Clinical Medicine Insights: Reproductive Health

REVIEW

Efficacy of Dapoxetine in the Treatment of Premature Ejaculation

Chris G. McMahon

Australian Centre for Sexual Health, Sydney, NSW, Australia. Corresponding author email: cmcmahon@acsh.com.au

Abstract

Introduction: Premature ejaculation (PE) is a common male sexual disorder which is associated with substantial personal and interpersonal negative psychological factors. Pharmacotherapy of PE with off-label antidepressant SSRI drugs is common. Development and regulatory approval of drugs specifically for the treatment of PE will reduce reliance on off-label treatments and serve to fill a unmet treatment need.

Aim: To review evidence supporting the efficacy and safety of dapoxetine in the treatment of PE.

Methods: MEDLINE and the proceedings of major international and regional scientific meetings during the period 1994–2010 were searched for publications or abstracts using the word dapoxetine in the title, abstract or keywords. This search was then manually cross-referenced for all papers. This review encompasses studies of dapoxetine pharmacokinetics, animal studies, human phase 1, 2 and 3 efficacy and safety studies and drug-interaction studies.

Results: Dapoxetine is a potent selective serotonin re-uptake inhibitor, which is administered on-demand 1–3 hours prior to planned sexual contact. Dapoxetine is rapidly absorbed and eliminated, resulting in minimal accumulation and has dose-proportional pharmacokinetics, which are unaffected by multiple dosing. Dapoxetine 30 mg and 60 mg has been evaluated in 5 randomized, double-blind, placebo-controlled studies in 6081 men aged ≥18 years. Outcome measures included stopwatch-measured intravaginal ejaculatory latency time (IELT), Premature Ejaculation Profile (PEP) inventory items, clinical global impression of change (CGIC) in PE, and adverse events. Mean IELT, all PEP items and CGIC improved significantly with both doses of dapoxetine vs. placebo ($P < 0.001$ for all). The most common treatment related adverse effects included nausea (11.0% for 30 mg, 22.2% for 60 mg), dizziness (586% for 30 mg, 10.9% for 60 mg), and headache (5.6% for 30 mg, 8.8% for 60 mg), and evaluation of validated rated scales demonstrated no SSRI class-related effects with dapoxetine use.

Conclusion: Dapoxetine, as the first drug developed for PE, is an effective and safe treatment for PE and represents a major advance in sexual medicine.

Keywords: premature ejaculation, selective serotonin re-uptake inhibitors (SSRIs), dapoxetine, intravaginal ejaculatory latency time (IELT)

Clinical Medicine Insights: Reproductive Health 2011:5 25–39

doi: 10.4137/CMRH.S7337

This article is available from http://www.la-press.com.

Introduction

Over the past 20–30 years, the premature ejaculation (PE) treatment paradigm, previously limited to behavioural psychotherapy, has expanded to include drug treatment.[1–3] Animal and human sexual psychopharmacological studies have demonstrated that serotonin (5-hydroxy-tryptamine, 5-HT) and 5-HT receptors are involved in ejaculation and confirm a role for selective serotonin re-uptake inhibitors (SSRIs) in the treatment of PE.[4–6] Multiple well-controlled evidence-based studies have demonstrated the efficacy and safety of SSRIs in delaying ejaculation, confirming their role as first-line agents for the treatment of lifelong and acquired PE.[7] More recently, there has been increased attention to the psychosocial consequences of PE, its epidemiology, its etiology and its pathophysiology by both clinicians and the pharmaceutical industry.[8–13]

Premature ejaculation (PE) has been estimated to occur in 4%–39% of men in the general community,[12,14–19] and is often reported as the most common male sexual disorder. There is, however, a substantial disparity between the incidence of PE in epidemiological studies which rely upon either patient self-report of PE and/or inconsistent and poorly validated definitions of PE,[11,13,19] and that suggested by community based stopwatch studies of the intravaginal ejaculation latency time (IELT), the time interval between penetration and ejaculation.[10] The latter demonstrates that the distribution of the IELT is positively skewed, with a median IELT of 5.4 minutes (range, 0.55–44.1 minutes), decreases with age and varies between countries, and supports the notion that IELTs of less than 1 minute are statistically abnormal compared to men in the general western population.[10]

The population of men with PE is not homogenous and comprises lifelong (primary) and acquired (secondary) PE.[20] Ejaculatory latency time is probably a genetically determined biological variable which differs between populations and cultures, ranging from extremely rapid through average to slow ejaculation. The view that some men have a genetic predisposition to lifelong PE is supported by animal studies showing a subgroup of persistent rapidly ejaculating Wistar rats,[6] an increased familial occurrence of lifelong PE,[5] a moderate genetic influence on PE in the Finnish twin study,[21] and the recent report that genetic polymorphism of the 5-HT transporter gene determines the regulation of IELT.[22] Acquired PE is commonly due to sexual performance anxiety,[23] psychological or relationship problems,[23] erectile dysfunction (ED),[24] and occasionally prostatitis,[25] hyperthyroidism,[26] or during withdrawal/detoxification from prescribed[27] or recreational drugs.[28]

The first contemporary multivariate evidence-based definition of lifelong PE was developed in 2008 by a panel of international experts, convened by the International Society for Sexual Medicine (ISSM), who agreed that the diagnostic criteria necessary to define PE are time from penetration to ejaculation, inability to delay ejaculation and negative personal consequences from PE. This panel defined lifelong PE as a male sexual dysfunction characterized by "… ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, the inability to delay ejaculation on all or nearly all vaginal penetrations, and the presence of negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy."[29]

The panel concluded that there is insufficient published evidence to propose an evidenced-based definition of acquired PE.[29] However, recent published data suggests that men with acquired PE have similar IELTs and report similar levels of ejaculatory control and distress, suggesting the possibility of a single unifying definition of PE.[30]

The development of consensus statements by the International Consultation on Sexual Dysfunction and treatment guidelines by the ISSM has done much to standardise the management of PE.[31–33]

Pharmacological Treatment of Premature Ejaculation

The off-label use of anti-depressant SSRIs including paroxetine, sertraline, fluoxetine, citalopram and fluvoxamine, and the serotonergic tricyclic clomipramine has revolutionized the approach to and treatment of PE. These drugs block axonal re-uptake of serotonin from the synapse by 5-HT transporters, resulting in enhanced 5-HT neurotransmission, stimulation of post-synaptic membrane 5-HT2C receptors and ejaculatory delay. However, the lack of an approved drug and the total reliance on off-label treatment represents a substantial unmet treatment

need. Consistent with this, one study suggests a low level of acceptance of off-label daily SSRIs and reports that 30% of treatment seeking lifelong PE men declined this therapy, most often due to fear of using an "antidepressant drug" and roughly 30% of patients who started therapy eventually discontinued it.[34] Following cessation of an SSRI, IELT will return to the pre-treatment value within 1–3 weeks in men with lifelong PE. However there is some preliminary evidence to suggest that treatment of comorbid risk factors in men with acquired PE, eg, erectile dysfunction (ED) and performance anxiety, may be associated with sustained improvement in IELT following SSRI withdrawal.[35]

Dapoxetine

Dapoxetine ((+)-(S)-N,N-dimethyl-(α)-[2(1naphthal enyloxy)ethyl]-benzenemethanamine hydrochloride, Janssen Cilag) is the first compound specifically developed for the treatment of PE. Dapoxetine is a potent SSRI (pKi = 8nM), structurally similar to fluoxetine (Fig. 1).[36] Equilibrium radioligand binding studies using human cells demonstrate that dapoxetine binds to 5-HT, norepinephrine (NE) and dopamine (DA) re-uptake transporters and inhibits uptake in the following order of potency: NE<5-HT>>DA.[37] Brain positron emission tomography (PET) studies have demonstrated significant displaceable binding of radiolabeled dapoxetine in the cerebral cortex and subcortical grey matter.[38]

Pharmacokinetics and metabolism

Dapoxetine undergoes rapid absorption and elimination resulting in minimal accumulation and has dose-proportional pharmacokinetics, which are unaffected by multiple dosing and do not vary between ethnic groups (Fig. 2).[39–41] The pharmacokinetic profile of dapoxetine suggests that it is a good candidate for on-demand treatment of PE.

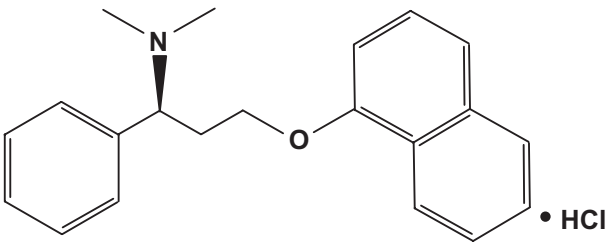

Figure 1. Molecular structure of Dapoxetine: (+)-(S)-N,N-dimethyl-(α)-[2(1naphthalenyloxy)ethyl]-benzenemethanamine hydrochloride.

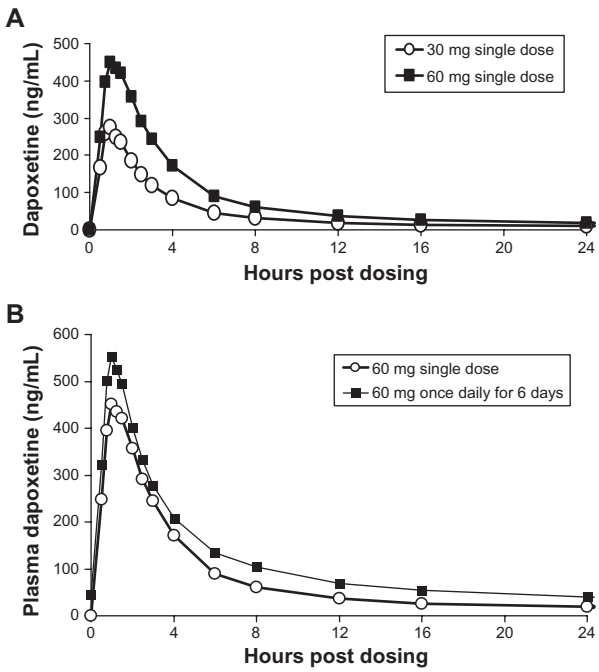

Figure 2. Plasma concentration profiles of dapoxetine after administration of a single dose or multiple doses of dapoxetine 30 mg (**A**) and dapoxetine 60 mg (**B**).[41]

The pharmacokinetics of single doses and multiple doses over 6–9 days (30, 60, 100, 140, or 160 mg) of dapoxetine have been evaluated. In a randomized, double-blind, placebo-controlled trial, single doses and multiple doses over 6 days of dapoxetine (60, 100, 140, or 160 mg) were administered to 77 healthy male volunteers.[39,40,42] Dapoxetine has a T_{max} of 1.4–2.0 hours and rapidly achieves peak plasma concentration (C_{max}) following oral administration. Both plasma concentration and area under the curve (AUC) are dose dependent up to 100 mg. The mean half-life of dapoxetine after a single dose was estimated using modeling as 1.3 to 1.5 hours. Dapoxetine plasma concentrations rapidly decline to about 5% of C_{max} at 24 hours. The terminal half-life of dapoxetine was 15–19 hours after a single dose and 20–24 hours after multiple doses of 30 and 60 mg respectively.

In a second pharmacokinetic study, single doses and multiple doses of dapoxetine (30, 60 mg) were evaluated in a randomized, open-label, 2-treatment, 2-period, crossover study of 42 healthy male volunteers over 9 days.[41] Subjects received a single dose of dapoxetine 30 mg or 60 mg on Day 1 (single-dose phase) and on days 4–9 (multiple-dose phase). Dapoxetine was rapidly absorbed, with mean maximal plasma concentrations of 297 and 498 ng/mL at 1.01

and 1.27 hours after single doses of dapoxetine 30 and 60 mg, respectively (Table 1). Elimination of dapoxetine was rapid and biphasic, with an initial half-life of 1.31 and 1.42 hours, and a terminal half-life of 18.7 and 21.9 hours following single doses of dapoxetine 30 and 60 mg, respectively. The pharmacokinetics of dapoxetine and its metabolites were not affected by repeated daily dosing and steady state plasma concentrations were reached within 4 days, with only modest accumulation of dapoxetine (approximately 1.5-fold) (Fig. 2B).

Food does not have a clinically significant effect on dapoxetine pharmacokinetics. Mean maximal plasma concentrations of dapoxetine decrease slightly after a high-fat meal, from 443 ng/mL (fasted) to 398 ng/mL (fed), and are delayed by approximately 0.5 hours following a high-fat meal (1.30 hours fasted, 1.83 hours fed).[40] The rate of absorption is modestly decreased, but there is no effect of food on the elimination of dapoxetine or the exposure to dapoxetine, as assessed by the area under the plasma concentration-versus-time curve (AUC). The frequency of nausea is decreased after a high-fat meal (24% [7/29] of fasted subjects and 14% [4/29] of fed subjects, respectively).

Dapoxetine is extensively metabolized in the liver by multiple isozymes to multiple metabolites, including desmethyldapoxetine, didesmethyldapoxetine and dapoxetine-n-oxide, which are eliminated primarily in the urine.[39,41] Although didesmethyldapoxetine is equipotent to the parent dapoxetine, its substantially lower plasma concentration, compared with dapoxetine, limits its pharmacological activity and it exerts little clinical effect, except when dapoxetine is coadministered with CYP3A4 or CYP2D6 inhibitors.

Table 1. Pharmacokinetics of single doses of Dapoxetine (30, 60 mg) and effect of food on pharmacokinetics.[39–41]

	Dapoxetine 30 mg	Dapoxetine 60 mg
C_{max} (ng/ml)	297	349
T_{max} (hr)	1.01	1.27
Initial $T^{1/2}$ (hr)	1.31	1.42
Terminal $T^{1/2}$ (hr)	18.7	21.0
Effect of high fat meal		
C_{max} (fasted)	–	443
C_{max} (high fat meal)	–	398
T_{max} (hr) (fasted)	–	1.30
T_{max} (hr) (high fat meal)	–	1.83

Animal studies

Animal studies using rat experimental models have demonstrated that acute treatment with oral, subcutaneous and IV dapoxetine inhibits ejaculation at doses as low as 1 mg/kg. Dapoxetine appears to inhibit the ejaculatory reflex at a supraspinal level with the lateral paragigantocellular nucleus (LPGi) as a necessary brain structure for this effect.[43]

Clement et al reported the effects of IV dapoxetine on the emission and ejection phases of ejaculation using p-chloroamphetamine (PCA)-induced ejaculation as an experimental model of ejaculation in anesthetized rats.[44] Intraseminal vesicle pressure and electromyograms of bulbospongiosus muscles were used as physiologic markers of the emission and ejection phases, respectively. At all doses, dapoxetine significantly reduced the proportion of rats displaying PCA-induced ejaculation in a dose-dependent manner, from 78% of rats with vehicle to 33%, 22%, and 13% of rats following IV dapoxetine 1, 3, and 10 mg/kg, respectively. Dapoxetine significantly decreased the AUC of PCA-induced intraseminal vesicle pressure increases and bulbospongiosus muscle contractile bursts by 78% at all doses, and by 91% following dapoxetine 1 and 10 mg/kg and by 85% following dapoxetine 3 mg/kg.

Using a different animal experimental model of the ejaculatory reflex in rats, Giuliano et al measured the latency, amplitude and duration of pudendal motoneuron reflex discharges (PMRD) elicited by stimulation of the dorsal nerve of the penis before and after IV injection of vehicle, dapoxetine or paroxetine (1, 3 and 10 mg/kg).[45] At the 3 doses of dapoxetine tested, the latency of PMRD following stimulation of the dorsal nerve of the penis was significantly increased and the amplitude and duration of PMRD decreased from baseline values. Acute IV paroxetine appeared less effective than dapoxetine.

In a behavioral study of sexually experienced rats, Gengo et al reported that treatment with subcutaneous or oral dapoxetine significantly delayed ejaculation compared to saline control (16 ± 4 min with subcut. vs. 10 ± 1 min in saline controls, $P < 0.05$) when administered 15, but not 60 or 180 minutes prior to exposure to receptive females.[46] The greatest delay in ejaculatory latency was observed in animals with shorter baseline latencies and oral dapoxetine did not

affect the latency in rats with a baseline latency longer than 10 minutes.

Clinical efficacy

The results of two phase 2 and five phase 3 trials have been published.[47–52] All were conducted prior to the development of the ISSM definition of lifelong PE and instead used DSM-IV criteria and a baseline IELT < 2 min on 75% of ≥4 sexual intercourse events as inclusion criteria.

Phase 2 trials

Dapoxetine dose-finding data has been derived from two multi-centre Phase 2 studies and used to determine the appropriate doses for Phase 3 studies. Both studies used a randomised, placebo-controlled, double-blind, 3-period, crossover study design and subjects with PE diagnosed according to DSM-IV criteria and a baseline IELT < 2 min on 75% of ≥4 sexual intercourse events. Study drug was administered 1 to 2 hours prior to planned sexual intercourse and subjects were required to attempt intercourse at least twice a week. The primary outcome measure was the partner-operated stopwatch IELT.

In study 1, 128/157 randomised subjects completed the study.[48] Subjects were randomised to receive dapoxetine 20 mg, dapoxetine 40 mg, or placebo for 4 weeks with no washout period between treatment arms. Baseline IELT (mean baseline IELT = 1.34 min) was estimated by patient recall. In study 2, 130/166 randomised subjects completed the study.[47] Subjects were randomised to receive dapoxetine 60 mg, dapoxetine 100 mg, or placebo for 2 weeks, separated by a 3 day washout period. Baseline IELT (mean baseline IELT = 1.01 min) was measured by partner operated stopwatch.

The intention-to-treat analysis of both studies demonstrated that all four doses of dapoxetine are effective, superior to placebo and increased IELT 2.0–3.2 fold over baseline in a dose-dependent fashion (Table 2).[47,48] The magnitude of effect of dapoxetine 20 mg on IELT was small. The most commonly reported adverse events (AEs) were nausea, diarrhoea, headache, dizziness. The incidence of most AEs appeared to be dose-dependent. The most common adverse event was nausea and occurred in 0.7%, 5.6% and 16.1% of subjects with placebo, dapoxetine 60 mg and dapoxetine 100 mg, respectively. Overall, dapoxetine 60 mg was better tolerated than dapoxetine 100 mg. Based on these results, doses of 30 mg and 60 mg were chosen for further investigation in Phase 3 efficacy and safety studies.

Phase 3 trials

The five randomised, placebo-controlled, phase 3 clinical trials comprised two identically designed studies conducted in the United States,[49] an international study conducted in 16 countries in Europe, Argentina, Brazil, Canada, Israel, Mexico, and South Africa,[50] a North American safety study[51] and an Australian and Asia-Pacific country study.[52] The treatment period ranged from 9 to 24 weeks. Overall, 6,081 men with a mean age of 40.6 years (range, 18–82 years) from 32 countries were enrolled with 4,232 (69.6%) subjects completed their study (Table 2). This is the largest efficacy and safety database for any agent intended to treat PE.

The DSM-IV-TR criteria and a baseline IELT < 2 min on 75% of ≥4 sexual intercourse events were used to enroll subjects in 4 of the 5 phase 3 studies.[49,50,52] Baseline average IELT was 0.9 minutes for subjects overall. However, 58% of subjects also met the ISSM criteria for lifelong PE.[53] Subjects reported having had PE for an average of 15.1 years, with 64.9% of subjects classified by the investigator as having life-long PE at screening. Demographic and baseline characteristics were similar across studies allowing an analysis of pooled phase 3 data.

Outcome measures included stopwatch IELT, the Premature Ejaculation Profile (PEP), a validated self administered 4 item tool that includes measures of perceived control over ejaculation, satisfaction with sexual intercourse, ejaculation-related personal distress, ejaculation-related interpersonal difficulty,[54] and subject response to a multi-dimensional clinical global impression of change (CGIC) in PE question: "Compared to the start of the study, would you describe your premature ejaculation problem as much worse, worse, slightly worse, no change, slightly better, better, or much better?"

An analysis of pooled phase 3 data confirms that dapoxetine 30 and 60 mg increased IELT and improved patient reported outcomes (PROs) of control, ejaculation related distress, interpersonal distress and sexual

Table 2. Results of Dapoxetine phase 2 and 3 studies.[47–52]

	Phase 2 studies						Phase 3 studies (Pooled)		
	Study 1[48]			Study 2[47]			Study 1–5[49–52]		
Age range (years)	18–60			18–65			18–82		
Inclusion criteria, IELT	DSM-IV TR, <2 min estimated			DSM-IV TR, <2 min by stopwatch			DSM-IV TR, <2 min by stopwatch		
Number subjects	157			166			6,081		
Treatment period	4 weeks per treatment			2 weeks per treatment			9–24 weeks, parallel, fixed dose		
Washout period	None			72 hours			None		
Dapoxetine dose	20 mg (n = 145)	40 mg (n = 141)	Placebo (n = 142)	60 mg (n = 144)	100 mg (n = 155)	Placebo (n = 145)	30 mg (n = 1,613)	60 mg (n = 1,611)	Placebo (n = 1,608)
Mean baseline IELT	1.34	1.34	1.34	1.01	1.01	1.01	0.9	0.9	0.9
Mean treatment IELT	2.72*	3.31†	2.22	2.86†	3.24†	2.07	3.1†	3.6†	1.9
IELT fold increase	2.0	2.5	1.7	2.9	3.2	2.0	2.5	3.0	1.6
"Good/very good" control									
% baseline	–	–	–	–	–	–	0.3	0.6	0.5
% study end	–	–	–	–	–	–	11.2†	26.2†	30.2
"Good/very good" satisfaction									
% baseline	–	–	–	–	–	–	15.5	14.7	15.5
% study end	–	–	–	–	–	–	24.4†	37.9†	42.8
"Quite a bit/extreme" personal distress									
% baseline	–	–	–	–	–	–	73.5	71.3	69.7
% study end	–	–	–	–	–	–	41.9†	28.2†	22.2
"Quite a bit/extreme" interpersonal distress									
% baseline	–	–	–	–	–	–	38.5	38.8	36.1
% study end	–	–	–	–	–	–	23.8†	6.0†	12.3
Discontinuation due to AE	0	2	0	0	9	1	3.5	8.8	1.0

Notes: *P = 0.042; †P < 0.0001 vs. placebo.

satisfaction, compared to placebo. Efficacy results were similar among each of the individual trials and for a pooled analysis, indicating that dapoxetine is consistently more efficacious than placebo regardless of a subject's demographic characteristics.

Increases in mean average IELT (Table 2) were significantly greater with both doses of dapoxetine vs. placebo beginning with the first dose of study medication (dapoxetine 30 mg, 2.3 minutes; dapoxetine 60 mg, 2.7 minutes; placebo, 1.5 minutes; $P < 0.001$ for both) and at all subsequent time points (all $P < 0.001$). By week 12, mean average IELT had increased to 3.1 and 3.6 minutes with dapoxetine 30 and 60 mg, respectively (vs. 1.9 minutes with placebo; $P < 0.001$ for both; Table 2).

However, as IELT in subjects with PE is distributed in a positively skewed pattern, reporting IELTs as arithmetic means may over-estimate the treatment response and the geometric mean IELT is more representative of the actual treatment effect.[55] Geometric mean average IELT increased from approximately 0.8 minutes at baseline to 2.0 and 2.3 minutes with dapoxetine 30 and 60 mg, respectively (vs. 1.3 minutes with placebo; $P < 0.001$ for both). Furthermore, as subjects have a broad range of baseline IELT values (0–120 sec), reporting mean raw trial-end IELT may be misleading by incorrectly suggesting all subjects respond to that extent. The trial-end fold increase in geometric mean IELT compared to baseline is more representative of true treatment outcome and must be regarded as the contemporary universal standard for reporting IELT. Geometric mean IELT fold increases of 2.5 and 3.0 were observed with dapoxetine 30 and 60 mg, respectively, vs. 1.6 for placebo ($P < 0.0001$ for both, Table 2). Fold increases were greater among men with very short baseline IELT values, suggesting that dapoxetine may be a useful treatment option for men with severe forms of PE, including anteportal ejaculation. Subjects with baseline average IELTs of 0.5–1.0 minute, and ≤0.5 minutes showed fold increases of 2.4, and 3.4, respectively, with dapoxetine 30 mg, and 3.0, and 4.3 with dapoxetine 60 mg compared to 1.6, and 1.7, respectively, with placebo treatment.

Control over ejaculation was reported as "good" or "very good" by <1.0% of subjects at baseline and improved to 26.2% and 30.2% with dapoxetine 30 and 60 mg, respectively, vs. 11.2% with placebo by week 12 ($P < 0.001$ for both; Table 2). Approximately 15% of subjects reported "good" or "very good" satisfaction with sexual intercourse at baseline; by week 12, this increased to 37.9% and 42.8% with dapoxetine 30 and 60 mg, respectively, vs. 24.4% with placebo ($P < 0.001$ for both; Table 2). While approximately 70% of subjects across groups reported "quite a bit" or "extremely" for their level of ejaculation-related personal distress at baseline, by week 12 this decreased to 28.2% and 22.2% with dapoxetine 30 and 60 mg, respectively, vs. 41.9% with placebo ($P < 0.001$ for both; Table 2). Approximately one-third of subjects reported "quite a bit" or "extremely" for their level of ejaculation-related interpersonal difficulty at baseline; by week 12 this decreased to 16.0% and 12.3% with dapoxetine 30 and 60 mg, respectively, vs. 23.8% with placebo ($P < 0.001$ for both; Table 2).

A significantly greater percentage of subjects reported that their PE was "better" or "much better" at week 12 with dapoxetine 30 (30.7%) and 60 mg (38.3%) than with placebo (13.9%; $P < 0.001$ for both). Similarly, 62.1% and 71.7% of subjects reported that their PE wssssas at least "slightly better" at week 12 with dapoxetine 30 and 60 mg, respectively, compared to 36.0% with placebo ($P < 0.001$ for both).

Several studies have reported that the effects of PE on the partner are integral to understanding the impact of PE on the male and on the sexual relationship.[9,56–58] If PE is to be regarded as a disorder that affects both subjects and their partners, partner PROs must be regarded as important measures in determining PE severity and treatment outcomes. Female partners reported their perception of the man's control over ejaculation and CGIC, their own satisfaction with sexual intercourse, interpersonal difficulty and personal distress. A significantly greater percentage of female partners reported that the man's control over ejaculation was "good" or "very good" with dapoxetine 30 (26.7%) and 60 mg (34.3%) vs. placebo at week 12 (11.9%; $P < 0.0001$ for both). Similarly, a significantly greater percentage of female partners reported that the man's PE was at least "better" with dapoxetine 30 (27.5%) and 60 mg (35.7%) vs. placebo (9.0%; $P < 0.001$ for both). A greater percentage of female partners reported that their own satisfaction with sexual intercourse was "good" or "very good" with dapoxetine 30 (37.5%) and 60 mg (44.7%) vs.

placebo (24.0%; $P < 0.001$ for both). Finally, there were significant decreases in both ejaculation-related personal distress and interpersonal difficulty in female partners of men treated with dapoxetine 30 and 60 mg vs. placebo ($P < 0.001$ for both).[50]

Safety and Tolerability

Across trials, dapoxetine 30 and 60 mg were well tolerated with a low incidence of severe AEs. More than 50% of all phase 3 AEs were reported at the first follow-up visit after 4 weeks of treatment and typically included gastrointestinal and central nervous system symptoms. The most frequently reported AEs were nausea, diarrhea, headache, dizziness, insomnia, somnolence, fatigue, and nasopharyngitis (Table 3). Unlike other SSRIs used to treat depression, which have been associated with high incidences of sexual dysfunction,[59,60] dapoxetine was associated with low rates of sexual dysfunction. The most common AE in this category was erectile dysfunction (placebo, 1.6%; dapoxetine 30 mg prn, 2.3%; dapoxetine 60 mg prn, 2.6%; dapoxetine 60 mg qd; 1.2%). AEs were dose-dependent and generally coincided with the pharmacokinetic profile of dapoxetine, occurring at the approximate time of peak serum concentrations [~1.3 hours] and lasting for approximately 1.5 hours. Most AEs were mild to moderate in severity, and few subjects across groups reported severe (~3%) or serious (≤1%) AEs. Adverse effects led to the discontinuation of 1.0%, 3.5%, 8.8%, and 10.0% of subjects with placebo, dapoxetine 30 mg prn, dapoxetine 60 mg prn, and dapoxetine 60 mg qd, respectively.

Cardiovascular safety

The cardiovascular assessment of dapoxetine was conducted throughout all stages of drug development, with findings from preclinical safety pharmacology studies, phase I clinical pharmacology studies investigating the effect of dapoxetine on QT/corrected QT (QTc) intervals in healthy men, and phase III, randomized, placebo-controlled studies evaluating the safety (and efficacy) of the drug. Preclinical safety pharmacology studies did not suggest an adverse electrophysiologic or hemodynamic effect with concentrations of dapoxetine up to 2-fold greater than recommended doses.[61] Phase I clinical pharmacology studies demonstrated that dapoxetine did not prolong the QT/QTc interval and had neither clinically significant electrocardiographic effects nor evidence of delayed repolarization or conduction effects, with dosing up to 4-fold greater than the maximum recommended dosage.[62] Phase III clinical studies of dapoxetine in men with PE indicated that dapoxetine was generally safe and well tolerated with the dosing regimens used (30 mg and 60 mg as required).[49–52,63,64]

Special attention was given to cardiovascular-related safety issues since syncope has been reported with marketed SSRIs and there were five cases of vasovagal syncope during dapoxetine phase I studies.[62] Events of syncope were reported during the clinical development program, with the majority occurring during study visits (on site) on day 1 following administration of the first dose when various procedures (eg, orthostatic maneuvers, venipunctures) were performed, suggesting that the procedures contributed to the incidence of syncope.

Table 3. Treatment-emergent adverse events occurring in ≥2% of subjects in pooled phase 3 data.[49–52]

Adverse event n (%)	Placebo (n = 1,857)	Dapoxetine 30 mg prn (n = 1,616)	Dapoxetine 60 mg prn (n = 2,106)	Dapoxetine 60 mg qd (n = 502)	Total dapoxetine (n = 4,224)
Nausea	41 (2.2)	178 (11.0)	467 (22.2)	86 (17.1)	731 (17.3)
Dizziness	40 (2.2)	94 (5.8)	230 (10.9)	75 (14.9)	399 (9.4)
Headache	89 (4.8)	91 (5.6)	185 (8.8)	56 (11.2)	332 (7.9)
Diarrhea	32 (1.7)	56 (3.5)	145 (6.9)	47 (9.4)	248 (5.9)
Somnolence	10 (0.5)	50 (3.1)	98 (4.7)	18 (3.6)	166 (3.9)
Fatigue	23 (1.2)	32 (2.0)	86 (4.1)	46 (9.2)	164 (3.9)
Insomnia	28 (1.5)	34 (2.1)	83 (3.9)	44 (8.8)	161 (3.8)
Nasopharyngitis	43 (2.3)	51 (3.2)	61 (2.9)	17 (3.4)	129 (3.1)

Across all five trials, syncope (including loss of consciousness) occurred in 0.05%, 0.06%, and 0.23% of subjects with placebo, dapoxetine 30 mg, and dapoxetine 60 mg, respectively. Syncope was not associated with symptomatic or sustained tachyarrythmia during Holter ECG monitoring in 3353 subjects.[50–52,63] The incidence of Holter-detected non-sustained ventricular tachycardia was similar between dapoxetine-treated subjects and those who received placebo, suggesting that dapoxetine is not arrhythmogenic and that tachyarrhythmia is thus unlikely to be the underlying mechanism responsible for syncope seen in the dapoxetine clinical program. There was a statistically nonsignificant increase in the number of single ventricular and supraventricular ectopic beats in the dapoxetine groups, but this finding is not considered clinically meaningful, given the generally benign nature of ventricular ectopic beats occurring on their own in the absence of structural heart disease.[65] Syncope appeared to be vasovagal in nature and generally occurred within 3 hours of dosing. Syncope was more common with the first dose of dapoxetine, occurring in 0.19% of subjects with the first dose of dapoxetine vs. 0.08% with a subsequent dose. Syncope occurred more frequently when dapoxetine was administered onsite (0.31%) vs. offsite (0.08%), which may relate to onsite study-related procedures such as venipuncture or orthostatic manoeuvres that are known to be associated with syncope. This was consistent with previous reports showing that these and similar factors contribute to or trigger vasovagal syncope. Findings of the dapoxetine development program demonstrate that dapoxetine is associated with vasovagal-mediated (neurocardiogenic) syncope. No other associated significant cardiovascular adverse events were identified.

Neurocognitive safety

Studies of SSRIs in patients with major psychiatric disorders, such as depression or obsessive compulsive disorder, suggest that SSRIs are potentially associated with certain safety risks, including neurocognitive adverse effects such as anxiety, hypomania, akathisia and changes in mood.[66–69] Systematic analysis of randomized controlled studies suggested a small increase in the risk of suicidal ideation or suicide attempts in youth[69] but not adults.[69,70] However, these SSRI safety risks have not been previously evaluated in men with PE. In the North American safety study[51] and the International Study,[50] SSRI-related neurocognitive side effects such as changes in mood, anxiety, akathisia or suicidality or sexual dysfunction were evaluated using a range of validated outcome measures including the Beck Depression Inventory II (BDI-II), the Montgomery-Asberg Depression Rating Scale (MADRS), the Hamilton Anxiety Scale (HAM-A), the Barnes Akathisia Rating Scale (BARS) and the International Index of Erectile Function (IIEF). Dapoxetine had no effect on mood, and was not associated with anxiety, akathisia or suicidality.

Withdrawal syndrome

Chronic SSRI treatment for psychiatric conditions is known to predispose patients to withdrawal symptoms if medication is suspended abruptly.[67,71] The SSRI Withdrawal Syndrome is characterized by dizziness, headache, nausea, vomiting and diarrhoea and occasionally agitation, impaired concentration, vivid dreams, depersonalization, irritability and suicidal ideation.[72,73] The risk of dapoxetine withdrawal syndrome was assessed with the Discontinuation-Emergent Signs and Symptoms (DESS) checklist following a 1-week withdrawal period during which subjects were re-randomised to either continue treatment with on-demand dapoxetine, daily dapoxetine or placebo or to switch from dapoxetine to placebo. The DESS comprises 43 possible withdrawal signs and symptoms, each rated and scored as new, old and worse, unchanged or improved or absent. There was a low incidence of SSRI withdrawal syndrome across treatment groups that was similar among patients who continued to take dapoxetine or placebo and those who switched to placebo during a 1-week withdrawal period. In the International study, the incidence of discontinuation syndrome was 3.0%, 1.1% and 1.3% for those continuing to take dapoxetine 30, 60 mg prn and placebo, respectively, and 3.3% for those who switched from dapoxetine 60 mg prn to placebo.[50] No subjects switching from dapoxetine 30 mg prn to placebo in this study showed evidence of the discontinuation syndrome. Dapoxetine is the only SSRI for which these symptoms have been systematically evaluated in a PE population.

The lack of chronic serotonergic stimulation with on-demand dapoxetine precludes serotonin receptor desensitization and the down-regulation of post-synaptic serotonin receptors that typically occurs with chronic SSRI use, such that on-demand dosing for PE may minimize the risk of withdrawal symptoms.[74]

Drug Interactions

No drug-drug interactions associated with dapoxetine have been reported. Co-administration of dapoxetine with ethanol did not produce significant changes in dapoxetine pharmacokinetics.[75] Mean peak plasma concentrations of dapoxetine, its metabolites and ethanol did not significantly change with co-administration and there were no clinically significant changes in ECGs, clinical laboratory results, physical examination and no serious AEs. Dapoxetine pharmacokinetics were similar with administration of dapoxetine alone and coadministration of tadalafil or sildenafil; the three treatments demonstrated comparable plasma concentration profiles for dapoxetine.[76] Dapoxetine absorption was rapid, and was not affected by coadministration of tadalafil or sildenafil. Following the peak (ie, C_{max}), dapoxetine elimination was rapid and biphasic with all three treatments, with an initial half-life of 1.5–1.6 h and a terminal half-life of 14.8–17.1 h. Plasma dapoxetine concentrations were less than 5% of C_{max} by 24 h. Dapoxetine AUC_{inf} remained unchanged when tadalafil was administered concomitantly; concomitant administration of sildenafil increased the dapoxetine AUC_{inf} by 22%. However, this was not regarded as clinically important as dapoxetine pharmacokinetics were similar. Dapoxetine had no clinically important effects on the pharmacokinetics or orthostatic profile of the adrenergic alpha-antagonist tamsulosin in men on a stable tamsulosin regimen.[77]

Coadministered potent CYP2D6 (desipramine, fluoxetine) or CYP3A4 (ketoconazole) inhibitors may increase dapoxetine exposure by up to 2-fold. Co-administartion of dapoxetine and potent CYP3A4 such as ketoconazole is contraindicated. Caution should be exercised in coadministartion of dapoxetine and moderate CYP3A4 inhibitors and potent CYP2D6 inhibitors such as fluoxetine. Doses up to 240 mg, 4-fold the recommended maximum dose, were administered to healthy volunteers in the Phase I studies and no unexpected AEs were observed.

Dosage and Administration

The recommended starting dose for all patients is 30 mg, taken as needed approximately 1 to 3 hours prior to sexual activity. The maximum recommended dosing frequency is once every 24 hours. If the effect of 30 mg is insufficient and the side effects are acceptable, the dose may be increased to the maximum recommended dose of 60 mg.

Regulatory Status

Dapoxetine was originally developed by Eli Lilly and Company as an antidepressant. The patent was sold to Johnson & Johnson in December 2003. In 2004, a New Drug Application (NDA) for dapoxetine was submitted to the FDA by the ALZA Corporation, a division of Johnson & Johnson, for the treatment of PE. The FDA issued a "not-approvable" letter for dapoxetine in October 2005, requiring additional clinical efficacy and safety data. Following completion of three additional efficacy/safety 3 studies, an expanded dossier of safety and efficacy data was submitted to Health Authorities and dapoxetine received approval in Sweden, Finland, Austria, Portugal, Germany, Italy, Spain, Mexico, South Korea, and New Zealand in 2009/2010. Approvals for dapoxetine are also anticipated in other European countries. In addition, filings for approval have been submitted in several other countries. Dapoxetine is not approved in USA where Phase 3 study continues.

The Place of Dapoxetine in the Treatment of PE

Men complaining of PE should be evaluated with a detailed medical and sexual history, a physical examination and appropriate investigations to establish the true presenting complaint, and identify obvious biological causes such as ED or genital/lower urinary tract infection. The multivariate evidence-based ISSM definition of lifelong PE provides the clinician a discriminating diagnostic tool and should form the basis for the office diagnosis of lifelong PE.[78] Recent data suggests that men with acquired PE have similar IELTs and report similar levels of ejaculatory control and distress, suggest the possibility of a single unifying definition of PE.[30]

The dapoxetine phase 2 and 3 study's enrollment criteria may result in a subject population who are not be totally representative of men who actively

seek treatment for PE. The use of the authority-based and not evidence-based DSM-IV-TR and baseline IELT < 2 min as dapoxetine phase 2 and 3 study inclusion criteria is likely to be associated with a high false-positive diagnosis of PE.[79] This potential for errors in the diagnosis of PE was demonstrated in two recent observational studies in which PE was diagnosed solely by the application of the DSM-IV-TR definition.[11,80] In one study, the IELT range extended from 0 to almost 28 minutes in DSM-IV-TR diagnosed PE, with 48% of subjects having an IELT in excess of 2 minutes. In addition, several studies suggest that 80%–90% of men seeking treatment for lifelong PE ejaculate within one minute.[35,81,82] These data forms the basis for the operationalisation of IELT in the ISSM definition of lifelong to PE to "… less than about one minute …".[29] However, in the 58% of phase 3 subjects who met the ISSM criteria for lifelong PE, IELT fold increases was superior to and PRO/CGIC scores equivalent to the entire study population, suggesting that the flawed inclusion criteria did not affect the study conclusions.

Effective pharmacological treatment of PE has previously been limited to daily off-label treatment with paroxetine 10–40 mg, clomipramine 12.5–50 mg, sertraline 50–200 mg, fluoxetine 20–40 mg and citalopram 20–40 mg (Table 4).[83] Following acute on-demand administration of a SSRI, increased synaptic 5-HT neurotransmission is down-regulated by presynaptic autoreceptors to prevent over-stimulation of postsynaptic 5-HT2C receptors. However, during chronic daily SSRI administration, a series of synaptic adaptive processes which may include presynaptic autoreceptor desensitisation, greatly enhances synaptic 5-HT neurotransmission.[84] As such, daily dosing of off-label antidepressant SSRIs is likely to be associated with more ejaculatory delay than on-demand dapoxetine although well-designed controlled head-to-head comparator studies have not been conducted. A meta-analysis of published efficacy data suggests that paroxetine exerts the strongest ejaculation delay, increasing IELT approximately 8.8 fold over baseline.[85] Whilst daily dosing of off-label antidepressant SSRIs is an effective treatment for men with anteportal or severe PE with very short IELTs, the higher fold increases of dapoxetine in this patient population suggest that dapoxetine is also a viable treatment option (Fig. 3). There is currently no published data which identify a meaningful and clinically significant threshold response to treatment. The point at which the IELT fold-increase achieved by intervention is associated with a significant reduction in personal distress probably represents a measure of intervention success. These data is currently not available but the author's anecdotal impression, derived from treatment of patients, suggests that a 3–4 fold-increase in IELT, as seen with dapoxetine, represents the threshold of intervention success. Similarly, there are no current data to suggest that fold increases above this threshold are associated with higher levels of patient satisfaction.

Dapoxetine can be used in men with either lifelong or acquired PE. Treatment should be initiated at a dose of 30 mg and titrated to a maximum dose of 60 mg based upon response and tolerability. In men with acquired PE and comorbid ED, dapoxetine can be co-prescribed with a phosphodiesterase type-5 inhibitor drug.

Table 4. Comparison of fold increases in IELT with meta-analysis data for daily paroxetine, sertraline, fluoxetine, clompipramine[7] and phase 3 data for on-demand Dapoxetine.[49–52]

Drug	Regulatory approval for PE	Dose	Mean fold increase in IELT
Selective serotonin reuptake inhibitor (SSRIs) antidepressants			
Paroxetine	No	10–40 mg/day	8.8
Sertraline	No	25–200 mg/day	4.1
Fluoxetine	No	5–20 mg/day	3.9
Serotonergic tricyclic antidepressant			
Clomipramine	No	25–50 mg/day	4.6
Dapoxetine	Yes*	30–60 mg 1–3 hours prior to intercourse	2.5–3.0
Placebo	–	–	1.4

Note: *See section 8 for full details of regulatory approval Figure 1.

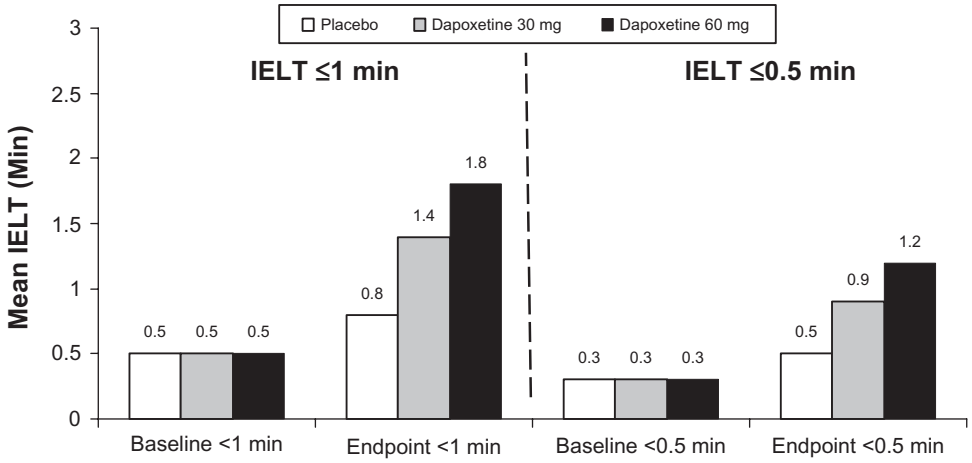

Figure 3. Intravaginal ejaculation latency times (IELT) at endpoint for baseline IELT ≤ 1 min and ≤0.5 min for placebo, dapoxetine 30 mg (IELT fold increase—<0.5 min 3.4, <1 min 2.7) and dapoxetine 60 mg (IELT fold increase—<0.5 min 4.3, <1 min 3.4).[63]

The criteria for the ideal PE drug remains controversial. However, the author is of the opinion that many men may prefer the convenience of "on-demand" dosing of dapoxetine compared to daily dosing. Men who infrequently engage in sexual intercourse may prefer on-demand treatment, whilst men in established relationships may prefer the convenience of daily medication. Well-designed preference trials will provide additional detailed insight into the role of on-demand dosing.

As any branch of medicine evolves, many drugs are routinely used "off-label" but may be regarded as part of standard care for a condition. Although off-label drug use is common it is often not supported by strong evidence.[86] Although the methodology of the initial off-label daily SSRI treatment studies was poor, later double blind and placebo-controlled studies of relatively small study populations (<100 subjects) confirmed their efficacy.[85,87–91] However, few studies included control over ejaculation and PE-related distress or bother as enrolment criteria or used validated patient-reported outcome instruments to evaluate these parameters. Furthermore, reporting of treatment-related adverse effects has been inconsistent across these trials. Unlike dapoxetine, most off-label SSRI drugs have not been specifically evaluated for known class-related safety effects including potential for withdrawal effects, treatment-emergent suicidality, and effects on mood and affect in men with PE. These studies fail to provide the same robust level of efficacy and safety evidence found in the dapoxetine phase 3 study populations of over 6000 subjects. Although regulatory approval is not always synonymous with superior treatment outcomes, it does assure prescribers that expert and regulatory peer review has demonstrated drug efficacy and safety.

Conclusions

Dapoxetine is an effective, safe and well-tolerated on-demand treatment for PE and, in the opinion of the author, is likely to fulfil the treatment needs of most patients. Although daily off-label antidepressant SSRI are effective treatments for PE, supportive studies are limited by small study populations, infrequent use of PROs of control, distress and satisfaction as outcome measures and inconsistent reporting of known SSRI class-related safety effects. Currently, dapoxetine has the largest efficacy and safety database for use in men with PE, and it is the only agent for which SSRI class-related effects have been studied in a PE population.

Conflict of Interest

Assoc Prof McMahon is an investigator, member of an advisory board and speaker's panel for Janssen-Cilag and Bayer Schering.

Disclosures

Author(s) have provided signed confirmations to the publisher of their compliance with all applicable legal and ethical obligations in respect to declaration of conflicts of interest, funding, authorship and contributorship, and compliance with ethical requirements in respect to treatment of human and animal test

subjects. If this article contains identifiable human subject(s) author(s) were required to supply signed patient consent prior to publication. Author(s) have confirmed that the published article is unique and not under consideration nor published by any other publication and that they have consent to reproduce any copyrighted material. The peer reviewers declared no conflicts of interest.

References

1. Semans JH. Premature ejaculation: a new approach. *South Med J*. 1956;49: 353–8.
2. Masters WH, Johnson VE. *Human Sexual Inadequacy*. Boston: Little Brown; 1970.
3. Jannini EA, Simonelli C, Lenzi A. Sexological approach to ejaculatory dysfunction. *Int J Androl*. 2002;25:317–23.
4. Olivier B, van Oorschot R, Waldinger MD. Serotonin, serotonergic receptors, selective serotonin reuptake inhibitors and sexual behaviour. *Int Clin Psychopharmacol*. 1998;13:S9–14.
5. Waldinger MD, Rietschel M, Nothen MM, Hengeveld MW, Olivier B. Familial occurrence of primary premature ejaculation. *Psychiatr Genet*. 1998;8:37–40.
6. Pattij T, Olivier B, Waldinger MD. Animal models of ejaculatory behavior. *Curr Pharm Des*. 2005;11:4069–77.
7. Waldinger MD, Zwinderman AH, Schweitzer DH, Olivier B. Relevance of methodological design for the interpretation of efficacy of drug treatment of premature ejaculation: a systematic review and meta-analysis. *Int J Impot Res*. 2004;16:369–81.
8. Metz ME, Pryor JL, Nesvacil LJ, Abuzzahab F Sr, Koznar J. Premature ejaculation: a psychophysiological review. *J Sex Marital Ther*. 1997;23: 3–23.
9. Symonds T, Roblin D, Hart K, Althof S. How does premature ejaculation impact a man's life? *J Sex Marital Ther*. 2003;29:361–70.
10. Waldinger MD, Quinn P, Dilleen M, Mundayat R, Schweitzer DH, Boolell M. A Multinational Population Survey of Intravaginal Ejaculation Latency Time. *J Sex Med*. 2005;2:492–97.
11. Patrick DL, Althof SE, Pryor JL, Rosen R, Rowland DL, Ho KF, et al. Premature Ejaculation: An Observational Study of Men and Their Partners. *J Sex Med*. 2005;2:58–367.
12. Porst H, Montorsi F, Rosen RC, Gaynor L, Grupe S, Alexander J. The Premature Ejaculation Prevalence and Attitudes (PEPA) survey: prevalence, comorbidities, and professional help-seeking. *Eur Urol*. 2007;51:816–23.
13. Giuliano F, Patrick DL, Porst H, La Pera G, Kokoszka A, Merchant S, et al. Premature ejaculation: results from a five-country European observational study. *Eur Urol*. 2008;53:1048–57.
14. Reading A, Wiest W. An analysis of self-reported sexual behavior in a sample of normal males. *Arch Sex Behav*. 1984;13:69–83.
15. Nathan SG. The epidemiology of the DSM-III psychosexual dysfunctions. *J Sex Marital Ther*. 1986;12:267–81.
16. Spector KR, Boyle M. The prevalence and perceived aetiology of male sexual problems in a non-clinical sample. *Br J Med Psychol*. 1986;59:351–8.
17. Spector IP, Carey M. Incidence and prevalence of the sexual dysfunctions: a critical review of the empirical literature. *Arch Sex Behav*. 1990;19:389.
18. Grenier G, Byers ES. The relationships among ejaculatory control, ejaculatory latency, and attempts to prolong heterosexual intercourse. *Arch Sex Behav*. 1997;26:27–47.
19. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA*. 1999;281:537–44.
20. Schapiro B. Premature ejaculation, a review of 1130 cases. *J Urol*. 1943;50: 374–79.
21. Jern P, Santtila P, Witting K, Alanko K, Harlaar N, Johansson A, et al. Premature and delayed ejaculation: genetic and environmental effects in a population-based sample of Finnish twins. *J Sex Med*. 2007;4:1739–49.
22. Janssen PK, Bakker SC, Rethelyi J, Zwinderman AH, Touw DJ, Olivier B, et al. Serotonin transporter promoter region (5-HTTLPR) polymorphism is associated with the intravaginal ejaculation latency time in Dutch men with lifelong premature ejaculation. *J Sex Med*. 2009;6:276–84.
23. Hartmann U, Schedlowski M, Kruger TH. Cognitive and partner-related factors in rapid ejaculation: Differences between dysfunctional and functional men. *World J Urol*. 2005;10:10.
24. Laumann EO, Nicolosi A, Glasser DB, Paik A, Gingell C, Moreira E, et al. Sexual problems among women and men aged 40–80 y: prevalence and correlates identified in the Global Study of Sexual Attitudes and Behaviors. *Int J Impot Res*. 2005;17:39–57.
25. Screponi E, Carosa E, Di Stasi SM, Pepe M, Carruba G, Jannini EA. Prevalence of chronic prostatitis in men with premature ejaculation. *Urology*. 2001;58:198–202.
26. Carani C, Isidori AM, Granata A, Carosa E, Maggi M, Lenzi A, et al. Multicenter Study on the Prevalence of Sexual Symptoms in Male Hypo- and Hyperthyroid Patients. *J Clin Endocrinol Metab*. 2005;90:6472–79.
27. Adson DE, Kotlyar M. Premature ejaculation associated with citalopram withdrawal. *Ann Pharmacother*. 2003;37:1804–6.
28. Peugh J, Belenko S. Alcohol, drugs and sexual function: a review. *J Psychoactive Drugs*. 2001;33:223–32.
29. McMahon CG, Althof SE, Waldinger MD, Porst H, Dean J, Sharlip ID, et al. An evidence-based definition of lifelong premature ejaculation: report of the International Society for Sexual Medicine (ISSM) ad hoc committee for the definition of premature ejaculation. *J Sex Med*. 2008;5:1590–606.
30. Porst H, McMahon CG, Althof SE, Sharlip I, Bull S, Aquilina JW, et al. Baseline characteristics and treatment outcomes for men with acquired or lifelong premature ejaculation with mild or no erectile dysfunction: integrated analyses of two phase 3 dapoxetine trials. *J Sex Med*. 2010 Apr 20. [Epub ahead of print.]
31. Althof SE, Abdo CH, Dean J, Hackett G, McCabe M, McMahon CG, et al. International Society for Sexual Medicine's guidelines for the diagnosis and treatment of premature ejaculation. *J Sex Med*. 7:2947–69.
32. McMahon C, Abdo C, Incrocci L, Perelman M, Rowland D, Waldinger M, et al. Disorders of orgasm and ejaculation in men. *J Sex Med*. 2004:1.
33. Rowland D, McMahon CG, Abdo C, Chen J, Jannini E, Waldinger MD, et al. Disorders of orgasm and ejaculation in men. *J Sex Med*. 7:1668–86.
34. Salonia A, Rocchini L, Sacca A, Pellucchi F, Ferrari M, Carro UD, et al. Acceptance of and discontinuation rate from paroxetine treatment in patients with lifelong premature ejaculation. *J Sex Med*. 2009;6:2868–77.
35. McMahon CG. Long term results of treatment of premature ejaculation with selective serotonin re-uptake inhibitors. *Int JImp Res*. 2002;14:S19.
36. Sorbera LA, Castaner J, Castaner RM. Dapoxetine hydrochloride. *Drugs Future*. 2004;29:1201–1205.
37. Gengo RJ, Giuliano F, McKenna KE, Chester A, Lovenberg T, Bonaventure P, et al. Monoaminergic Transporter Binding and Inhibition Profile of Dapoxetine, A medication for the Treatment of Premature Ejaculation. *J Urol*. 2005;173:230, abstract 878.
38. Livni E, Satterlee W, Robey RL, Alt CA, Van Meter EE, Babich JW, et al. Synthesis of [11C]dapoxetine. HCl, a serotonin re-uptake inhibitor: biodistribution in rat and preliminary PET imaging in the monkey. *Nucl Med Biol*. 1994;21:669–75.
39. Dresser MJ, Lindert K, Lin D. Pharmacokinetics of single and multiple escalating doses of dapoxetine in healthy volunteers. *Clin Pharmacol Ther*. 2004;75:113, abstract P1.
40. Dresser MJ, Kang D, Staehr P, Gidwani S, Guo C, Mulhall JP, et al. Pharmacokinetics of dapoxetine, a new treatment for premature ejaculation: Impact of age and effects of a high-fat meal. *J Clin Pharmacol*. 2006;46: 1023–9.
41. Modi NB, Dresser MJ, Simon M, Lin D, Desai D, Gupta S. Single- and multiple-dose pharmacokinetics of dapoxetine hydrochloride, a novel agent for the treatment of premature ejaculation. *J Clin Pharmacol*. 2006;46: 301–9.
42. Thyssen A, Sharma O, Tianmei S, Aquilina JW, Vandebosch A, Wang SS, et al. Pharmacokinetics of Dapoxetine Hydrochloride in Healthy Chinese, Japanese, and Caucasian Men. *J Clin Pharmacol*. 2010 Jan 23. [Epub ahead of print.]

43. Clement P, Bernabe J, Gengo P, Denys P, Laurin M, Alexandre L, et al. Supraspinal site of action for the inhibition of ejaculatory reflex by dapoxetine. *Eur Urol*. 2007;51:825–32.
44. Clement P, Bernabe P, Gengo P, Roussel D, Giuliano F. Dapoxetine inhibits p-Chloroamphetamine-induced ejaculation in Anesthetized Rats. *J Sex Med*. 2006;Book of Abstracts—8th Congress of the European Society for Sexual Medicine: 55:abstract P-02–159.
45. Giuliano F, Bernabe J, Gengo P, Alexandre L, Clement P. Effect of acute dapoxetine administration on the pudendal motoneuron reflex in anesthetized rats: comparison with paroxetine. *J Urol*. 2007;177:386–9.
46. Gengo PJ, Marson L, Gravitt A. Actions of Dapoxetine in Ejaculation and Sexual Behaviour in Rats. *J Sex Med*. 2006;Book of Abstracts—8th Congress of the European Society for Sexual Medicine: 28:abstract MP-01–74.
47. Hellstrom WJ, Gittelman M, Althof S. Dapoxetine HCl for the treatment of premature ejaculation: A Phase II, randomised, double-blind, placebo controlled study. *J Sex Med*. 2004;1(Suppl 1):59, abstract 097.
48. Hellstrom WJ, Althof S, Gittelman M, Streidle C, Ho KF, Kell S, et al. Dapoxetine for the treatment of men with premature ejaculation (PE):dose-finding analysis. *J Urol*. 2005;173:238, abstract 877.
49. Pryor JL, Althof SE, Steidle C, Rosen RC, Hellstrom WJ, Shabsigh R, et al. Efficacy and tolerability of dapoxetine in treatment of premature ejaculation: an integrated analysis of two double-blind, randomised controlled trials. *Lancet*. 2006;368:929–37.
50. Buvat J, Tesfaye F, Rothman M, Rivas DA, Giuliano F. Dapoxetine for the treatment of premature ejaculation: results from a randomized, double-blind, placebo-controlled phase 3 trial in 22 countries. *Eur Urol*. 2009;55: 957–67.
51. Kaufman JM, Rosen RC, Mudumbi RV, Tesfaye F, Hashmonay R, Rivas D. Treatment benefit of dapoxetine for premature ejaculation: results from a placebo-controlled phase III trial. *BJU Int*. 2009;103:651–8.
52. McMahon C, Kim SW, Park NC, Chang CP, Rivas D, Tesfaye F, et al. Treatment of premature ejaculation in the Asia-Pacific region: results from a phase III double-blind, parallel-group study of dapoxetine. *J Sex Med*. 2010;7:256–68.
53. Porst H, McMahon C, Althof S, Sharlip I, Bull S, Aquilina J, et al. Baseline characteristics and treatment outcome for men with acquired or lifelong premature ejaculation with mild or no erectile dysfunction: Integrated analyses of three phase 3 dapoxetine trials. *J Sex Med*. 2010:Accepted for Publication.
54. Patrick DL, Giuliano F, Ho KF, Gagnon DD, McNulty P, Rothman M. The Premature Ejaculation Profile: validation of self-reported outcome measures for research and practice. *BJU Int*. 2009;103:358–64.
55. Waldinger MD, Zwinderman AH, Olivier B, Schweitzer DH. Geometric Mean IELT and Premature Ejaculation: Appropriate Statistics to Avoid Overestimation of Treatment Efficacy. *J Sex Med*. 2008;5:492–99.
56. McMahon CG. Clinical trial methodology in premature ejaculation observational, interventional, and treatment preference studies—part II—study design, outcome measures, data analysis, and reporting. *J Sex Med*. 2008;5: 1817–33.
57. Byers ES, Grenier G. Premature or rapid ejaculation: heterosexual couples' perceptions of men's ejaculatory behavior. *Arch Sex Behav*. 2003;32: 261–70.
58. Metz ME, Pryor JL. Premature ejaculation: a psychophysiological approach for assessment and management. *J Sex Marital Ther*. 2000;26:293–320.
59. Montejo AL, Llorca G, Izquierdo JA, Rico-Villademoros F. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. Spanish Working Group for the Study of Psychotropic-Related Sexual Dysfunction. *J Clin Psychiatry*. 2001;62: 10–21.
60. Lane RM. A critical review of selective serotonin reuptake inhibitor-related sexual dysfunction; incidence, possible aetiology and implications for management. *J Psychopharmacol*. 1997;11:72–82.
61. Public assessment report scientific discussion: priligy dapoxetine hydrochloride film-coated tablets, 30 and 60 mg. Läkemedelsverket Medical Products Agency, December 2008. Available from URL: http://www.lakemedelsverket.se/SPC_PIL/Pdf/par/Priligy%20film%20coated%20tablets%2030%20and%2060%20mg.pdf. [Accessed 2011 May 25.]
62. Modi NB, Nath R, Staehr P, Gupta SK, Aquilina JW, Rivas D. Pharmacokinetic, pharmacodynamic, and electrocardiographic effects of dapoxetine and moxifloxacin compared with placebo in healthy adult male subjects. *J Clin Pharmacol*. 2009;49:634–42.
63. McMahon CG, Althof SE, Kaufman JM, Buvat J, Levine SB, Aquilina JW, et al. Efficacy and safety of dapoxetine for the treatment of premature ejaculation: integrated analysis of results from five phase 3 trials. *J Sex Med*. 2010;8:524–39.
64. Shabsigh R, Patrick DL, Rowland DL, Bull SA, Tesfaye F, Rothman M. Perceived control over ejaculation is central to treatment benefit in men with premature ejaculation: results from phase III trials with dapoxetine. *BJU Int*. 2008;102:824–8.
65. Ng GA. Treating patients with ventricular ectopic beats. *Heart*. 2006;92: 1707–2.
66. Coupland NJ, Bell CJ, Potokar JP. Serotonin reuptake inhibitor withdrawal. *J Clin Psychopharmacol*. 1996;16:356–62.
67. Zajecka J, Tracy KA, Mitchell S. Discontinuation symptoms after treatment with serotonin reuptake inhibitors: a literature review. *J Clin Psychiatry*. 1997;58:291–7.
68. Tamam L, Ozpoyraz N. Selective serotonin reuptake inhibitor discontinuation syndrome: a review. *Adv Ther*. 2002;19:17–26.
69. Khan A, Khan S, Kolts R, Brown WA. Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo: analysis of FDA reports. *Am J Psychiatry*. 2003;160:790–2.
70. Mann JJ, Emslie G, Baldessarini RJ, Beardslee W, Fawcett JA, Goodwin FK, et al. ACNP Task Force report on SSRIs and suicidal behavior in youth. *Neuropsychopharmacology*. 2006;31:473–92.
71. Zajecka J, Fawcett J, Schaff M, Jeffriess H, Guy C. The role of serotonin in sexual dysfunction: fluoxetine-associated orgasm dysfunction. *J Clin Psychiatry*. 1991;52:66–8.
72. Ditto KE. SSRI discontinuation syndrome. Awareness as an approach to prevention. *Postgrad Med*. 2003;114:79–84.
73. Black K, Shea CA, Dursun S, Kutcher S. Selective serotonin reuptake inhibitor discontinuation syndrome: proposed diagnostic criteria. *J Psychiatry Neurosci*. 2000;25:255–61.
74. Waldinger MD. Premature ejaculation: definition and drug treatment. *Drugs*. 2007;67:547–68.
75. Modi NB, Dresser M, Desai D, Edgar C, Wesnes K. Dapoxetine has no pharmacokinetic or cognitive interactions with ethanol in healthy male volunteers. *J Clin Pharmacol*. 2007;47:315–22.
76. Dresser MJ, Desai D, Gidwani S, Seftel AD, Modi NB. Dapoxetine, a novel treatment for premature ejaculation, does not have pharmacokinetic interactions with phosphodiesterase-5 inhibitors. *Int J Impot Res*. 2005.
77. Modi NB, Kell S, Aquilina J, Rivas D. Effect of dapoxetine on the pharmacokinetics and hemodynamic effects of tamsulosin in men on a stable dose of tamsulosin. *J Clin Pharmacol*. 2008;48:1438–50.
78. McMahon CG, Althof SE, Waldinger MD, Porst H, Dean J, Sharlip ID, et al. An Evidence-Based Definition of Lifelong Premature Ejaculation: Report of the International Society for Sexual Medicine (ISSM) Ad Hoc Committee for the Definition of Premature Ejaculation. *J Sex Med*. 2008.
79. Waldinger MD, Zwinderman AH, Olivier B, Schweitzer DH. Proposal for a Definition of Lifelong Premature Ejaculation Based on Epidemiological Stopwatch Data. *J Sex Med*. 2005;2:498–507.
80. Giuliano F, Patrick DL, Porst H, La Pera G, Kokoszka A, Merchant S, et al. Premature Ejaculation: Results from a Five-Country European Observational Study. *Eur Urol*. 2007 Oct 16. [Epub ahead of print.]
81. Waldinger M, Hengeveld M, Zwinderman A, Olivier B. An empirical operationalization of DSM-IV diagnostic criteria for premature ejaculation. *Int J Psychiatry Clin Pract*. 1998;2:287–93.
82. Waldinger MD, Zwinderman AH, Olivier B, Schweitzer DH. The majority of men with lifelong premature ejaculation prefer daily drug treatment: an observation study in a consecutive group of Dutch men. *J Sex Med*. 2007;4:1028–37.
83. McMahon CG, Abdo C, Incrocci I, Perelman M, Rowland D, Stuckey B, et al. Disorders of orgasm and ejaculation in men. In: Lue TF, Basson R, Rosen R, Giuliano F, Khoury S, Montorsi F, eds. *Sexual Medicine*: *Sexual Dysfunctions in Men and Women (2nd International Consultation on Sexual Dysfunctions-Paris)*. Paris, France: Health Publications; 2004:409–68.

84. Waldinger MD, Berendsen HH, Blok BF, Olivier B, Holstege G. Premature ejaculation and serotonergic antidepressants-induced delayed ejaculation: the involvement of the serotonergic system. *Behav Brain Res*. 1998;92: 111–8.
85. Waldinger M. Towards evidenced based drug treatment research on premature ejaculation: a critical evaluation of methodology. *J Impotence Research*. 2003;15:309–13.
86. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. *Arch Intern Med*. 2006;166:1021–6.
87. Atmaca M, Kuloglu M, Tezcan E, Semercioz A. The efficacy of citalopram in the treatment of premature ejaculation: a placebo-controlled study. *Int J Impot Res*. 2002;14:502–5.
88. McMahon CG. Treatment of premature ejaculation with sertraline hydrochloride: a single-blind placebo controlled crossover study. *J Urol*. 1998; 159:1935–8.
89. Kara H, Aydin S, Yucel M, Agargun MY, Odabas O, Yilmaz Y. The efficacy of fluoxetine in the treatment of premature ejaculation: a double-blind placebo controlled study. *J Urol*. 1996;156:1631–2.
90. Waldinger MD, Hengeveld MW, Zwinderman AH. Paroxetine treatment of premature ejaculation: a double-blind, randomized, placebo-controlled study. *Am J Psychiatry*. 1994;151:1377–9.
91. Goodman RE. An assessment of clomipramine (Anafranil) in the treatment of premature ejaculation. *J Int Med Res*. 1980;8:53–9.