REVIEW ARTICLE

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Efficacy and safety of dapoxetine in treatment of premature ejaculation: an evidence-based review

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SUMMARY

Background: Premature ejaculation (PE) is a major issue in male sexual health, with a global prevalence 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, behavioural methods and off-label use of selective serotonin reuptake inhibitors (SSRIs) usually used to treat depression and other psychological disorders. Dapoxetine is the only SSRI specifically designed to treat PE. **Mechanism of action:** Dapoxetine hydrochloride is a potent inhibitor of serotonin reuptake transporters. Dapoxetine is suited for 'on-demand' treatment of PE because of its rapid absorption and short initial half-life. **Efficacy:** Evidence from published studies showed that dapoxetine 30 mg or 60 mg taken 'on-demand' results in a significant increase in intravaginal ejaculatory latency time (IELT) when compared with placebo. Most 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 significantly reduced interpersonal difficulties. **Safety:** The most common adverse events with dapoxetine are nausea, dizziness, somnolence, headache, diarrhoea and insomnia. Usually they do not lead to drug discontinuation. **Conclusion:** Dapoxetine is the only effective and safe available on-label oral treatment for PE, and its use can result in better quality of life for the patient and their sexual partner.

Review criteria

A literature search was performed in August 2015 using MEDLINE and Web of Science searching the terms 'premature ejaculation', 'dapoxetine', '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, randomised, placebo-controlled clinical trials (RCTs). The references listed in identified articles were used as a further source of relevant studies.

Message for the clinic

Dapoxetine is the only drug licensed for the oral treatment of premature ejaculation (PE). Profile of dapoxetine makes on-demand treatment feasible for a majority of qualified patients. Dapoxetine 30 mg or 60 mg has been shown to be an efficacious and tolerable treatment both for lifelong and acquired PE, improving the IELT and most of the patient-reported outcomes. Multiple studies confirmed dapoxetine as an effective treatment for PE, resulting in better quality of life for the patient and the couple.

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Background

The International Society of Sexual Medicine's (ISSM) Guidelines' definition of premature ejaculation (PE) consists of a male sexual dysfunction that shows the following features: ejaculation that always or nearly always occurs before or within about 1 min of vaginal penetration from the first sexual experience (lifelong premature ejaculation – LPE), or a clinically significant reduction in latency time, often to about 3 min or less (acquired premature ejaculation – APE); the inability to delay ejaculation on all or almost all vaginal penetrations; and negative personal consequences, such as frustration, distress, bother and/or the avoidance of sexual intimacy (1). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (2) definition of PE is coherent with the ISSM definition and includes the approximately 1-min intravaginal ejaculatory latency time (IELT) criteria and the presence of negative distress. Ejaculation before the penetration refers to men who ejaculate prior to vaginal penetration and is considered the most severe form of PE (3).

Premature ejaculation is the most common sexual dysfunction in men, with a prevalence estimated to be between 20% and 40% (4). The ambiguity about prevalence is because of the intimate nature of the condition and, until recently, the lack of a universal evidence-based definition. It is likely that many men still do not admit to having the condition and do not seek medical advice for PE (5).

The aetiology of PE has been sought in different areas and many potential factors have been proposed (6). Traditionally, PE was thought to be psychologically based, as a result of anxiety or conditioning towards rapid ejaculation based on rushed early sexual experiences (7). Then, in the last 20 years,

somatic and neurobiological aetiologies have been hypothesised (7). Over time numerous biological factors have been proposed including: hypersensitivity of the glans penis (8), robust cortical representation of the pudendal nerve (9), disturbances in central serotonergic neurotransmission (10), erectile difficulties and other sexual comorbidities (11), prostatitis (12), detoxification from prescribed medications (13), recreational drugs (14), chronic pelvic pain syndrome and urological disorders of the lower urinary tract (13), and thyroid disorders (15). None of these aetiologies has been confirmed in large studies.

Serotonin is the neurotransmitter of most interest in the control of ejaculation and has the strongest data in animal and human models (16). Serotonin dysregulation as an aetiological hypothesis for LPE has been postulated by Waldinger who hypothesised that LPE can be explained by a hyposensitivity of the 5-HT2C and/or hypersensitivity of the 5-HT1A receptors (17). This hypothesis explains only a small percentage (2–5%) of complaints of PE in the general population (16).

Dopamine and oxytocin have a stimulatory effect on ejaculation in animal studies (18). The biology of these neurotransmitters related to ejaculation is less well studied but it appears to play an important role in ejaculation.

The hormonal regulation of male reproduction and sexuality is well established, but endocrine control of ejaculation is still not completely clarified. Recently it was found in studies on large populations that the endocrine system is involved in the control of ejaculatory function and that prolactin and testosterone play independent roles (19).

Men affected by APE report, as common findings, prostatic inflammation and chronic bacterial prostatitis (20). A direct influence of inflammation in the pathogenesis of a few cases of APE seems plausible (21).

Scarce prevalence data of PE in men who have sex with men (MSM) is currently available. Existing studies report that a substantial proportion of MSM experience PE and the bother associated with it. Most studies hint a similar prevalence of concern about early ejaculation in MSM compared with men who have sex with women only (MSW) (22). Some older studies have suggested that the rate of distressing ejaculation problems in MSM is lower than in MSW (23). It is plausible that differences in relationships and sexual activities may be responsible for some of these differences (24).

Overall, psychological, emotional and relationship factors can initiate or worsen PE. These factors may be psychological factors (performance anxiety, body image, depression, alexithymia), developmental sexual abuse, attitudes towards sex internalised during childhood) and/or relationship factors (decreased intimacy, partner conflict) (25). It is likely that psychological factors may lead to PE or vice versa. It is plausible that the relationship is reciprocal with either PE or the other factor causing exacerbation of the other.

Different approaches are currently available to target PE, from psychotherapy and behavioural treatments to several forms of off-label pharmacotherapy.

In this context, psychotherapy for men and partners suffering from PE has two goals. First aim is to help men develop sexual skills that enable them to delay ejaculation while broadening their sexual schemes, gaining higher sexual self-confidence and weakening performance anxiety. The second goal aims at solving psychological and relationship issues that may have arisen, or precipitated as consequence of the PE symptom for the man, partner, or couple. Behavioural treatments do not exclude a concomitant pharmacological treatment. The synergic approach of psychotherapy and pharmacological treatment leads to better results when treating PE (26).

Many forms of pharmacotherapy have been used to treat PE (27). Topical local anaesthetics (LA) (28), selective serotonin reuptake inhibitors (SSRIs) (29,30), tramadol (31), phosphodiesterase type 5 inhibitors (PDE5i) (32) and alpha adrenergic blockers (33) have been used to target PE. The use of topical LA, such as lidocaine, prilocaine or benzocaine to reduce the sensitivity of the glans penis is the first known pharmacological treatment for PE (34).

The introduction of the SSRIs (e.g. paroxetine, sertraline, fluoxetine and more recently citalopram) along with the tricyclic antidepressant clomipramine was a revolution in the treatment of PE. These drugs block the reuptake of serotonin from the synaptic cleft of central serotonergic neurons by 5-HT transporters, thus resulting in enhanced 5-HT neurotransmission and stimulation of postsynaptic 5-HT receptors (33). All traditional SSRIs have been implemented mainly as off-label daily dosing therapies for PE (9,29,30,35–40). Recently dapoxetine was developed specifically for treating PE and currently is the only SSRI approved and indicated for treatment of PE (41).

Dapoxetine – mechanism of action

Dapoxetine hydrochloride is a potent inhibitor of serotonin reuptake transporters (42,43). While other SSRIs are halogenated molecules, dapoxetine includes a naphthyl moiety; these differences can explain some of the differences in its pharmacokinetics in comparison with the other SSRIs (44).

Dapoxetine is suited for 'on-demand' treatment of PE because of its rapid absorption (5) and short initial half-life, while the other SSRIs share a daily dosing, increasing the risk of class treatment-emergent adverse events (TEAEs). It reaches peak plasma concentrations at about 1.5 h after dosing, compared with 6 h for fluoxetine and 5 h for paroxetine (45). Dapoxetine shows rapid decrease in plasma concentration with plasma levels low as 4% 24 h post dosing (46).

After multiple dosing, the pharmacokinetic of dapoxetine is unaffected, and it does not accumulate significantly (45).

Efficacy

Dapoxetine has been approved for the treatment of PE in over 50 countries worldwide.

The efficacy of dapoxetine for treatment of PE was assessed for the first time by Pryor et al. in a prospectively predefined integrated analysis of two 12-week randomised, double-blind, placebo-controlled, phase III trials of identical design done independently, in parallel, at 121 sites in the USA (47). Two thousand, six hundred and fourteen men with moderate-to-severe PE in stable, heterosexual relationships were randomised to placebo (n = 870), to 30 mg dapoxetine (n = 874), or to 60 mg dapoxetine (n = 870) on-demand (as needed, 1–3 h before anticipated sexual activity). The primary end-point was IELT at week 12 or final visit, measured by stopwatch. All analyses were done on an intention-to-treat basis. At baseline, 1623 men (62%) had IELT of 1 min or less, with mean IELT values similar across groups. At week 12, both dapoxetine doses were better than placebo ($p < 0.0001$, each dose vs. placebo), and 60 mg dapoxetine was better than 30 mg dapoxetine ($p = 0.0007$). Overall, IELT increased in all three groups, but the increase was greatest in those on dapoxetine. At the study end-point, 109 (14%) of 787 patients on placebo, 232 (29%) of 801 on 30 mg dapoxetine, and 261 (34%) of 763 on 60 mg dapoxetine had an IELT of 3 min or more. Dapoxetine was better than placebo on the first dose and at all subsequent time points analysed. After the first dose of dapoxetine or placebo, the mean participant-recorded IELT for the first event increased from baseline to 1.38 (SD 1.84) min with placebo, 2.05 (3.02) min with 30 mg dapoxetine, and 2.41 (3.82) min with 60 mg dapoxetine. The Authors concluded that dapoxetine plays a positive and an active role in increasing IELT (47) (Table 1).

Kaufman et al. reported in 2009 a randomised, double-blind, placebo-controlled, phase III trial enrolling men aged ≥ 18 years, from the USA and Canada, who had a Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) diagnosis of PE (41). One thousand, two hundred and thirty-eight men were randomised to receive placebo or dapoxetine 60 mg as needed or once daily for 9 weeks. The once-daily treatment arm was included for analysis of withdrawal symptoms. Patients completed the Premature Ejaculation Profile (PEP) on day 1 (before dosing), and on days 28 and 63 (or study end-point), which comprised the outcome measures for perceived control over ejaculation, satisfaction with sexual intercourse, and personal distress and interpersonal difficulty related to ejaculation. The patient-reported global impression of change (PGIC) in PE was reported on day 63 (or study end-point). Treatment benefit measures included the composite criteria of at least a two-category increase in perceived control over ejaculation and at least a one-category decrease in personal distress related to ejaculation from baseline at study end-point. At baseline, around 5% of patients in any treatment group reported 'not at all' or 'a little bit' of personal distress related to ejaculation, which increased to 54.3% of those receiving dapoxetine (vs. 35.3% with placebo; $p < 0.001$). Similarly, 43.0% and 40.9% of men in the placebo and dapoxetine groups, respectively, reported 'not at all' or 'a little bit' of interpersonal difficulty related to ejaculation at baseline, which increased to 76.8% and 64.2% of those with dapoxetine and placebo respectively ($p < 0.001$). The percentage of men who achieved

Table 1 Summary of efficacy data from Pryor et al, Lancet, 2006

		All patients (IELT ≤ 2 min)			Patients with baseline IELT > 1 to ≤ 2 min			Patients with baseline IELT ≤ 1 min		
	Mean IELT, min (SD)	Placebo	Dapoxetine 30 mg	Dapoxetine 60 mg	Placebo	Dapoxetine 30 mg	Dapoxetine 60 mg	Placebo	Dapoxetine 30 mg	Dapoxetine 60 mg
Pryor (47)	Baseline	0.90 (0.47)	0.92 (0.50)	0.91 (0.48)	1.39 (0.31)	1.41 (0.31)	1.38 (0.32)	0.61 (0.26)	0.62 (0.32)	0.61 (0.29)
	12 weeks	1.75 (2.21)	2.78 (3.48)	3.32 (3.68)	2.51 (2.72)	3.79 (3.14)	4.43 (4.12)	1.28 (1.48)	1.63 (3.53)	2.67 (3.24)

the composite criteria with dapoxetine 'as needed' was 47.6%, vs. 21.7% with placebo (difference from placebo, 25.9%; $p < 0.001$) (41). The distribution of responses for the PEP among men who achieved the composite criteria was similar to that reported for men without PE in a previous observational study in the USA (42) (Table 2).

Shabsigh et al. conducted in 2008 a subanalysis of combined data from all treatment groups in an integrated analysis (43) of two identically designed, 12-week, double-blind, randomised, placebo-controlled trials of dapoxetine (the same trials evaluated by Pryor et al. (47). The authors assessed the utility of perceived control over ejaculation ('control') in the evaluation of treatment benefit in men with PE, and to compare effects associated with a two-category or greater increase in this variable between men receiving dapoxetine and placebo. Two thousand, six hundred and fourteen men met the DSM-IV-TR criteria for PE, had a stopwatch-measured IELT of ≤ 2 min in $\geq 75\%$ of events in a 2-week baseline period, and self-reported moderate or severe PE. Men received placebo or dapoxetine 30 or 60 mg, 1–3 h before intercourse. The stopwatch-measured IELT was recorded for each episode; the PGIC (7-point scale, 'much worse' to 'much better'), control and satisfaction with sexual intercourse (5-point scales, 'very poor' to 'very good') were assessed monthly. The utility of a two-category or greater increase in control was evaluated by examining the relationship of this variable with IELT and satisfaction with sexual intercourse. Of 2341 men with baseline and end-point assessments, 96.8% reported 'very poor' or 'poor' control at baseline, and 748 (32%) reported a two-category or greater increase in control after treatment. More than 95% of those men rated their PE as 'slightly better', 'better' or 'much better' on the PGIC; 67.1% gave ratings of 'better' or 'much better.' They also had greater improvements in IELT than men with less than a two-category increase in control, with a mean (SD) change from baseline of 3.7 (4.3) vs. 0.77 (1.8) min, respectively, and a greater percentage reported good or very good satisfaction with sexual intercourse than men with less than a two-category increase in control (74% vs. 19% respectively). The proportions of men with a two-category or greater increase in control with dapoxetine 30 and 60 mg were 36.3% and 44.5% respectively (vs. 15% with placebo). The Authors conclude that a two-category or greater increase in control (5-point scale) is useful for assessing the treatment benefit in men with PE; it corresponds with improvements in the man's perception of his condition, substantially greater prolongation of IELT and higher levels of satisfaction with sexual intercourse. The authors concluded that dapoxetine improved patient's control over ejaculation, prolonged the sexual intercourse and increased the level of patient's personal satisfaction (43).

Table 2 Summary of efficacy data from Kaufman et al, BJU Int, 2009

Kaufman (41)	Placebo	Dapoxetine 60 mg prn
Personal distress related to ejaculation (SD)		
Baseline	2.8 (0.82)	2.8 (0.81)
8 weeks	2.0 (1.05)	1.5 (1.05)
Interpersonal difficulty related to ejaculation (SD)		
Baseline	1.8 (1.14)	1.7 (1.06)
8 weeks	1.1 (1.04)	0.8 (1.00)
Perceived control over ejaculation (SD)		
Baseline	0.6 (0.59)	0.6 (0.61)
8 weeks	1.6 (1.02)	2.1 (1.13)
Satisfaction with sexual intercourse (SD)		
Baseline	1.5 (0.79)	1.4 (0.83)
8 weeks	2.0 (1.01)	2.5 (1.11)

Buvat et al. in order to evaluate the long-term efficacy and safety of dapoxetine in men with PE, conducted a randomised, double-blind, parallel-group, placebo-controlled, phase 3 trial, conducted in 22 countries, enrolled men ($N = 1162$) ≥ 18 years of age who met the DMS (fourth edition, text revision) criteria for PE for ≥ 6 months, with IELT ≤ 2 min in $\geq 75\%$ of intercourse episodes at baseline (48). Of 1162 subjects randomised, 618 men completed the study (53%). Mean average IELT increased from 0.9 min at baseline (all groups) to 1.9 min, 3.2 min, and 3.5 min with placebo and dapoxetine 30 mg and dapoxetine 60 mg, respectively, at study end-point. Geometric mean IELT increased from 0.7 min at baseline to 1.1 min, 1.8 min and 2.3 min, respectively, at study end-point. All PEP measures and IELTs improved significantly with dapoxetine vs. placebo at week 12 and week 24 ($p < 0.001$ for all) (48). Limitations of this study included the exclusion of men who were not in long-term monogamous relationships (48) (Table 3).

McMahon et al. evaluated the efficacy and safety of dapoxetine 30 mg and 60 mg on-demand (prn) in men with PE from the Asia-Pacific region (35). The authors conducted a randomised, double-blind, parallel-group, placebo-controlled trial enrolled men who were 18 years or older, in a monogamous, heterosexual relationship for at least 6 months, who met the DSM-IV-TR criteria for PE for at least 6 months and had IELT of 2 min or less in at least 75% of sexual intercourse episodes. Subjects received placebo, dapoxetine 30 mg or dapoxetine 60 mg prn (1–3 h before intercourse) for 12 weeks. Of the 1067

Table 3 Summary of efficacy data from Buvat et al, Eur Urol, 2009

	All patients (IELT ≤ 2 min)			Patients with baseline IELT ≤ 1 min			Patients with baseline IELT ≤ 0.5 min		
Buvat (48)	**Placebo**	**Dapoxetine 30 mg**	**Dapoxetine 60 mg**	**Placebo**	**Dapoxetine 30 mg**	**Dapoxetine 60 mg**	**Placebo**	**Dapoxetine 30 mg**	**Dapoxetine 60 mg**
Aritmetic mean IELT, min (SD)									
Baseline	0.9 (0.51)	0.9 (0.50)	0.9 (0.49)	0.5 (0.27)	0.6 (0.27)	0.5 (0.28)	0.3 (0.13)	0.3 (0.14)	0.3 (0.14)
24 weeks	1.9 (2.89)	3.1 (4.88)	3.5 (3.80)	1.3 (2.12)	2.5 (5.26)	2.8 (3.66)	0.8 (1.7)	1.5 (2.06)	1.8 (2.04)
Geometric mean IELT, min (SE)									
Baseline	0.7 (1.04)	0.7 (1.04)	0.7 (1.04)	0.5 (1.04)	0.5 (1.04)	0.4 (1.05)	0.3 (1.06)	0.3 (1.06)	0.2 (1.08)
24 weeks	1.1 (1.06)	1.8 (1.06)	2.3 (1.06)	0.7 (1.07)	1.3 (1.07)	1.7 (1.07)	0.4 (1.11)	0.9 (1.13)	1.2 (1.11)
Geometric mean fold increase at 24 weeks (SE)	1.5 (1.05)	2.5 (1.05)	3.3 (1.05)	1.5 (1.06)	2.8 (1.07)	3.9 (1.07)	1.5 (1.09)	3.4 (1.12)	5.0 (1.11)
Achieved composite PRO criteria for clinical benefit at 24 weeks (%)	45 (13.0)	91 (25.3)	131 (37.1)	18 (8.5)	49 (21.6)	74 (34.6)	6 (6.5)	19 (20.0)	32 (33.7)
Achieved ≥ one-category increase in satisfaction with sexual intercourse at 24 weeks (%)	124 (35.7)	174 (48.5)	197 (55.8)	61 (28.6)	100 (44.1)	117 (54.7)	25 (26.6)	42 (44.2)	50 (52.6)
Achieved ≥ one-category decrease in personal distress related to ejaculation at 24 weeks (%)	166 (47.8)	216 (60.0)	242 (68.6)	87 (40.8)	131 (57.7)	146 (68.2)	32 (34.4)	51 (53.7)	67 (70.5)
Achieved a CGI rating of 'better' or 'much better' at 24 weeks (%)	54 (15.6)	110 (30.6)	138 (39.2)	22 (10.3)	57 (25.2)	75 (35.0)	7 (7.4)	17 (18.1)	31 (32.6)

subjects randomised, 858 completed the study. Mean average IELT increased from approximately 1.1 min at baseline (across groups) to 2.4, 3.9 and 4.2 min with placebo, dapoxetine 30 mg and dapoxetine 60 mg respectively; geometric mean average IELT increased from approximately 0.9 min at baseline (across groups) to 1.8, 2.7 and 3.1 min respectively. All measures and the clinical global impression of change (CGIC) were significantly improved with dapoxetine vs. placebo at study end-point ($p \leq 0.005$ for all). Dapoxetine treatment significantly prolonged IELT and improved PEP measures and was generally well tolerated in men with PE in the Asia-Pacific region (35) (Table 4).

Porst et al. carried out an integrated analysis (49) of baseline characteristics and treatment outcomes from two phase 3 dapoxetine trials in men with acquired or lifelong PE and mild or no erectile dysfunction (ED). Data were analysed from two randomised, double-blind, placebo-controlled, phase 3 clinical trials (International and Asia-Pacific) that evaluated efficacy and safety of dapoxetine (30 mg or 60 mg as needed) in patients with PE. Men were ≥ 18 years, in a stable monogamous relationship for ≥ 6 months, met DSM-IV-TR criteria for PE for ≥ 6 months, had an erectile function domain of the International Index of erectile Function (IIEF-EF) score ≥ 21, and had a IELT ≤ 2 min in ≥ 75% of intercourse episodes. Demographics, sexual history and PE symptoms at baseline, and mean IELT and patient-reported outcomes (PROs) at study end (week 12), were analysed for men with acquired or lifelong PE and mild or no ED (Erectile Function score 21–25 vs. ≥ 26). Baseline characteristics, except duration of PE, were similar in men with APE and lifelong PE, with no other differentiating features by ED status. Dapoxetine treatment improved significantly mean IELT (arithmetic and geometric) and PRO responses (perceived control over ejaculation, satisfaction with sexual intercourse, ejaculation-related personal distress and interpersonal difficulty) for acquired and lifelong subtypes, but the presence of mild ED diminished PRO responsiveness in both subtypes, particularly those with lifelong PE. The Authors conclude that baseline characteristics and treatment outcomes were generally similar in men with acquired and lifelong PE. The presence of mild ED appears to be associated with a more modest treatment response, irrespective of APE or lifelong PE subtype (49).

McMahon et al. presented integrated efficacy and safety data from phase 3 trials of dapoxetine (37). Data were from five randomised, multicenter, double-blind, placebo-controlled studies conducted in over 25 countries (35,41,47,48). Data from 6081 men ≥ 18 years who met the DSM-IV-TR criteria for PE were analysed. Dapoxetine 30 and 60 mg on-demand (prn; 1–3 h before intercourse) were

Table 4 Summary of efficacy data from McMahon et al, J Sex, Med, 2010

McMahon (35)	Patients with baseline IELT ≤ 0.5 min			Patients with baseline IELT ≤ 1 min			Patients with baseline IELT >1 min to 2 min			All patients (IELT ≤ 2 min)		
	Placebo	Dapoxetine 30 mg	Dapoxetine 60 mg	Placebo	Dapoxetine 30 mg	Dapoxetine 60 mg	Placebo	Dapoxetine 30 mg	Dapoxetine 60 mg	Placebo	Dapoxetine 30 mg	Dapoxetine 60 mg
Average IELT, min (SD)												
Baseline	0.3 (0.15)	0.3 (0.14)	0.3 (0.15)	0.6 (0.26)	0.7 (0.26)	0.6 (0.27)	1.4 (0.25)	1.4 (0.23)	1.0 (0.47)	1.0 (0.47)	1.1 (0.45)	1.1 (0.48)
12 weeks	1.3 (2.25)	2.6 (3.50)	2.2 (2.14)	1.6 (2.00)	2.9 (3.93)	3.3 (3.63)	3.1 (1.86)	4.6 (3.81)	5.0 (4.06)	2.4 (2.05)	3.9 (3.94)	4.2 (3.97)
Geometric mean average IELT, min (SE)												
Baseline	0.3 (1.10)	0.3 (1.09)	0.3 (1.11)	0.5 (1.05)	0.6 (1.05)	0.5 (1.05)	1.4 (1.01)	1.4 (1.01)	0.9 (1.04)	0.9 (1.04)	1.0 (1.03)	0.9 (1.04)
12 weeks	0.7 (1.15)	1.5 (1.20)	1.5 (1.15)	1.1 (1.07)	1.9 (1.08)	2.2 (1.07)	2.6 (1.04)	3.5 (1.06)	4.0 (1.05)	1.8 (1.05)	2.7 (1.05)	3.1 (1.05)
Geometric mean fold increase at 12 weeks (SE)	2.8 (1.15)	5.7 (1.22)	5.8 (1.19)	2.1 (1.07)	3.3 (1.08)	4.0 (1.08)	1.9 (1.04)	2.5 (1.06)	2.8 (1.04)	2.0 (1.04)	2.8 (1.05)	3.3 (1.05)
Achieved composite PRO criteria for clinical benefit at 12 weeks (%)	8 (16.0)	9 (24.3)	16 (34.0)	27 (17.8)	46 (31.5)	47 (30.7)	47 (24.9)	68 (37.2)	78 (42.6)	74 (21.7)	114 (34.7)	125 (37.2)
Achieved 1-category or greater increase in satisfaction with sexual intercourse at 12 weeks (%)	28 (56.0)	26 (70.3)	32 (68.1)	82 (53.9)	95 (65.1)	110 (71.9)	115 (60.8)	133 (72.7)	145 (79.2)	197 (57.8)	228 (69.3)	255 (75.9)
Achieved 1-category or greater decrease in personal distress related to ejaculation at 12 weeks (%)	22 (44.0)	20 (54.1)	29 (61.7)	72 (47.4)	92 (63.0)	99 (64.7)	119 (63.0)	127 (69.4)	146 (79.3)	191 (56.0)	219 (66.6)	245 (72.2)
Achieved a CGI rating of at least 'slightly better' at 12 weeks (%)	21 (42.0)	26 (70.3)	39 (83.0)	63 (41.4)	102 (69.9)	115 (75.2)	117 (61.9)	133 (72.7)	152 (82.6)	180 (52.8)	235 (71.4)	267 (79.2)
Achieved a CGI rating of at least 'better' at 12 weeks (%)	7 (14.0)	13 (35.1)	17 (36.2)	24 (15.8)	43 (29.5)	54 (35.3)	51 (27.0)	80 (43.7)	86 (46.7)	75 (22.0)	123 (37.4)	140 (41.5)

evaluated for either 12 or 24 weeks in four studies; one study evaluated dapoxetine 60 mg daily or prn for 9 weeks. Average IELT (mean, geometric mean) increased from baseline [across groups, 0.9 (0.49) min, 0.8 (1.01) min] to a significantly greater extent with dapoxetine 30 [3.1 (3.91) min, 2.0 (1.03) min] and 60 mg [3.6 (3.85) min, 2.3 (1.03) min] vs. placebo [1.9 (2.43) min, 1.3 (1.02) min; $p < 0.001$ for all] at week 12. All PEP items and CGIC improved significantly with both doses of dapoxetine vs. placebo ($p < 0.001$ for all). In this diverse population, dapoxetine significantly improved all aspects of PE (37).

McMahon et al. evaluated efficacy and safety of prn dapoxetine 30 mg and 60 mg in men with PE and ED who were being treated with PDE5i (50). The authors conducted a randomised, double-blind, placebo-controlled, flexible-dose, multicenter study enrolling men ≥ 18 years who met diagnostic criteria for PE including IELT of ≤ 2 min in ≥ 75% of sexual intercourse episodes, who were on a stable regimen of PDE5i, and had IIEF-erectile function domain score ≥ 21. Subjects received placebo, dapoxetine 30 mg or dapoxetine 60 mg prn (1–3 h before intercourse) for 12 weeks. Of 495 subjects randomised, 429 completed the study. Arithmetic mean average IELT significantly increased with dapoxetine vs. placebo at end-point (5.2 vs. 3.4 min) and weeks 4, 8 and 12 ($p \leq 0.002$ for all). Men who described their PE at least 'better' using the CGIC were significantly greater with dapoxetine vs. placebo at end-point (56.5% vs. 35.4%) and weeks 4, 8 and 12 ($p \leq 0.001$ for all). Significantly better outcomes were also reported with dapoxetine vs. placebo on PEP measures. In men with PE and comorbid ED on a stable regimen of PDE5i, dapoxetine provided meaningful treatment benefit and was generally well tolerated (50) (Table 5).

Yue et al. conducted a meta-analysis (51) including five RCTs comparing dapoxetine with placebo (35,41,47,48,50). Dapoxetine was more effective than placebo for IELT [weighted mean difference = 1.47; 95% confidence interval (CI) = 1.22–1.71; $p < 0.00001$]. For the four PROs, dapoxetine was also more effective [for CGIC, odds ratio (OR) = 3.19; 95% CI, 2.47–4.11; $p < 0.00001$; for composite PROs criteria for clinical benefit, OR = 2.29; 95% CI, 1.74–3.00; $p < 0.00001$; for satisfaction with sexual intercourse, OR = 1.89; 95% CI, 1.68–2.12; $p < 0.00001$; for decrease in personal distress related to ejaculation, OR = 0.72; 95% CI, 0.57–0.90; $p < 0.00001$]. The Authors conclude that dapoxetine is effective and well tolerated for either lifelong or acquired PE, but the long-term benefits and safety remain to be investigated (51) (Table 6).

Tolerability and safety

Oral dapoxetine is indicated for the treatment of PE in 18–64 years old men. The recommended starting dose is 30 mg prn, 1–3 h before the sexual intercourse, with a maximum dosing frequency of once every 24 h (5). The dose may be increased to 60 mg based on efficacy and tolerability (5).

Dapoxetine is contraindicated in patients with significant pathological cardiac conditions [such as heart failure (New York Heart Association [NYHA] class II–IV)], conduction abnormalities (second- or third-degree atrioventricular block or sick sinus syndrome) not treated with a permanent pacemaker, significant ischemic heart disease or significant valvular disease.

Dapoxetine is not recommended in men with moderate-to-severe hepatic impairment and in men treated with concomitant therapy with potent cytochrome P450 3A4 inhibitors (ketoconazole, ritonavir, telithromycin), thioridazine, monoamine oxidase inhibitors, serotonin reuptake inhibitors (5). Likewise, dapoxetine is contraindicated 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 acquired from the product monograph (http://www.medsafe.govt.nz/profs/datasheet/p/Priligytab.pdf).

Studies with concomitant use of dapoxetine and PDE5i did not show any significant interaction between the studied compound and either sildenafil 100 mg or tadalafil 20 mg (52).

Pryor et al. found that common adverse events (AEs) (30 mg and 60 mg dapoxetine respectively) were nausea (8.7%, 20.1%), diarrhoea (3.9%, 6.8%), headache (5.9%, 6.8%), and dizziness (3.0%, 6.2%) (47). Kaufman et al. reported that the most common AEs were nausea, dizziness, headache, diarrhoea and insomnia, which were more common with dapoxetine than with placebo (41). Shabsigh et al. reported that nausea, headache and upper respiratory tract infection were the most common AEs reported by men with a two-category or greater increase in control (15.8%, 7.4% and 6.6% respectively) and those without (8.5%, 5.5% and 6.5% respectively) (43). Buvat et al. reported that the most common AEs were nausea, dizziness, diarrhoea and headache. AEs led to discontinuation in 1.3%, 3.9% and 8.2% of subjects with placebo and dapoxetine 30 mg and dapoxetine 60 mg, respectively (48). McMahon et al. reported that the most common TEAEs with dapoxetine included nausea, dizziness, somnolence, headache, vomiting, diarrhoea and nasopharyngitis; TEAEs led to discontinuation in 0.3%, 1.7%, and 5.1% of subjects with placebo, dapoxetine 30 mg,

Table 5 Summary of efficacy data from McMahon et al, J Sex Med, 2013

	Baseline IELT ≤ 1 min		Baseline IELT >1 min		Short half-life PDE5 inhibitor		Long half-life PDE5 inhibitor		All patients	
McMahon (50)	**Placebo**	**Dapoxetine**	**Placebo**	**Dapoxetine**	**Placebo**	**Dapoxetine**	**Placebo**	**Dapoxetine**	**Placebo**	**Dapoxetine**
Average IELT, min (SD)										
Baseline	0.7 (0.27)	0.6 (0.30)	15. (0.41)	1.5 (0.35)	1.1 (0.47)	1.1 (0.54)	1.1 (0.59)	1.1 (0.57)	1.1 (0.53)	1.1 (0.55)
12 weeks	2.5 (2.80)	4.1 (5.24)	4.3 (3.94)	6.1 (6.06)	3.6 (3.24)	5.6 (6.62)	3.3 (3.83)	4.8 (4.90)	3.4 (3.54)	5.2 (5.78)
Geometric mean average IELT, min (SE)										
Baseline	0.6 (1.06)	0.6 (1.06)	1.5 (1.02)	1.5 (1.02)	1.0 (1.06)	1.0 (1.05)	0.9 (1.06)	0.9 (1.07)	1.0 (1.04)	0.9 (1.04)
12 weeks	1.5 (1.11)	2.2 (1.11)	3.3 (1.07)	4.7 (1.06)	2.3 (1.10)	3.6 (1.10)	2.1 (1.09)	3.1 (1.07)	2.2 (1.07)	3.3 (1.07)
Geometric mean fold increase at 12 weeks (SE)	2.4 (1.10)	4.0 (1.10)	2.2 (1.07)	3.1 (1.07)	2.4 (1.09)	3.6 (1.09)	2.3 (1.08)	3.4 (1.08)	2.3 (1.06)	3.5 (1.06)
Achieved a CGIC rating of at least 'better' at 12 weeks (%)	28 (25.5)	55 (57.4)	53 (44.5)	84 (64.6)	41 (36.0)	66 (55.5)	40 (34.8)	73 (57.5)	81 (35.4)	139 (56.5)
Achieved one-category or greater increase in satisfaction with sexual intercourse at 12 weeks (%)	60 (54.5)	67 (57.8)	66 (55.5)	96 (73.8)	58 (50.9)	68 (57.1)	68 (59.1)	95 (74.8)	126 (55.0)	163 (66.3)
Achieved one-category or greater decrease in personal distress related to ejaculation at 12 weeks (%)	73 (66.4)	88 (75.9)	81 (68.1)	100 (76.9)	79 (69.3)	90 (75.6)	75 (65.2)	98 (77.2)	154 (67.2)	188 (76.4)
Achieved composite PRO criteria for clinical benefit at 12 weeks (%)	37 (33.6)	43 (37.1)	33 (27.7)	64 (49.2)	40 (35.1)	52 (43.7)	30 (26.1)	55 (43.3)	70 (30.6)	107 (43.5)

Table 6 Summary of efficacy data from Yue et al, Urology, 2015

	Dapoxetine 30 mg*			Placebo				
Yue (51)	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**Mean difference**
Buvat (48)	3.2	4.88	363	1.9	2.89	339	10.7%	1.30 [0.71, 1.89]
McMahon (35)	3.9	3.94	354	2.4	2.05	357	14.1%	1.50 [1.04, 1.96]
Pryor (47)	2.78	3.48	874	1.75	2.21	870	21.2%	1.03 [0.76, 1.30]
Subtotal (95% CI)			1591			1566	46%	1.22 [0.92, 1.52]
	Dapoxetine 60 mg†			**Placebo**				
Yue (51)	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**Mean difference**
Buvat (48)	3.5	3.8	355	1.9	2.89	339	13.0%	1.60 [1.10, 2.10]
McMahon (35)	4.2	3.97	356	2.4	2.05	357	14.1%	1.80 [1.34, 2.26]
Pryor (47)	3.32	3.68	870	1.75	2.21	870	20.7%	1.57 [1.28, 1.86]
Subtotal (95% CI)			1591			1566	47.7%	1.63 [1.41, 1.85]
	Dapoxetine 60 mg‡			**Dapoxetine 30 mg**				
Yue (51)	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**Mean difference**
Buvat (48)	3.2	4.88	363	3.5	3.8	355	17.2%	−0.30 [−0.94, 0.34]
McMahon (35)	3.9	3.94	354	4.2	3.97	356	20.7%	−0.30 [−0.88, 0.28]
Pryor (47)	2.78	3.48	874	3.32	3.68	870	62.1%	−0.54 [−0.88, −0.20]
Total (95% CI)			1591			1581	100%	−0.45 [−071, −0.18]

*Heterogeneity: $Tau^2 = 0.03$; $\chi^2 = 3.15$, df = 2 (p = 0.21); $I^2 = 37\%$. Test for overall effect: $Z = 7.90$ (p < 0.00001). †Heterogeneity: $Tau^2 = 0.00$; $\chi^2 = 0.70$, df = 2 (p = 0.71); $I^2 = 0\%$. Test for overall effect: $Z = 14.58$ (p < 0.00001). ‡Heterogeneity: $Tau^2 = 0.74$; $\chi^2 = 3.15$, df = 2 (p = 0.69; $I^2 = 0\%$. Test for overall effect: $Z = 3.32$ (p < 0.0009).

and dapoxetine 60 mg respectively (35). McMahon et al., reported that the most common AEs included nausea, dizziness and headache, and evaluation of validated instruments demonstrated no anxiety, akathisia, suicidality or changes in mood with dapoxetine use and no discontinuation syndrome following abrupt withdrawal (37). McMahon et al. reported incidence of TEAEs was 20.0% and 29.6% in placebo- and dapoxetine-treated subjects respectively (p = 0.0135). TEAEs led to discontinuation in 1.6% of subjects in both groups. Most frequent TEAEs were known to have adverse drug reactions of dapoxetine treatment including nausea (9.2%), headache (4.4%), diarrhoea (3.6%), dizziness (2.4%) and dizziness postural (2.4%) (50).

Authors' opinion

According to the authors' everyday clinical practice, dapoxetine should be recommended at the starting dose of 30 mg prn 2 h before the sexual intercourse along with a glass of water with the indication that the drug is taken with adequate sexual stimulation for at least six consecutive attempts before a dose adjustment, both in terms of up titration as well as discontinuation. Both for dapoxetine 30 mg and 60 mg no serious AEs have ever been encountered in the postmarketing real-life clinical setting (53), irrespective of age. In other words, we believe that, irrespective of age, dapoxetine is generally well tolerated, and the dose should be determined by the physician after assessing the baseline severity and aetiology of PE and the potential concomitant presence of ED.

We clinically support the concept of a combination of dapoxetine and sexual behavioural treatment, as it has been recently reported by Cormio et al. (54); indeed, the combination of dapoxetine and behavioural treatment usually provides better results than dapoxetine alone in the management of patients with lifelong PE. Behavioural treatment is to be regarded as a synergic approach with pharmacotherapy, not a stand alone option for PE.

In clinical terms, this must be closely linked to the need for a predosing comprehensive assessment of patients who need to discuss their expectations with respect to the real treatment possibilities in terms of effectiveness and tolerability profile; indeed, without a constant and careful follow-up especially of

patients with lifelong PE the risk of a treatment drop-off remains very high in real-life (55), despite the excellent properties of this compound. To this regard, the authors suggest an initial 3-month follow-up, then a 6-month follow-up and finally one office visit on a yearly basis.

Conclusion

Dapoxetine is the only oral drug licensed for PE in adult males. The pharmacology of dapoxetine makes it adequate for on-demand treatment in most patients in terms of IELT and PROs improvement, leading to flexibility and convenience for the patient. The studies available to date report that dapoxetine 30 mg or 60 mg is an effective and tolerable treatment for lifelong and acquired PE, which improves significantly not only the main disease symptom of IELT but also most PROs, such as an increased control over ejaculation and the reduction of the personal distress related to PE. Dapoxetine is a routinely recommended treatment for PE, and its use can result in better quality of life for the patient and their sexual partner.

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