Dapoxetine: a pharmacological therapy for the treatment of premature ejaculation

Premature ejaculation (PE) is one of the most common male sexual dysfunctions, characterized by reduced intravaginal ejaculatory latency time (IELT) and self-perceived lack of control over ejaculation. PE can place a substantial burden on the sexual satisfaction of the couple and negatively impact their quality of life. Dapoxetine is a short-acting selective serotonin reuptake inhibitor and the first pharmacotherapy approved for the treatment of men with PE. The pharmacokinetic profile of dapoxetine makes it particularly well-suited for the on-demand treatment of PE. Dapoxetine has been investigated in five randomized, placebo-controlled Phase III trials involving 6081 men with PE. Dapoxetine (30 and 60 mg) significantly increased mean IELT across the trials ($p \leq 0.001$ both doses vs placebo) up to 24 weeks. Increases in IELT with dapoxetine were observed in men with baseline IELTs ranging from less than 0.5 to 2.0 min, and were accompanied by improvements in patient-reported outcomes (control, satisfaction, distress and interpersonal difficulty) for both the man and his partner. The approval of dapoxetine offers new hope to men with PE.

KEYWORDS: dapoxetine ■ premature ejaculation ■ PRILIGY® ■ selective serotonin reuptake inhibitors

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Classification & definition of premature ejaculation

Premature ejaculation (PE) can be broadly classified as 'lifelong' (primary), characterized by onset from the first sexual encounter and persisting throughout life, or 'acquired' (secondary), which tends to have either a gradual or sudden onset following previously normal ejaculation [1,2]. Several definitions of PE exist, including the widely quoted American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th edition, Text Revision (DSM-IV-TR) [3], and the first evidence-based and multidimensional definition from the International Society for Sexual Medicine [4]. The essential components deemed by the International Society for Sexual Medicine to define PE are rapidity of ejaculation (always or nearly always occurring before or within approximately 1 min of vaginal penetration), perceived control over ejaculation and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy [4]. However, it should be noted that this definition is applicable only to men with lifelong PE, as there are currently insufficient robust data available to propose an evidence-based definition of acquired PE [4].

Epidemiology, impact & diagnosis of PE

Accumulating evidence suggests that PE is the most common male sexual dysfunction [5]. The estimates of PE prevalence vary considerably [6]. Depending on the methodology, study population and cut-off criteria used in studies evaluating the prevalence of PE, the reported proportion of men affected with the condition at some point in their life ranges from 0.5 to 31% [6–11]. Data from the comprehensive, multinational, internet-based PE Prevalence and Attitudes (PEPA) survey, conducted among 12,133 men aged 18–70 years in the USA, Germany and Italy, indicated that the prevalence of self-reported PE was 22.7% [9]. Relying on self-reported complaints of PE may risk overestimating the prevalence of this condition. Some men with quite long intravaginal ejaculatory latency times (IELTs) may complain of rapid ejaculation, but simply have unrealistic expectations of sexual performance. The variable prevalence rates of PE have been extensively discussed in a review by Waldinger and Schweitzer [12].

In contrast to another common sexual dysfunction, erectile dysfunction, which tends to affect older age men [10,13], the prevalence of PE is generally more consistent across different age groups [13]. There is some evidence to suggest that PE has a genetic etiology [14,15]. Nevertheless, the genetic basis of PE and how heritable components of this condition interplay with environmental factors remains to be fully elucidated [16].

Premature ejaculation can have a negative impact on both the man and his partner [17–19]. Persistent lack of control over ejaculation can lead

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to sexual dissatisfaction, emotional distress, anxiety, feelings of inadequacy, loss of self-esteem and, ultimately, detrimental effects on relationships and quality of life [17–19]. Despite the psychosocial burden of PE, it has been suggested that this disorder remains under-reported, underdetected and undertreated in clinical practice, owing to, at least in part, several patient- and physician-related barriers [17,19–21]. For example, physicians often refrain from inquiring about sexual dysfunction with their patients and men are often reluctant to discuss it with a healthcare professional because they are too embarrassed or feel stigmatized [17,19,20]. A striking observation from the PEPA survey was that only 9% of men with PE reported having consulted a physician regarding the condition [9].

The diagnosis of PE is largely based on the man's sexual and medical history [17,20]. Identifying the timeframe over which PE has been problematic and the frequency of PE episodes is crucial in determining whether the PE is lifelong or acquired, and whether it is generalized or situational [22]. Quantitative measures of IELT have been proposed as a basis for diagnosing PE [7,23,24]. However, IELT only assesses one characteristic of the condition and does not capture the multidimensional nature of PE [25,26]. There also appears to be a degree of inherent overlap in terms of ejaculatory latency between men with PE and men without PE [26]. Recent European Association of Urology (EAU) guidelines state that the use of IELT alone is not sufficient to define all cases of PE [1]. In everyday clinical practice, diagnosis should be multidimensional and assess IELT, control over ejaculation, and distress and interpersonal difficulty caused by ejaculatory dysfunction [1].

Results from the PEPA survey indicated that men who described themselves as having PE were more likely to report other sexual dysfunctions and psychological disturbances, compared with men without PE [9]. More specifically, PEPA survey data demonstrated that a significant proportion of men with PE had comorbid erectile dysfunction (31.9%; $p < 0.05$ vs control group, i.e., men without PE) [9]. The prevalence of prostatitis in men with primary PE (n = 94) or secondary PE (n = 59), compared with a control group of non-PE men (n = 100), has been investigated in a cohort study. Overall, prostatic inflammation and prostatic infection were found in 64 and 52% of all 153 men with PE (i.e., either primary or secondary PE), respectively, compared with none in the control group ($p < 0.05$ vs control) [27]. Furthermore, there was a significantly higher prevalence of chronic bacterial prostatitis in men with secondary PE, compared with those with primary PE (73 vs 41%, respectively; $p < 0.05$) [27]. Findings from a study involving 48 men with thyroid hormone disorders demonstrated that 17 out of 34 (50%) men with hyperthyroidism were found to have PE [28]. After treatment to normalize levels of thyroid hormone in hyperthyroid subjects, the proportion of men with PE reduced from 50 to 15% [28]. Taken together, these data highlight that careful medical and physical examination of the man with PE is imperative to identify any potential underlying or comorbid conditions, such as erectile dysfunction, prostatitis or thyroid dysfunction, that may also require treatment [1]. A recently updated treatment guideline endorsed by the EAU is available to assist in the management of PE and erectile dysfunction. The EAU guideline provides a comprehensive summary of the diagnosis and treatment of each of these sexual disorders [1]. EAU guidelines suggest that any other sexual dysfunction, (e.g., erectile dysfunction) or genitourinary infection (e.g., prostatitis) should be treated first [1].

Pathophysiology of PE

The precise pathophysiology of PE has yet to be defined in humans, although there is evidence, primarily from experimental animal studies, supporting the involvement of neurobiological as well as psychogenic factors [21,29,30]. The neurophysiology of ejaculation is highly complex [29]. Ejaculation is considered both a reflexive and cerebral process mediated by a spinal control center, known as the 'spinal ejaculation generator', located in the lumbosacral spinal cord [29–31]. The spinal ejaculation generator modulates the emission and expulsion phases of ejaculation by coordinating genital sensory input, motor outputs and descending supraspinal modulation from several brain regions [29–31].

Several neurotransmitter systems have been implicated in the ejaculatory process, with serotonin (5-hydroxytryptamine [5-HT]) neurons having a fundamental role [2,21,29]. Evidence indicates that 5-HT, throughout brain descending pathways, exerts an inhibitory effect on ejaculation and may have a role in the neuropathophysiology of PE [21,29]. Activation of the postsynaptic 5-HT receptors following release of 5-HT into the synaptic cleft from presynaptic axonal vesicles prolongs ejaculatory latency (**Figure 1**) [31]. In order to prevent overstimulation of postsynaptic 5-HT receptors upon release of 5-HT (in this context, leading to too much inhibition of ejaculation), serotonergic neurons regulate their own activity through three main inhibitory feedback mechanisms [21]: activation of presynaptic 5-HT_{1A} autoreceptors decreases

the firing rate of the 5-HT neuron, inhibiting the release of 5-HT into the synaptic cleft; activation of presynaptic 5-HT$_{1B}$ autoreceptors reduces 5-HT release into the synaptic cleft; and 5-HT reuptake transporters (5-HTT), located at the presynaptic terminals and serotonergic cell bodies, bind to and remove 5-HT from the synaptic cleft back into the presynaptic neuron.

It has been postulated that men with minimal levels of 5-HT neurotransmission and/or hyposensitivity of postsynaptic 5-HT receptors in the brainstem or spinal cord have a genetically predetermined low threshold set point that results in less inhibition and, therefore, rapid ejaculation [29,32]. Men with a low threshold set point are likely to only have marginal control over ejaculation and, therefore, can only sustain minimal levels of sexual arousal before ejaculation [29,32]. The 5-HT neurotransmitter system, therefore, represents a potential target for pharmacological intervention in the treatment of PE.

Pharmacological treatment of PE using antidepressants

Antidepressant selective serotonin reuptake inhibitors (SSRIs; e.g., paroxetine, fluoxetine and sertraline) block 5-HTTs, thereby raising levels of 5-HT in the synaptic cleft and in the space around the cell body [2,21,29]. SSRIs are known to delay ejaculation and, because of this effect, they are often used (albeit off-label) for the treatment of PE [1,31]. These agents have half-lives ranging from 21 h (paroxetine) to 4 days (fluoxetine) [33], and are intended for chronic dosing in the treatment of psychiatric disorders [34]. Daily dosing of paroxetine was found to be superior to other antidepressant SSRIs, as it provided the strongest delay in ejaculation [35]. Moreover, daily dosing of antidepressant SSRIs produced greater ejaculation-delaying effects compared with on-demand dosing of antidepressant SSRIs [31,36]. On-demand treatment with paroxetine had no clinically relevant ejaculation delay in men with lifelong PE (who had a baseline IELT of <1 min), with a 1.41-fold increase of IELT when taken approximately 5 h before intercourse [37]. Interestingly, the same study demonstrated that the tricyclic antidepressant clomipramine (which, although not a SSRI, does inhibit 5-HT transport) delayed ejaculation when taken on-demand approximately 5 h before intercourse, increasing IELT by 4.05-fold [37]. Both drugs were associated with mostly mild but annoying nonsexual side effects on the coitus day and the following day [37]. The precise mechanism of action of SSRIs in treating PE is not yet well understood and it remains to be elucidated why the SSRIs are not equal in their ability to delay ejaculation [21]. The possible mechanisms of action that underpin chronic and acute administration

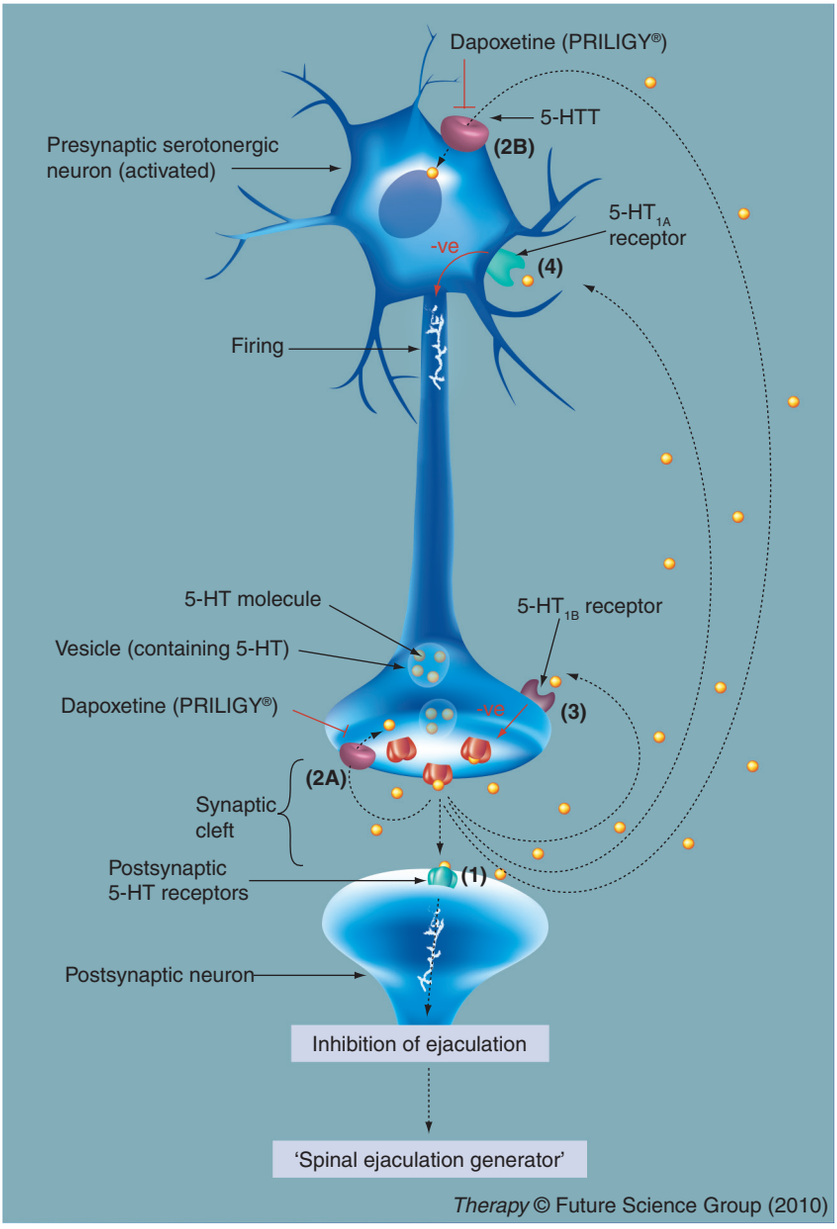

Figure 1. Serotonergic neuronal control of ejaculation and possible inhibitory feedback mechanisms that may prevent overstimulation of postsynaptic 5-HT receptors throughout brain descending pathways.
(1) 5-HT is released into the synaptic cleft following activation of the presynaptic neuron and subsequent fusion of 5-HT-containing vesicles with the plasma membrane. 5-HT binds to postsynaptic 5-HT receptors and exerts an inhibitory effect on ejaculation by prolonging ejaculatory latency. **(2A & B)** 5-HT is removed from the synaptic cleft back into the presynaptic neuron via the 5-HTT located at the presynaptic terminals and at the cell bodies. Dapoxetine prolongs ejaculation by inhibiting the 5-HTT, which leads to increased levels of 5-HT in the synaptic cleft. **(3)** The binding of 5-HT to presynaptic 5-HT$_{1B}$ autoreceptors inhibits the release of 5-HT into the synaptic cleft. **(4)** The binding of 5-HT to presynaptic 5-HT$_{1A}$ autoreceptors reduces the firing rate of the neuron and inhibits the release of 5-HT into the synaptic cleft, thereby reducing inhibition of ejaculation.
5-HT: 5-hydroxytryptamine (serotonin); 5-HTT: 5-HT transporter.
Data taken from [21,29–31].

of antidepressant SSRIs, which may account for the greater ejaculatory delaying effects observed with chronic dosing, have been discussed in detail elsewhere [21]. Chronic administration of conventional antidepressant SSRIs results in a persistent increase in 5-HT levels in the synapse and around the cell body, which causes desensitization of the autoreceptors over a few weeks and, consequently, to less inhibition on 5-HT release [21]. Acute dosing of conventional antidepressant SSRIs leads to an initial increase in 5-HT; however, subsequent activation of autoreceptors, leading to diminished 5-HT release, compensates within minutes for this initial increase in 5-HT caused by blockade of 5-HTT [21]. The overall net effect of chronic versus acute administration of conventional antidepressant SSRIs is greater 5-HT release into the synapse, more enhanced 5-HT neurotransmission and, subsequently, a stronger activation of postsynaptic 5-HT receptors [38]. Therefore, continuous rather than transient blockade of 5-HT with conventional antidepressant SSRIs may be more effective at increasing ejaculatory delay over the long term. Nevertheless, it is possible that SSRIs with a short time to maximum plasma concentration, high maximum plasma concentration and short half-lives may have a sufficient pharmacodynamic effect on 5-HT neurons to produce a clinically meaningful delay in ejaculation almost immediately after the first dose [39].

Pharmacology of dapoxetine

Dapoxetine (PRILIGY®; Janssen-Cilag EMEA, a division of Janssen Pharmaceutica NV, Beerse, Belgium) is a short-acting SSRI and the first oral agent to be approved for the on-demand treatment of PE. It is authorized for the treatment of PE in Argentina, Austria, Finland, Germany, Italy, Macau, Mexico, New Zealand, Portugal, Spain, South Korea and Sweden, with approvals in other countries pending.

Dapoxetine is a potent inhibitor of the 5-HTT (Figure 1) and represents the first of a new generation of pharmacotherapies developed specifically for the treatment of men with PE [31,40]. Dapoxetine ((+)-(*S*)-*N*,*N*-dimethyl-(α)-[2-(1-naphthalenyloxy)ethyl]-benzenemethanamine) hydrochloride is a water-soluble, off-white powder with a molecular weight of 341.9 [40]. The recommended starting dose of dapoxetine for all patients (men aged 18–64 years) is 30 mg, taken as needed approximately 1–3 h prior to sexual activity [41]. The maximum recommended dosing frequency is once every 24 h [41]. The dose may be increased to the maximum recommended dose of 60 mg, if the effect of 30 mg is insufficient and the side effects are acceptable [41]. It is recommended that dapoxetine be taken with a glass of water, with or without food, but not with alcohol [41].

Pharmacokinetics of dapoxetine

Dapoxetine has a pharmacokinetic profile that differentiates it from other SSRIs and makes it a viable option for the on-demand treatment of PE [40,42]. Studies in healthy male volunteers showed that a single dose of orally administered dapoxetine 30 and 60 mg was rapidly absorbed, reaching a high maximum plasma concentration of 297 and 498 ng/ml, respectively, after 1.01 and 1.27 h (Table 1) [42]. Elimination of dapoxetine 30 and 60 mg was also rapid and biphasic, with an initial half-life of 1.31 and 1.42 h, respectively, and terminal half-life of 18.7 and 21.9 h. In contrast to other SSRIs, dapoxetine is almost completely eliminated from the body within 24 h (at 24 h plasma levels are <5% of peak values) and has minimal-to-modest accumulation after daily dosing [33,42]. Multiple dosing of dapoxetine had a similar pharmacokinetic profile to single dosing, and also led to minimal accumulation [42].

Dapoxetine is distributed rapidly throughout the body, has an absolute bioavailability of 42%, is 99% protein-bound and has a volume of distribution of 2.1 l/kg [40]. It is extensively metabolized to phase I and II metabolites by multiple enzymes, including cytochrome P450 isoforms and flavin monooxygenase 1 [42]. Dapoxetine-*N*-oxide is the primary circulating metabolite, but *in vitro* studies demonstrate that it is inactive and, therefore, does not contribute to clinical efficacy [42]. Dapoxetine is excreted in the urine, primarily as the metabolized drug [42]. Dapoxetine has no clinically relevant pharmacokinetic interactions with the phosphodiesterase-5 inhibitors (PD5Is) tadalafil and sildenafil, which are used to treat erectile dysfunction [43]. Age or consumption of a high-fat meal has only a modest effect on the pharmacokinetics of dapoxetine in healthy men [44].

Clinical development program of dapoxetine in PE

Dapoxetine has been assessed for the treatment of PE in five Phase III, randomized, double-blind, parallel-group, placebo-controlled clinical trials involving 6081 individuals (Table 2) [45–48]. The trials included two in the USA (identical design allowing an integrated analysis of the data) [45], an international trial (conducted in Europe, North and South America, Israel, and South Africa) [46], one in the Asia–Pacific region [47] and one in North America (conducted in Canada and the USA) [48].

All five trials had a similar design that included a baseline period (lasting 1–4 weeks) and a randomized treatment period (lasting 9–24 weeks) [45–48]; two trials also included a withdrawal period to allow assessment of SSRI discontinuation syndrome [46,48]. Men enrolled in the five trials were 18 years of age or more, in a stable, heterosexual relationship for more than 6 months and were diagnosed with PE according to DSM-IV-TR criteria; four trials also required a baseline stopwatch-measured IELT of less than 2 min in 75% or more of sexual encounters [45–47]. Outcome measures were stopwatch-measured IELT (held by the partner) [45–47], patient-reported outcomes (PROs) evaluated using the PE Profile (PEP) (a validated measure comprising four items related to PE [49]: control, satisfaction, distress and interpersonal difficulty, each assessed on a five-point scale) [45–48], clinical global impression of change (CGI; a validated assessment of change in overall condition, scored on a seven-point scale [50]: from -3 'much worse' to +3 'much better') [45–48] and partner PROs [45,46]. Additional measures included assessing withdrawal effects following discontinuation of treatment [46,48], as well as safety and tolerability [45–48].

Two key postmarketing studies are currently underway to further assess the efficacy and safety of dapoxetine in PE. The first is the 12-week, randomized, Phase III, COUPLE study to evaluate the efficacy and safety of dapoxetine, compared with placebo, in men with PE and erectile dysfunction who are being treated with a PD5I for their erectile dysfunction [101]. The second is the 12-week observational PAUSE study to evaluate the safety of dapoxetine or alternative care in men with PE treated in the clinical practice setting [102].

Clinical efficacy of dapoxetine in PE

Intravaginal ejaculatory latency time

Compared with placebo, dapoxetine 30 and 60 mg significantly and consistently increased mean IELT at 12–24 weeks above baseline values across the clinical trials ($p \leq 0.001$ both doses vs placebo) (**Figure 2**) [45–47]. Mean IELT increased from 0.9–1.1 min at baseline to 2.8–3.9 min and 3.3–4.2 min with dapoxetine 30 and 60 mg, respectively, compared with 1.8–2.4 min for placebo ($p \leq 0.001$ both doses vs placebo). Significant improvements in mean IELT with dapoxetine were observed after the first dose and at all subsequent time points at 4-week intervals up to the 12 and 24 week end points ($p \leq 0.001$ both doses vs placebo) [45–48]. At 12 and 24 weeks, dapoxetine 60 mg produced a greater increase in mean IELT than the 30 mg dose [45–48].

Table 1. Key single-dose (day 1) pharmacokinetic parameters (mean and standard deviation) of 30 and 60 mg dapoxetine.

Parameter	Dapoxetine 30 mg mean (standard deviation)	Dapoxetine 60 mg mean (standard deviation)
C_{max}	297 ng/ml (130)	498 ng/ml (180)
T_{max}	1.01 h (0.34)	1.27 h (0.44)
Initial $t_{½}$	1.31 h (0.15)	1.42 h (0.13)
Terminal $t_{½}$	18.7 h (7.1)	21.9 h (10.0)

C_{max}: Maximum plasma concentration; $t_{½}$: Half-life; T_{max}: Time to maximum plasma concentration. Data taken from [42].

Two of the dapoxetine Phase III clinical studies also reported geometric mean IELT [46,47]. In the international study, geometric mean IELT increased from 0.7 min at baseline to 1.1 min with placebo, 1.8 min ($p < 0.001$ vs placebo) with dapoxetine 30 mg and 2.3 min ($p < 0.001$ vs placebo) with dapoxetine 60 mg, at 24 weeks [46]; corresponding geometric fold increases were 1.5, 2.5 and 3.3, respectively ($p < 0.001$ both doses vs placebo) [46]. In the Asia–Pacific study, geometric mean IELT increased from 0.9 min at baseline to 1.8 min with placebo, 2.7 min ($p < 0.0001$ vs placebo) with dapoxetine 30 mg and 3.1 min ($p < 0.0001$ vs placebo) with dapoxetine 60 mg, at 12 weeks [47]; corresponding geometric fold increases were 2.0, 2.8 and 3.3, respectively ($p < 0.0001$ both doses vs placebo) [47].

Subgroup analyses across the clinical trials demonstrated that dapoxetine was better than placebo at increasing mean IELT at 12 and 24 weeks in men with baseline IELTs of 0.5 min or less, 1 min or less or 2 min or less [45–47]. The greatest increases in mean IELT at 12 and 24 weeks were observed in men with lower initial baseline

Table 2. Phase III clinical trial program of dapoxetine involving 6081 men with premature ejaculation.

Trial (by country or region)	Subjects (n)	Number of sites	Duration (weeks)	Ref.
USA†	2614	121 sites in the USA	12	[45]
International	1162	130 sites in Europe, North and South America, Israel and South Africa	24	[46]
Asia–Pacific	1067	52 sites in Asia and Australia	12	[47]
North America	1238	91 sites in Canada and the USA	9	[48]

†The US data comprise an integrated analysis of two identically designed trials.

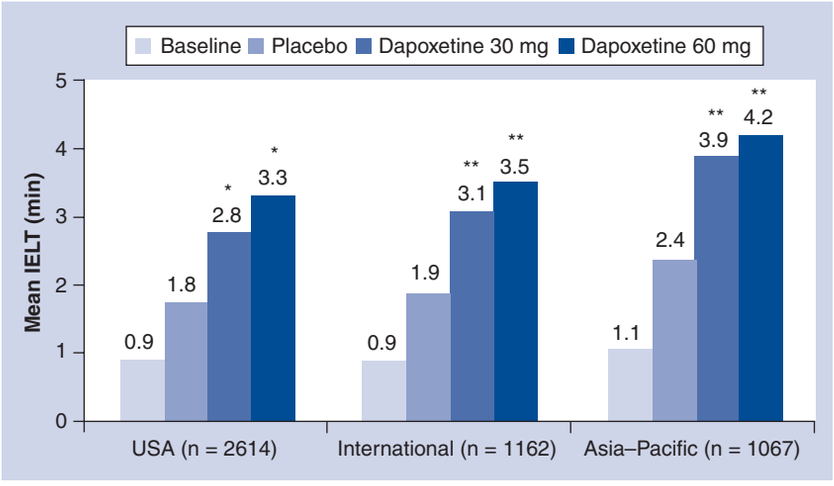

Figure 2. Mean intravaginal ejaculatory latency time at baseline and study end points (week 12 in the US and Asia–Pacific trials, and week 24 in the international trial). The US data comprise an integrated analysis of two identically designed trials. Baseline values are combined for placebo, and dapoxetine 30 and 60 mg groups within each trial.
*p ≤ 0.0001 versus placebo.
**p ≤ 0.001 versus placebo.
IELT: Intravaginal ejaculatory latency time.
Data taken from [45–47].

IELTs [45–47]. Increases in geometric mean IELT were also greater with dapoxetine than placebo at study end points across these baseline IELT strata [46,47].

A recent integrated analysis of two randomized, placebo-controlled, Phase III studies was undertaken to assess the efficacy of dapoxetine in 2228 men who were classified as having either lifelong or acquired PE at screening [51]. Significant ($p < 0.001$) differences were observed in arithmetic and geometric mean IELT at study end point for both dapoxetine 30 and 60 mg, compared with placebo, in men with lifelong or acquired PE, without concomitant erectile dysfunction [51].

Patient-reported outcomes

Significant improvements in PEP-assessed PROs (i.e., increased control and satisfaction, and decreased distress and interpersonal difficulty) were observed with dapoxetine 30 and 60 mg, compared with placebo ($p < 0.05$ for both doses) [46]. Improvements in PEP outcomes were apparent across the clinical trials after the first dose of either 30 or 60 mg dapoxetine, and were maintained to the study end points [45–48].

In addition, female partners of men with PE receiving dapoxetine 30 or 60 mg reported meaningful benefit from treatment [52]. At baseline, less than 5% of female partners reported that the man's control over ejaculation was 'good' or 'very good'; at study end point, this increased to 25.0 and 32.3% for female partners of men treated with dapoxetine 30 or 60 mg, respectively, compared with 14.4% for placebo ($p < 0.001$ for both doses) [52]. At baseline, less than 16% of female partners reported 'good' or 'very good' satisfaction with sexual intercourse; at study end point, this increased to 33.8 and 39.1% for female partners of men treated with dapoxetine 30 or 60 mg, respectively, compared with 19.4% for placebo ($p < 0.001$ for both doses) [52]. Female partners of men who received dapoxetine also reported significant ($p < 0.001$ for both doses) decreases in personal distress and interpersonal difficulty related to ejaculation, compared with placebo [52].

Composite PRO criteria (i.e., an increase of ≥2 categories in control and a decrease of ≥1 category in distress) is a useful tool for assessing treatment benefit [53]. A greater proportion of men treated with dapoxetine achieved the composite PRO definition of clinical benefit at 24 weeks, compared with placebo (25.3 and 37.1% with dapoxetine 30 and 60 mg, respectively, vs 13.0% with placebo; $p \leq 0.001$ both doses) (Figure 3) [46]. Treatment benefits were observed with dapoxetine over placebo in men with a range of baseline IELTs up to 2 min [46]. Similar composite PRO outcomes as those obtained at 24 weeks were observed with dapoxetine, compared with placebo, at 9 and 12 weeks [46–48].

For the CGI measure, significantly more men treated with dapoxetine 30 or 60 mg reported that their PE was at least 'better' at 24 weeks, compared with placebo (30.6 and 39.2% with dapoxetine 30 and 60 mg, respectively, vs 15.6% with placebo; $p \leq 0.001$ both doses) (Figure 4) [46]. Similar improvements in CGI ratings were obtained with dapoxetine over placebo in men with a range of baseline IELTs up to 2 min [46].

The recent integrated analysis of two randomized, placebo-controlled, Phase III studies investigated the efficacy, in terms of improvement in PROs, of dapoxetine in men with either lifelong or acquired PE [51]. Significant differences ($p < 0.05$) were observed for all PRO (control over ejaculation, satisfaction with sexual intercourse, personal distress and interpersonal difficulty) at the study end point for both dapoxetine 30 and 60 mg, compared with placebo, in men with lifelong or acquired PE and no erectile dysfunction [51].

Safety & tolerability of dapoxetine

Results from the five Phase III clinical trials demonstrated that dapoxetine was generally well tolerated, with an acceptable safety profile [45–48]. Commonly reported adverse events with dapoxetine 30 and 60 mg included nausea (10.9 and 22.0%, respectively, vs 2.1% with placebo),

dizziness (5.7 and 10.6% vs 2.0% with placebo), headache (5.5 and 8.0% vs 4.8% with placebo), diarrhea (3.5 and 6.6% vs 1.4% with placebo) and somnolence (3.4 and 4.7% vs 0.5% with placebo) (TABLE 3) [45–48]. Adverse events were generally mild in severity, transient and dose related [45–48]. The incidence of serious adverse events across the five trials was low, occurring in 0.3–1.0 and 0.5–0.8% of subjects treated with dapoxetine 30 and 60 mg, respectively, and 0.8–1.0% with placebo [45–48]. Results have also demonstrated that dapoxetine was not associated with withdrawal syndrome following abrupt discontinuation [54].

Other possible treatments for PE

Several other treatment options have been evaluated in PE, including topical anesthetic preparations, PD5Is, behavioral techniques, psychotherapy and sexual (i.e., relationship) counseling [1,55].

Topical Eutectic-Like Mixture for PE (TEMPE®; Plethora Solutions PLC, London, UK) is a metered-dose aerosol containing local anesthetics lidocaine and prilocaine [56,57], which is being developed for the treatment of PE. Preliminary findings showed encouraging improvements in IELT and PROs with TEMPE [56,57]. In a Phase II study involving 54 men with PE, mean change in IELT from baseline was 2.4-times higher in the TEMPE group versus placebo ($p < 0.01$) [57]. Most patients (83%) considered the spray easy to use [57]. Local numbness occurred in three (12%) of the TEMPE-treated patients [57].

A topical anesthetic cream (often referred to as EMLA cream) containing lidocaine and prilocaine is available. This is applied to the penis approximately 20 min before intercourse to provide local analgesia. The efficacy of lidocaine–prilocaine-based cream has been demonstrated in men with PE [58,59]. In a small-scale study involving 42 men with PE, lidocaine–prilocaine cream increased mean IELT from 1.49 to 8.45 min ($p < 0.001$) [58]. Side effects of this treatment include loss of erection due to numbness of the genitals [59] and there is also the possibility that the partner's vagina could become contaminated with the cream during intercourse, leading to a loss of sensation [60].

Phosphodiesterase-5 inhibitors have also been investigated as a possible treatment for men with PE. Results from a randomized study showed that although sildenafil did not significantly increase IELT, compared with placebo, this drug significantly ($p < 0.05$) increased the perception of ejaculatory control, ejaculatory confidence and overall sexual satisfaction [61]. In another study in 42 men with lifelong PE, changes in geometric mean IELT from baseline to 16 weeks were superior with vardenafil (0.6 vs 4.5 min, $p < 0.01$) versus placebo (0.7 vs 0.9 min, not significant) [62]. Common adverse events for the PD5Is were headache, flushing and dyspepsia [61,62]. PD5Is can be

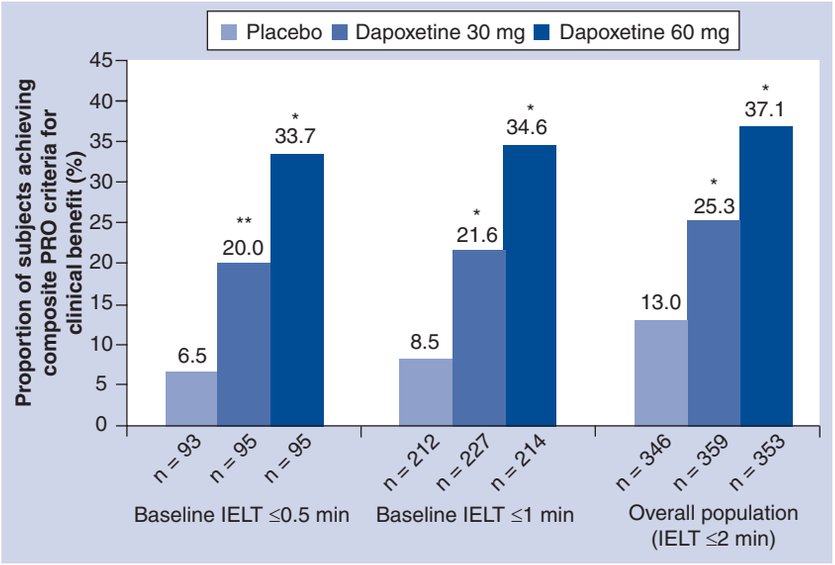

Figure 3. Composite patient-reported outcome criteria (an increase of ≥2 categories in control and a decrease of ≥1 category in distress) for clinical benefit at week 24 by baseline intravaginal ejaculatory latency time.
*p ≤ 0.001 versus placebo.
**p = 0.024 versus placebo.
IELT: Intravaginal ejaculatory latency time; PRO: Patient-reported outcome.
Data taken from [46].

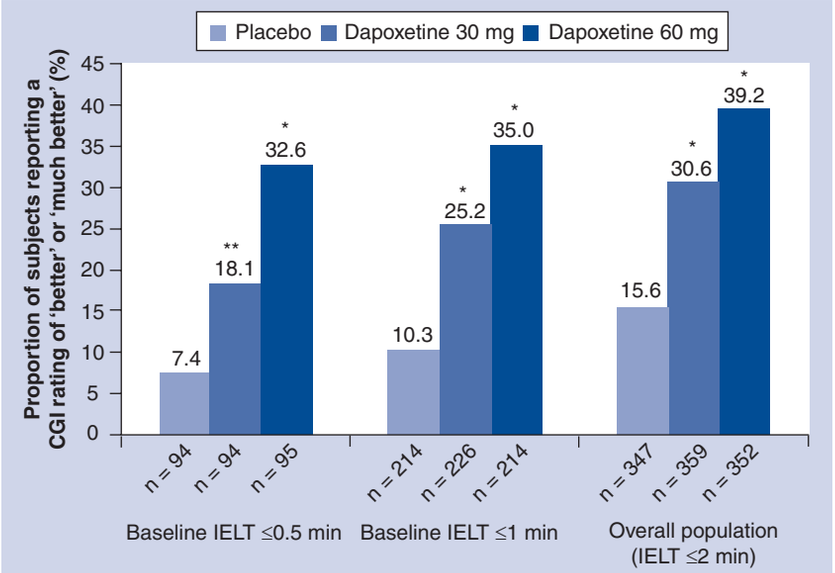

Figure 4. Clinical global impression of change rating of 'better' or 'much better' at week 24 by baseline intravaginal ejaculatory latency time.
*p ≤ 0.001 versus placebo.
**p = 0.048 versus placebo.
CGI: Clinical global impression of change; IELT: Intravaginal ejaculatory latency time.
Data taken from [46].

Table 3. Commonly reported treatment-emergent adverse events in men receiving dapoxetine or placebo across the Phase III clinical trials.

Treatment	Nausea n (%)	Dizziness n (%)	Headache n (%)	Diarrhea n (%)	Somnolence n (%)	Ref.
***USA*[†]**						
PBO[‡] n = 872	17 (1.9)	7 (0.8)	35 (4.0)	12 (1.4)	2 (0.2)	[45]
DPX 30 mg[‡] n = 876	76 (8.7)	26 (3.0)	52 (5.9)	34 (3.9)	28 (3.2)	
DPX 60 mg n = 870	175 (20.1)	54 (6.2)	59 (6.8)	59 (6.8)	32 (3.7)	
***International*[§]**						
PBO n = 385	11 (2.9)	10 (2.6)	32 (8.3)	6 (1.6)	4 (1.0)	[46]
DPX 30 mg n = 388	64 (16.5)	10 (2.6)	25 (6.4)	15 (3.9)	15 (3.9)	
DPX 60 mg n = 389	119 (30.6)	52 (13.4)	53 (13.6)	44 (11.3)	28 (7.2)	
***Asia–Pacific*[¶]**						
PBO n = 357	7 (2.0)	14 (3.9)	7 (2.0)	3 (0.8)	2 (0.6)	[47]
DPX 30 mg n = 354	37 (10.5)	37 (10.5)	12 (3.4)	7 (2.0)	12 (3.4)	
DPX 60 mg n = 356	94 (26.4)	67 (18.8)	17 (4.8)	6 (1.7)	22 (6.2)	
***North America*[§]**						
PBO n = 245	4 (1.6)	7 (2.9)	15 (6.1)	5 (2.0)	2 (0.8)	[48]
DPX 60 mg n = 491	75 (15.3)	50 (10.2)	40 (8.1)	30 (6.1)	18 (3.7)	
Total (from published clinical trial data)						
PBO n = 1859	39 (2.1)	38 (2.0)	89 (4.8)	26 (1.4)	10 (0.5)	[45–48]
DPX 30 mg n = 1618	177 (10.9)	93 (5.7)	89 (5.5)	56 (3.5)	55 (3.4)	
DPX 60 mg n = 2106	463 (22.0)	223 (10.6)	169 (8.0)	139 (6.6)	100 (4.7)	

[†]The US data comprise an integrated analysis of two identically designed trials.
[‡]Four patients who inadvertently received placebo and dapoxetine 30 mg were counted in both treatment groups.
[§]Occurring in 2% or more of subjects.
[¶]Occurring in 1% or more of subjects.
DPX: Dapoxetine; PBO: Placebo.

considered the first-line treatment option in men with PE and concomitant erectile dysfunction. However, further investigation is necessary to clarify the role of PD5Is in treating men who have either PE without coexisting erectile dysfunction.

Historically, PE was considered to be primarily a psychological problem [23,63]. In accordance with this perception, behavioral therapies (e.g., 'squeeze' and 'stop–start' techniques), psychotherapy and sexual counseling have been mainstays in the management of PE for many years [64]. The aims of psychosexual intervention in PE are to help the man and his partner increase satisfaction, regain confidence and intimacy, reduce anxiety, resolve interpersonal difficulties and promote communication between the couple [65]. Despite short-term outcome successes with behavioral techniques [65], they are cumbersome [2] and their long-term benefit is uncertain [66].

Conclusion & future perspective

Premature ejaculation is a relatively common sexual disorder that has a multifactoral pathogenesis, for which an approved pharmacotherapy (i.e., dapoxetine) is now available [29]. Recent EAU guidelines recommend pharmacotherapy as the basis of treatment for PE – particularly in lifelong PE [1].

Dapoxetine is the first orally administered pharmacotherapy to be approved for the treatment of PE. On-demand dapoxetine (30 and 60 mg) administered 1–3 h prior to intercourse effectively delayed objective time to ejaculation (i.e., increased mean IELT) by approximately three- to four-fold, compared with placebo [45–48]. There has been some debate over the magnitude of placebo response (approximately twofold vs three- to four-fold with dapoxetine) and the inclusion of men with an IELT up to 2 min in the dapoxetine clinical trials [67]. The answer to why relatively small ejaculation-delaying effects from treatment, compared with placebo, can have clinically meaningful benefits for men with PE remains to be fully elucidated [67]. It has been suggested that subjective feelings of improvement after taking a drug with a small effect are caused by psychological factors [67]. Interestingly, it has been noted that baseline IELT is important for predicting the likely effects of placebo in clinical studies [68]. For example, the magnitude of the placebo response is likely to be higher in men with a baseline IELT of 1–2 min than in men with an IELT of less than 1 min [68]. Nevertheless, increases in IELT in the overall patient population who received dapoxetine were significantly higher than those obtained with placebo and were observed in men

with baseline IELTs ranging from 30 s or less up to 2 min [45–48]. PE is not characterized solely by short ejaculatory latency, but also psychological factors such as feelings of control over ejaculation and satisfaction with intercourse [69]. By including men with an IELT up to 2 min, the dapoxetine studies did not discriminate men who had an IELT of more than 1 min but a reduced psychological well-being as a result of their condition. In the clinical practice setting, the clinician should have flexibility to diagnose PE in treatment-seeking men who have concerns regarding ejaculating within 1–2 min, without stigmatizing men who also ejaculate within this timeframe, but have no complaints of PE.

It has been suggested that geometric mean IELT values are more representative of treatment response, providing a measure of central tendency that is less affected by outliers and, therefore, should be used to assess drug-induced ejaculatory delay [46,47,67,70,71]. Increases in geometric mean IELT (and corresponding fold increases) were also significantly higher with dapoxetine, compared with placebo, in the overall patient population and across the baseline IELT strata [46,47].

Dapoxetine also improved subjective patient-reported measures of the disorder by increasing sense of control over ejaculation and sexual satisfaction, as well as decreasing distress and interpersonal difficulty for both the man and his partner [45–48]. In addition, dapoxetine is generally well tolerated and has a manageable side-effect profile in men treated for PE [45–48]. Dapoxetine is well suited for the treatment of PE because this drug has a pharmacokinetic profile that enables it to provide clinical benefit with on-demand administration [40,42]. An observational questionnaire survey in 88 Dutch men with lifelong PE indicated that most men (81%) would favor uninterrupted daily treatment to delay ejaculation, because it would not interfere with the spontaneity of having intercourse [72]. Larger-scale investigation is warranted in different countries and cultures to get a better understanding of what aspects of on-demand or daily drug treatment are preferred by men with PE, according to their frequency of sexual activity.

Studies investigating pharmacologic treatments in men with acquired PE are hampered by a lack of standardized criteria to categorize this type of PE [51]. In addition, some patients do not achieve good ejaculatory control despite being successfully treated for prostatitis [73] or hyperthyroidism [28]. Patients may also develop a secondary psychologic concern over their ability to delay ejaculation, which necessitates counseling and/or pharmacologic intervention [46]. Although dapoxetine might be expected to have activity only in lifelong PE that has a hypothetical neurobiologic etiology, this does not appear to be the case [46]. Recent results from an integrated analysis of two randomized, placebo-controlled, Phase III trials demonstrated that dapoxetine improved IELT and PROs (control, satisfaction, distress and interpersonal difficulty) in men with lifelong or acquired PE [51].

Since both neurobiological and psychological factors appear to have a role in PE, it is possible that a combined treatment approach would provide additional clinical benefits over those obtained with a single intervention [63]. For example, combination approaches that incorporate pharmacotherapy (e.g., dapoxetine) with behavioral techniques, psychotherapy and/or sexual counseling may help optimize clinical outcomes [63]. Results from studies investigating combination approaches (i.e., pharmacotherapy in conjunction with behavioral, psychotherapy and/or sexual counseling), as well as PD5Is, will be invaluable to help guide future treatment decisions and further optimize the management of PE.

Findings from a recent survey evaluating 'real-world' practice patterns of 207 urologists in the USA highlighted some important findings on how various presentations of PE would be managed [74]. Results indicated that although half (51%) of the urologists reported that they would inquire regarding the sexual partner, very few (≤8%) would evaluate, refer or treat the partner [74]. The fundamental aims of treatment in PE are to allow the man to establish a sense of control over ejaculation and the couple to have satisfaction with sexual intercourse [2]. It is conceivable that the couple as a whole could benefit from including the partner in the therapy [75]. Moreover, regular follow-up with the man (and his partner) is vital to monitor outcomes and side effects from treatment, and make informed adjustments to treatment, as necessary.

The field of PE has evolved remarkably over the past few years and it is apparent that interest in medical treatment for PE is becoming increasingly widespread [76]. Nevertheless, there are a number of barriers to overcome in the future to further improve the clinical benefits for the man and his partner. Efforts are required to continue to raise awareness among the general public, as well as healthcare professionals, on the availability of an approved treatment for PE (i.e., dapoxetine), differentiate PE from erectile dysfunction, and improve the willingness of men to discuss their

symptoms and seek help [22]. Further increasing the awareness of PE and reducing the reluctance of both men and clinicians to initiate dialog regarding sexual health-related issues will help minimize the risk of misdiagnosis and undertreatment [22].

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Executive summary

Premature ejaculation

- Premature ejaculation (PE) is one of the most common male sexual dysfunctions, with a prevalence rate of 0.5–31.0%.
- PE is classified as lifelong (primary) or acquired (secondary).
- It can have a major negative impact on the quality of life of both the man and his partner.
- PE appears to be a multidimensional disorder, comprising neurobiological and psychological components.

Mechanism of action of dapoxetine

- Dapoxetine is short-acting, orally administered, selective serotonin reuptake inhibitor that increases levels of serotonin in the synaptic cleft, thereby inhibiting ejaculation.

Pharmacokinetic profile of dapoxetine

- Dapoxetine is rapidly absorbed (reaching peak plasma concentrations after 1.0–1.3 h) and eliminated (initial half-life of 1.3–1.4 h; at 24 h plasma levels are <5% of peak values).
- It is extensively metabolized and has minimal accumulation after daily or multiple dosing.
- Dapoxetine has no clinically relevant interactions with phosphodiesterase-5 inhibitors used to treat erectile dysfunction.

Clinical efficacy of dapoxetine

- Dapoxetine has been evaluated in five randomized, placebo-controlled Phase III trials lasting 9–24 weeks involving 6081 men with PE.
- Dapoxetine (30 and 60 mg) consistently and significantly increased mean intravaginal ejaculatory latency time across the trials ($p \leq 0.001$ both doses vs placebo) for up to 24 weeks.
- Increases in intravaginal ejaculatory latency time with dapoxetine were observed in men with baseline intravaginal ejaculatory latency times ranging from 0.5 min or less to 2 min.
- Compared with placebo, dapoxetine significantly improved patient-reported outcomes (control, satisfaction, distress and interpersonal difficulty) in men and female partners.

Safety & tolerability of dapoxetine

- Dapoxetine was generally well tolerated across the clinical trials; side effects were typically mild in severity, transient and dose related.
- Common side effects with dapoxetine were nausea, dizziness, headache, diarrhea and somnolence.
- No withdrawal syndrome observed following abrupt cessation of dapoxetine.

Dosing of dapoxetine

- The recommended starting dose of dapoxetine is 30 mg taken as needed 1–3 h before intercourse; dose can be increased to 60 mg if required; maximum dosing frequency is once every 24 h.

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