. In the RCT by Kaufman et al, the proportion of patients taking on-demand dapoxetine 60 mg who reported “not at all” or “a little bit” of interpersonal difficulty related to ejaculation increased from 40.9% at baseline to 76.8% at the 9-week study endpoint, compared with 43.0% to 64.2% for those taking placebo. Although comparative statistical analyses have not been employed in all of the above studies, the evidence suggests that dapoxetine (30 mg or 60 mg) is associated with an improvement in ejaculation-related interpersonal difficulty when compared with placebo.

CGI of change in premature ejaculation

The CGI of change in PE is a measure of a patient’s overall perception of how their PE has changed following treatment. Patients’ CGI responses following dapoxetine therapy are reported in six studies listed in Table 3 (note that three of these studies refer to this as patient global impression of change in PE or patient-reported global impression). The two integrated analyses reporting this outcome found significantly better CGI scores compared with placebo at study endpoint. In one of these, the proportions of patients who reported their condition to be “slightly better”, “better”, or “much better” at the end of the study (12 weeks) were 58% (dapoxetine 30 mg) and 67% (dapoxetine 60 mg), compared with 26% with placebo ($P < 0.0001$ for both dapoxetine doses vs placebo). Similarly, the study by McMahon et al found the proportions of patients who reported their PE to be at least “slightly better” at 12 weeks were 62.1% (dapoxetine 30 mg) and 71.7% (dapoxetine 60 mg), compared with 36.0% with placebo ($P < 0.0001$ for both dapoxetine doses vs placebo).

All three of the RCTs in Table 3 found significantly better CGI scores with dapoxetine therapy compared with placebo at the study endpoints. At the 12-week end-of-treatment phase in the McMahon study, the proportions of patients who reported their PE to be at least “slightly better” were
71.4% (dapoxetine 30 mg), 79.2% (dapoxetine 60 mg), and 52.8% (placebo, \( P < 0.001 \) for both doses of dapoxetine vs placebo).\(^4^4\) The corresponding proportions for patients in this study who reported their PE to be at least “better” were 37.4% (dapoxetine 30 mg), 41.5% (dapoxetine 60 mg), and 22.0% (placebo, \( P < 0.001 \) for both doses of dapoxetine vs placebo).\(^4^4\)

The subanalysis by Shabsigh et al (of the integrated analysis reported by Pryor et al\(^4^7\)) showed how perceived control over ejaculation is important for achieving an improved overall impression of PE.\(^4^9\) For example, 38.7% of patients who reported at least a one-category increase in control also reported a CGI rating of “better” or “much better”. Moreover, 67.1% of patients who reported at least a two-category increase in control also reported a CGI rating of “better” or “much better”. Overall, dapoxetine (30 mg or 60 mg) is clearly associated with greater perceived overall improvement in PE compared with placebo.

**Patient-reported outcome-defined level of clinical benefit**

Three of the RCTs in Table 3 also reported a predefined composite clinical outcome as a measure of clinical benefit following dapoxetine treatment.\(^4^4\),\(^4^8\),\(^5^2\) It has been previously established that this composite is associated with improvements in IELT, satisfaction with intercourse, and the patients’ global perception of PE.\(^4^9\) The composite patient-reported outcome was defined as a “two-category or greater increase in perceived control over ejaculation, and a one-category or greater decrease in ejaculation-related personal distress”.

All three studies found a significantly greater proportion of patients achieving the composite patient-reported outcome with dapoxetine 30 mg or 60 mg than with placebo at the end of the treatment period. In the paper by McMahon et al, the proportions achieving the composite patient-reported outcome were 34.7% (dapoxetine 30 mg) and 37.2% (dapoxetine 60 mg), compared with 21.7% for placebo (\( P < 0.001 \) for both doses of dapoxetine vs placebo). In the same study, patients achieving the composite patient-reported outcome reported longer IELTs than those reported by the overall treatment groups, ie, 5.4 minutes vs 3.9 minutes (dapoxetine 30 mg) and 4.2 minutes (dapoxetine 60 mg).\(^4^4\)

The proportion of patients who achieved the composite patient-reported outcome was even larger in the Kaufman et al study in which 47.6% of patients who took dapoxetine 60 mg on-demand achieved the composite patient-reported outcome, compared with 21.7% of those taking placebo (\( P < 0.001 \) for the difference between dapoxetine and placebo).\(^5^2\) This trial was only 9 weeks in duration, but positive results for this outcome measure were evident in the longer term. After 24 weeks of dapoxetine therapy, the trial by Buvat et al found 25.3% and 37.1% of patients achieved the composite patient-reported outcome with dapoxetine 30 mg and 60 mg, respectively, compared with 13.0% with placebo (\( P < 0.001 \) for both dapoxetine doses vs placebo).\(^4^8\)

**Economic evidence**

Our literature search found no published health economics studies on the use of dapoxetine in adult patients with PE. The economic costs of dapoxetine should be assessed individually in all the countries where it is approved, since the relative costs to the health care provider differ according to local health care structure, currency, and costs of alternative therapy. Country-specific health economics studies are needed to answer the following questions:

- Is on-demand use of dapoxetine more cost-effective than long-term once-daily use of other SSRIs for treatment of PE?
- Is on-demand use of dapoxetine more cost-effective than psychotherapy?

**Dosage, administration, and formulation**

Oral dapoxetine is indicated for the treatment of men aged 18–64 years with premature ejaculation. The recommended starting dose is 30 mg (administered with water) as needed, 1–3 hours prior to sexual intercourse (with a maximum dosing frequency of once every 24 hours). The dose may be increased to 60 mg (the maximum recommended dose) based on efficacy and tolerability. Each film-coated tablet contains either 30 mg or 60 mg dapoxetine hydrochloride, and may be administered with or without food.

Dapoxetine is contraindicated in men with moderate to severe hepatic impairment and in those receiving concomitant therapy with potent cytochrome P450 3A4 inhibitors (eg, ketoconazole, ritonavir, telithromycin), tricyclic antidepressants, monoamine oxidase inhibitors, serotonin reuptake inhibitors (eg, SSRIs, serotonin-norepinephrine reuptake inhibitors, tricyclic antidepressants) or other medicinal/herbal products with serotonergic effects (eg, hypericum [St John’s wort]). Dapoxetine is not recommended in men with severe renal impairment, and caution is advised in men with mild to moderate renal impairment. Alcohol and recreational drugs should be avoided when taking dapoxetine. The above information is taken from the product monograph.
Studies with concomitant use of dapoxetine and phosphodiesterase type 5 inhibitors do not show any significant interaction with tadalafil 20 mg or sildenafil 100 mg.

**Place in therapy**

The strongest evidence for the use of dapoxetine in adult males with premature ejaculation is for the main disease-oriented outcome of IELT, reported in seven of the nine publications identified in our literature search (see Table 4). Dapoxetine significantly and consistently increased IELT by approximately 3–4 minutes, representing a 3–4-fold increase in IELT. Placebo, in contrast, generally resulted in just a two-fold increase in IELT. The disease-oriented efficacy of dapoxetine has been shown in the studies examined here to be supported by positive effects in all patient-reported outcomes, which together indicate a significant improvement in wellbeing and quality of life. Importantly, clear evidence was found for improvements in interpersonal relationships, suggesting that both sexual partners benefitted from dapoxetine treatment.

Despite a historical distinction between lifelong and acquired PE based on the time of life at which PE occurs, there is no evidence for a difference in response to dapoxetine in males with lifelong or acquired PE. Although increases in IELT were generally slightly smaller for those with lifelong PE than those with acquired PE (see Table 2), the differences were not deemed sufficiently large to discriminate between them. Moreover, differences between the two PE subtypes were less evident for patient-reported outcomes. This adds weight to the proposal for a single, unified definition of PE. However, this evidence is based on just one integrated analysis of two trials so further research is needed to verify these data.

It is encouraging that the results obtained with dapoxetine therapy during trials of 9–24 weeks’ duration have been shown to be maintained during long-term on-demand use. However, it must be noted that evidence for this presently comes from one 9-month study of level 3 quality (it was nonrandomized and had no control group) in which patient-reported outcomes were measured, but not IELT. Therefore, more trials are required to add further evidence for the efficacy of long-term dapoxetine use in PE.

The great benefit of dapoxetine for the treatment of PE when compared with other SSRIs is that it can be taken as needed, which not only allows great flexibility and convenience but also limits exposure to adverse events. In all the studies examined above, dapoxetine tolerability has been consistently favorable; adverse events associated with dapoxetine are dose-dependent and tend to be nonsevere and non-serious. The most commonly reported treatment-emergent adverse events were nausea, dizziness, somnolence, diarrhea, headache, and vomiting. Table 5 shows the frequency of these treatment-emergent adverse events in the RCTs examined

**Table 4** Summary of core evidence for dapoxetine in the treatment of lifelong or acquired premature ejaculation

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Evidence</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease-oriented evidence</strong></td>
<td></td>
<td>Dapoxetine is consistently better than placebo at significantly increasing intravaginal ejaculatory latency time</td>
</tr>
<tr>
<td>Increase in intravaginal ejaculatory latency time</td>
<td>Substantial</td>
<td></td>
</tr>
<tr>
<td><strong>Patient-oriented evidence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived improvement in control over ejaculation</td>
<td>Clear</td>
<td>Dapoxetine is better than placebo at giving men greater perceived control over ejaculation</td>
</tr>
<tr>
<td>Greater satisfaction with sexual intercourse</td>
<td>Clear</td>
<td>Dapoxetine gives patients greater satisfaction with intercourse compared with placebo</td>
</tr>
<tr>
<td>Less personal distress related to ejaculation</td>
<td>Clear</td>
<td>Distress ratings are significantly reduced with dapoxetine compared with placebo</td>
</tr>
<tr>
<td>Less interpersonal difficulty related to ejaculation</td>
<td>Clear</td>
<td>Significantly reduced ratings for interpersonal difficulty with dapoxetine compared with placebo</td>
</tr>
<tr>
<td>Improved clinical global impression of change in premature ejaculation</td>
<td>Clear</td>
<td>More patients who received dapoxetine reported a positive change in premature ejaculation compared with those who received placebo</td>
</tr>
<tr>
<td><strong>Economic evidence</strong></td>
<td>No evidence</td>
<td></td>
</tr>
<tr>
<td>On-demand use of dapoxetine is more cost-effective than long-term once-daily use of other selective serotonin reuptake inhibitors for treatment of premature ejaculation</td>
<td></td>
<td>Health economics studies are needed</td>
</tr>
<tr>
<td>On-demand use of dapoxetine is more cost-effective than psychotherapy</td>
<td>No evidence</td>
<td>Health economics studies are needed</td>
</tr>
</tbody>
</table>
Table 5 Summary of frequently reported treatment-emergent adverse events in trials of dapoxetine for the treatment of premature ejaculation

<table>
<thead>
<tr>
<th>Reference</th>
<th>Design</th>
<th>Treatment and dose</th>
<th>Nausea</th>
<th>Diarrhea</th>
<th>Headache</th>
<th>Dizziness</th>
<th>Somnolence</th>
<th>Vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pryor et al46,47</td>
<td>Integrated analysis of two studies</td>
<td>DPX 30 mg or 60 mg, or PBO</td>
<td>8.7</td>
<td>3.9</td>
<td>5.9</td>
<td>3.0</td>
<td>3.2</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DPX 30</td>
<td>20.1</td>
<td>6.8</td>
<td>6.8</td>
<td>6.2</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>DPX 60</td>
<td>1.9</td>
<td>1.4</td>
<td>4.0</td>
<td>0.8</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>McMahon et al44,48</td>
<td>Double-blind RCT, 12 weeks, n = 1067</td>
<td>DPX 30 mg or 60 mg, or PBO</td>
<td>10.5</td>
<td>2.0</td>
<td>3.4</td>
<td>10.5</td>
<td>3.4</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DPX 30</td>
<td>26.4</td>
<td>1.7</td>
<td>4.8</td>
<td>18.8</td>
<td>6.2</td>
<td>2.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DPX 60</td>
<td>2.0</td>
<td>0.8</td>
<td>2.0</td>
<td>3.9</td>
<td>0.6</td>
<td>0</td>
</tr>
<tr>
<td>Buvat et al48</td>
<td>Double-blind RCT, 24 weeks, n = 1162</td>
<td>DPX 30 mg or 60 mg, or PBO</td>
<td>16.5</td>
<td>3.9</td>
<td>6.4</td>
<td>7.7</td>
<td>3.9</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DPX 30</td>
<td>30.6</td>
<td>11.3</td>
<td>13.6</td>
<td>13.4</td>
<td>7.2</td>
<td>3.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DPX 60</td>
<td>2.9</td>
<td>1.6</td>
<td>8.3</td>
<td>2.6</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Kaufman et al52,53</td>
<td>Double-blind RCT, 9 weeks, n = 1238</td>
<td>DPX 60 mg or PBO</td>
<td>15.3</td>
<td>6.1</td>
<td>8.1</td>
<td>10.2</td>
<td>3.7</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DPX 60</td>
<td>1.6</td>
<td>2.0</td>
<td>6.1</td>
<td>2.9</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Safarinejad43</td>
<td>Double-blind RCT, 12 weeks, n = 212</td>
<td>DPX 60 mg (30 mg twice daily), or PBO</td>
<td>5.4</td>
<td>5.4</td>
<td>4.3</td>
<td>3.2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DPX 60</td>
<td>1.0</td>
<td>0.0</td>
<td>1.0</td>
<td>0.0</td>
<td>–</td>
<td></td>
</tr>
</tbody>
</table>

Notes: *Treatment-emergent adverse events more frequent with dapoxetine than with placebo; †occurring in ≥1% of subjects; ‡occurring in ≥2% of subjects.

Abbreviations: RCT, randomized, placebo-controlled trial; PBO, placebo; DPX, dapoxetine.

above for efficacy (please refer to the original publications for full lists of adverse events).

Less frequently reported treatment-emergent adverse events include erectile dysfunction, flushing, palpitations, upper respiratory tract infection, nasopharyngitis, loss of libido, insomnia, fatigue, dry mouth, anxiety, hyperhidrosis, abdominal pain, back pain, and asthenia.43,44,46,48

As may be expected, discontinuations due to treatment-emergent adverse events in the studies described here were reportedly more frequent with dapoxetine than with placebo, and more frequent with dapoxetine 60 mg than with 30 mg. For example, in the trial by McMahon et al, 1.7% of patients on dapoxetine 30 mg and 5.1% on dapoxetine 60 mg discontinued the study, compared with 0.3% of patients on placebo.44 Nausea and dizziness were the most common treatment-emergent adverse events reported to cause discontinuation.44 Similarly, Buvat et al state nausea to be the most common treatment-emergent adverse event leading to discontinuation (1% of patients on dapoxetine 30 mg, 2.6% on dapoxetine 60 mg, and 0.3% on placebo).48 In the trials by Pryor et al and Safarinejad, 5% and 6% of patients, respectively, discontinued due to treatment-emergent adverse events.43,46

Data on cardiovascular adverse events associated with dapoxetine in PE are somewhat inconsistent. In the study reported by Buvat et al, one patient experienced ventricular tachycardia and another patient had a transient ischemic attack (both receiving dapoxetine 30 mg), and a third patient experienced syncope followed by sinus bradycardia and sinus arrest (after receiving dapoxetine 60 mg). A fourth patient experienced syncope while on the higher dapoxetine dose.48 The trial by Kaufman et al reported syncope in two patients taking dapoxetine 60 mg on-demand and in two patients taking the same dose once daily.52 In contrast, only one patient on dapoxetine (30 mg, plus two on placebo) experienced nonsustained ventricular tachycardia, and no patients reported any episodes of syncope in the McMahon et al trial, leading the authors to conclude that dapoxetine had no arrhythmogenic effects.44 A recent review of the cardiovascular safety profile of dapoxetine has examined data from the complete dapoxetine development program, including preclinical and Phase I studies, as well as the Phase III RCTs included in this review. It was concluded that dapoxetine is associated with vasovagal-mediated syncope (a temporary inability of the brain to control blood pressure and heart rate adequately causing syncope), but otherwise caused no other cardiovascular adverse events.55

Conclusion

Dapoxetine is the only drug specifically formulated and licensed for PE in adult males. The unique pharmacology of dapoxetine makes it ideal for on-demand dosing, allowing great convenience and flexibility for the patient. The clinical evidence published to date indicates that dapoxetine 30 mg or 60 mg is an efficacious and tolerable treatment for lifelong and acquired PE, leading to significant improvement not only in the main disease symptom of IELT, but also in all patient-reported outcomes. Dapoxetine is clearly a promising treatment option for PE, and its use can result in greater quality
of life for the patient and their sexual partner. With the recent greater emphasis on research in the field of PE, it is hoped that the evidence base for a range of treatments, both topical and oral, will grow and prove valuable for patients.

**Disclosure**

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**References**


