Efficacy and tolerability of dapoxetine in treatment of premature ejaculation: an integrated analysis of two double-blind, randomised controlled trials

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Summary

Background **No drugs are approved for treatment of premature ejaculation. Our aim was to determine the efficacy and tolerability of on-demand dapoxetine in patients with severe premature ejaculation.**

Methods **We determined the efficacy of dapoxetine 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. Men with moderate-to-severe premature ejaculation in stable, heterosexual relationships took placebo (n=870), 30 mg dapoxetine (874), or 60 mg dapoxetine (870) on-demand (as needed, 1–3 h before anticipated sexual activity). The primary endpoint was intravaginal ejaculatory latency time (IELT) measured by stopwatch. Safety and tolerability were assessed. All analyses were done on an intention-to-treat basis. The trials are registered at ClinicalTrials.gov, numbers NCT00211107 and NCT00211094.**

Findings **672, 676, and 610 patients completed in the placebo, 30 mg dapoxetine, and 60 mg dapoxetine groups, respectively. Dapoxetine significantly prolonged IELT (p<0·0001, all doses *vs* placebo). Mean IELT at baseline was 0·90 (SD 0·47) minute, 0·92 (0·50) minute, and 0·91 (0·48) minute, and at study endpoint (week 12 or final visit) was 1·75 (2·21) minutes for placebo, 2·78 (3·48) minutes for 30 mg dapoxetine, and 3·32 (3·68) minutes for 60 mg dapoxetine. Both dapoxetine doses were effective on the first dose. Common adverse events (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%).**

Interpretation **On-demand dapoxetine is an effective and generally well tolerated treatment for men with moderate-to-severe premature ejaculation.**

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Introduction

Premature ejaculation is thought to be the most common male sexual dysfunction, with a prevalence of 21–33%.[1–3] It can be a source of distress for many men, although some are less affected or cope more effectively with the condition.[1–5] In men who are affected by this problem, premature ejaculation can adversely affect self-image, interfere with sexual satisfaction and the sexual relationship,[1,2,4,5] and negatively affect the overall quality of life of men and their partners.[6,7]

Although the condition is highly undertreated, selective serotonin reuptake inhibitors (SSRIs), which were developed to treat depression and other psychiatric disorders, are used increasingly as off-label treatment for premature ejaculation, on the basis of their side-effect of delayed ejaculation.[5,8–12] However, these compounds were not developed to treat premature ejaculation, are long acting, and are associated with drawbacks.[5] SSRI adverse effects include psychiatric and neurological issues, dermatological reactions, anticholinergic side-effects, changes in bodyweight, cognitive impairment, drug-drug interactions, and sexual side-effects (eg, erectile dysfunction and loss of libido).[13–19] The rate and mean duration of each type of adverse event varies with the SSRI agent. Conventional SSRIs have longer half-lives and generally take longer to reach peak concentrations.[13] Overdose of SSRIs (and drug-drug interactions between SSRIs and other agents that enhance central nervous system serotonergic activity) can lead to the serotonin syndrome.[20] Patients receiving continuous-dose SSRI therapy are more likely to have drug-drug interactions with concomitant medications and must adjust their SSRI doses accordingly.[18]

The underlying pathophysiology of premature ejaculation is not completely understood, although both physiological and psychological components could contribute to the condition. Psychopharmacological studies suggest that premature ejaculation might be related to diminished serotonergic neurotransmission through pathways that control ejaculation.[21,22] Dapoxetine is a short acting SSRI developed specifically for the treatment of premature ejaculation.[23] The drug's mechanism of action is thought to be related to inhibition of neuronal reuptake of serotonin and subsequent potentiation of serotonin activity.[23] By contrast with SSRIs approved for depression, which take 2 weeks or longer to reach steady-state concentration,[13] dapoxetine has a unique pharmacokinetic profile, with a short time to maximum serum concentration (about 1 h) and rapid elimination (initial half-life of 1·2 h). By 24 h, plasma

concentrations are less than 5% of peak values.[24] These attributes make dapoxetine suitable for on-demand therapy.

We report results from a prespecified integrated analysis of two identically designed clinical trials to determine the efficacy and tolerability of on-demand dapoxetine at two doses in patients with premature ejaculation.

Methods

Patients

As part of a development programme, two large multicentre, randomised, double-blind, placebo-controlled, 12-week clinical trials of identical design were done independently, but in parallel, from June, 2003, to June, 2004. Both pivotal trials were first analysed separately and shown to have highly significant and similar results for the primary endpoint and all secondary endpoints. An integrated analysis of these two studies, defined a priori, is reported here to facilitate additional subanalyses and interpretation of treatment effects.

The patient population consisted of men with premature ejaculation who were more severely affected with the condition than the general population of men self-identifying with symptoms of premature ejaculation in surveys.[1–3] 2614 men and their partners were randomised at 121 clinical research sites in the USA. Patients were over 18 years of age and in a stable sexual relationship with a female partner for at least 6 months. Men had to meet the diagnostic criteria for premature ejaculation as specified in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, text revision (DSM-IV-TR):[25] onset of orgasm and ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wished, in most intercourse episodes in the 6 months before enrolment, and marked distress or interpersonal difficulty due to premature ejaculation. Furthermore, intravaginal ejaculatory latency times (IELTs) were recorded in an event log. Men were required to have an IELT, as measured by a partner-held stopwatch, of 2 minutes or less in at least three of four (or 75%) evaluable events occurring during a 2-week baseline period.[26] Severity of premature ejaculation was further assessed by patients' responses to the statement: "I consider the severity of my rapid ejaculation problem to be (none, mild, moderate, severe)." Men who regarded themselves as having no or mild premature ejaculation were excluded. These criteria for IELT and severity of premature ejaculation ensured that a subset of men with severe premature ejaculation problems was studied.

Other exclusion criteria included erectile dysfunction or other forms of sexual dysfunction, concomitant use of SSRIs or tricyclic antidepressants, history of major psychiatric disorder, or use of other forms of therapy for premature ejaculation (pharmacological or behavioural). Patients whose partners had problems with self-reported female sexual dysfunction were excluded.

The studies were reviewed by each centre's Institutional Review Board in accordance with the Code of Federal Regulations and Institutional Review Board policies and were undertaken in accordance with the guidelines for Good Clinical Practice. All participants provided signed written informed consent before any study-specific procedures were done.

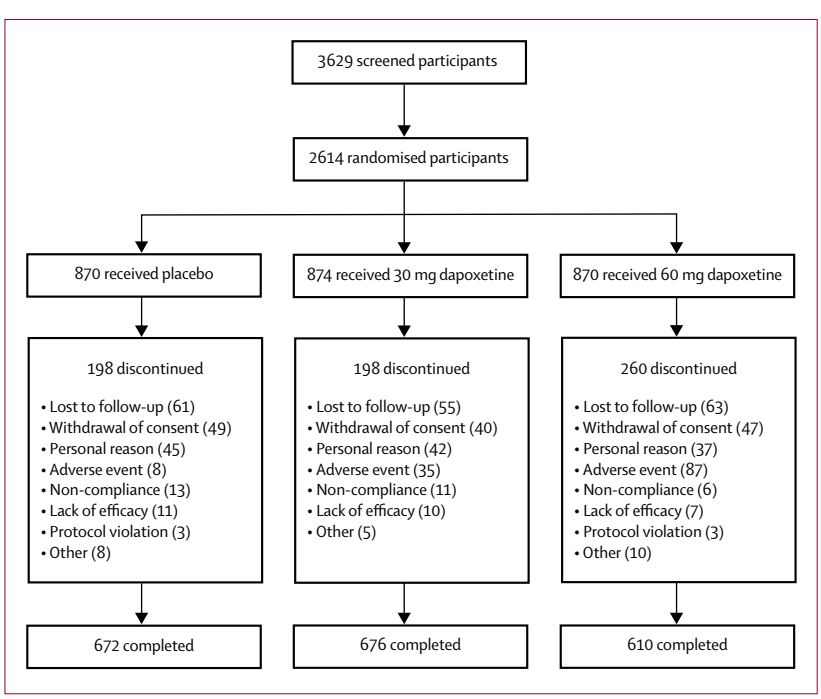

Figure 1: **Trial profile**

Procedures

Couples were instructed to attempt sexual intercourse four or more times during the 2-week baseline period and six or more times per month during the 12-week treatment period (minimum of 24 h between doses of medication), and to record IELT for the first event after each dose in the event log.

At the end of the baseline period, patients were stratified on the basis of average IELT during the previous 2 weeks of 1 minute or less or more than 1 minute. At each centre, patients were randomly assigned within each stratum 1:1:1 by a computerised interactive voice recognition system to receive placebo, 30 mg dapoxetine, or 60 mg dapoxetine, and given 30 doses of study medication (one dose was two tablets; tablets in all groups were identical in appearance); one dose was to be taken 1–3 h before anticipated sexual intercourse, and only one dose was allowed per 24-h period. Dapoxetine doses of 30 mg and 60 mg were selected on the basis of efficacy and safety findings from two previously completed phase II studies in which dapoxetine doses ranged from 20 mg to 100 mg, taken as needed.[27] Ejaculation-delaying techniques and behavioural therapy were to be avoided. Patients agreed not to change the type and brand of condom, if used, during the study.

Treatment efficacy was assessed at 4, 8, and 12 weeks. The primary endpoint was IELT at week 12 or final visit. IELT was defined as the mean duration of intercourse attempts since the last clinic visit (past 4 weeks) for which intravaginal ejaculation was reported; ejaculation occurring before penetration was assigned an IELT of 0 minutes. During the screening visit, participants and partners received instructions on the IELT measurement technique, in which partners were to activate the supplied stopwatch on vaginal penetration during sexual intercourse and to stop the stopwatch on either intravaginal ejaculation or withdrawal without ejaculation. The time noted on the stopwatch at this point was recorded as the duration of sexual intercourse until ejaculation or withdrawal. This technique has been validated elsewhere.[26]

As suggested by the DSM-IV-TR and others in the field,[1,2,4,25,28,29] many factors are included in the definition of premature ejaculation, such as timing of ejaculatory response, control over ejaculation, and satisfaction with sexual intercourse. Therefore, although IELT serves as an objective measure of biological response to treatment, key secondary endpoints were included to encompass the multifaceted nature of premature ejaculation. These endpoints included three items from the male and female versions of the premature ejaculation profile, a set of validated single-item self-report measures of premature ejaculation. Patient items included the questions: (1) "Over the past month, was your control over ejaculation during sexual intercourse (very poor, poor, fair, good, very good)?" and (2) "Over the past month, was your satisfaction with sexual intercourse (very poor, poor, fair, good, very good)?"[26] Partners of patients also rated their own satisfaction with intercourse. Every endpoint was assessed at all visits; responses were rated on 5-point scales (0=very poor to 4=very good). Patients also indicated their impression of severity and change in their condition. Severity was measured by responses to the statement: "Over the past month, I consider the severity of my rapid ejaculation problem to be (none [0], mild [1], moderate [2], severe [3])" at each visit. Patient global impression of change was assessed at weeks 4, 8, and 12 (much worse, worse, slightly worse, no change, slightly better, better, or much better than at start of treatment) with a 7-point scale (–3=much worse to 3=much better).[30]

Vital signs and adverse events were recorded at each visit; laboratory testing was done at screening, week 4, and week 12 or final visit. Investigators assessed adverse event severity as mild, moderate, or severe and classified adverse events as probably, possibly, or not related to study drug.

Statistical analysis

We tested for differences in the three treatment groups. Provided that an overall treatment difference at the 0·05 significance level was seen, pair-wise comparisons between the three groups were then done at this level. The overall α level is preserved with this hierarchical procedure, because the tests done constitute a closed family of tests. Each trial was designed with a target sample size of 300 completers per group. A sample size of 300 patients per group would be sufficient to detect a 1·0-minute difference in IELT between the best performing and worst performing treatments with 98% power.

We analysed IELT with an analysis of covariance (ANCOVA) model with treatment, centre, and stratum main effects, treatment-by-stratum interaction effects, and adjustment for baseline IELT. IELT after the first dose was analysed with the same ANCOVA model.

We analysed all secondary endpoints with χ^2 tests for dichotomous endpoints generated from the ordinal scales. The specific transformations of the 4-point or 5-point scales into dichotomous variables assist in the interpretation of treatment effects. All secondary endpoints except patient global impression of change were analysed in terms of change from baseline with an analysis of variance (ANOVA) model with treatment,

	Placebo (n=870)	30 mg dapoxetine (n=874)	60 mg dapoxetine (n=870)
Age			
Age (years)	40·3 (9·55)	40·3 (9·10)	40·9 (9·09)
Age distribution			
18–29 years	120 (14%)	95 (11%)	97 (11%)
30–39 years	312 (36%)	335 (38%)	291 (33%)
40–49 years	289 (33%)	318 (36%)	336 (39%)
50–64 years	137 (16%)	118 (14%)	142 (16%)
≥65 years	12 (1%)	8 (1%)	4 (1%)
Race			
White	765 (88%)	751 (86%)	753 (87%)
Black	44 (5%)	56 (6%)	57 (7%)
Asian	10 (1%)	14 (2%)	16 (2%)
Hispanic	39 (5%)	46 (5%)	43 (5%)
Other	12 (1%)	7 (1%)	1 (0·1%)
Premature ejaculation			
Mean duration (years)	16·0 (10·7)	15·6 (10·6)	16·3 (10·5)
Type			
Primary/lifelong	571 (66%)	560 (64%)	563 (65%)
Secondary/acquired	299 (34%)	314 (36%)	307 (35%)
Severity			
Moderate	234 (27%)	248 (28%)	227 (26%)
Severe	633 (73%)	625 (72%)	641 (74%)
Other characteristics			
Married	749 (86%)	771 (88%)	747 (86%)
Patients with selected medical history*			
Diabetes	16 (2%)	18 (2%)	25 (3%)
Hyperlipidaemia	121 (14%)	105 (12%)	131 (15%)
Hypertension	77 (9%)	90 (10%)	102 (12%)
Psychiatric disorders†	57 (7%)	36 (4%)	51 (6%)

Data are mean (SD) or number (%), unless otherwise indicated. Percentages do not always total 100% due to rounding. *A patient could be reported in more than one category. †Includes attention deficit disorder, anxiety, bipolar, and depression.

Table 1: **Patient demographics and baseline characteristics**

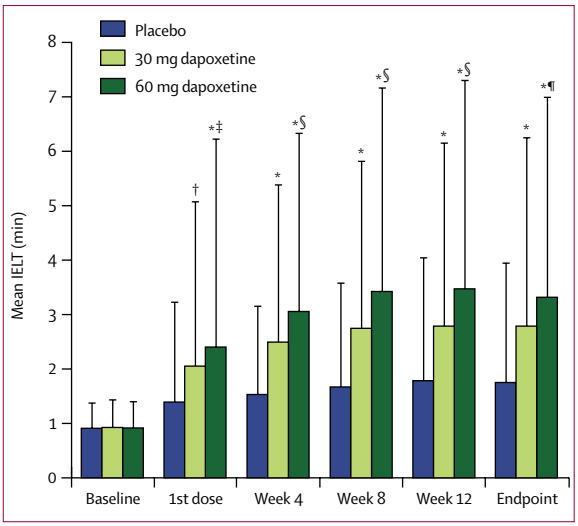

Figure 2: **Mean IELT during the study**
Study endpoint represents final visit values (week 12 or last visit). *p<0·0001 *vs* placebo; †p=0·0006 *vs* placebo; ‡p=0·0072 *vs* 30 mg; §p<0·0001 *vs* 30 mg; ||p=0·0007 *vs* 30 mg. Error bars=SD.

centre, stratum main effects, and treatment-by-stratum interaction effects. Patient global impression of change, measured post-treatment, was analysed in accordance with the same ANOVA model, with post-treatment score as the dependent variable.

To determine the effects of dapoxetine relative to time from dosing to event, IELT was grouped into intervals of 30 minutes to 1 h, 3 to over 4 h, and 4 h or more in sub-analyses. We calculated mean IELT per time interval with the patient's average IELT for that interval. To help to interpret reported changes in mean IELT, data were pooled across treatment arms, and mean IELT changes were derived by patient global impression of change category (anchoring technique).[30,31]

The primary time point for analysis was study endpoint, defined as assessment at week 12 for patients who completed the study and as the last available post-baseline assessment for patients who did not. To assess the robustness of the primary results, we did an additional analysis, in which the baseline assessment was carried forward for patients without post-baseline assessments. All analyses were done on an intention-to-treat basis.

The trials are registered at ClinicalTrials.gov, numbers NCT00211107 and NCT00211094.

Role of the funding source

ALZA Corporation designed the study, obtained the data, and did the data analysis. All authors had full access to all the data in the study, participated in writing the manuscript, and had final responsibility for editing, completion, and the decision to submit the manuscript for publication.

	Placebo	30 mg dapoxetine	60 mg dapoxetine
All patients	n=870	n=874	n=870
Baseline	0·90 (0·47)	0·92 (0·50)	0·91 (0·48)
End of study	1·75 (2·21)	2·78 (3·48)*	3·32 (3·68)*†
Least-square mean difference *vs* placebo (95% CI)	..	1·11 (0·80–1·43)	1·66 (1.35–1·98)
Patients with baseline IELT >1 to ≤2 min	n=328	n=332	n=328
Baseline	1·39 (0·31)	1·41 (0·31)	1·38 (0·32)
End of study	2·51 (2·72)	3·79 (3·14)*	4·43 (4·12)*‡
Least-square mean difference *vs* placebo (95% CI)	..	1·27 (0·72–1·82)	1·95 (1·39–2·51)
Patients with baseline IELT ≤1 min	n=541	n=542	n=540
Baseline	0·61 (0·26)	0·62 (0·32)	0·61 (0·29)
End of study	1·28 (1·67)	2·19 (3·54)*	2·67 (3·24)*§
Least-square mean difference *vs* placebo (95% CI)	..	0·91 (0·54–1·27)	1·39 (1·02–1·76)
Patients with baseline IELT ≤30 s (post-hoc analysis)	n=200	n=184	n=187
Baseline	0·34 (0·12)	0·32 (0·14)	0·32 (0·14)
End of study	0·86 (1·48)	1·63 (3·53)||	2·17 (3·64)*¶
Least-square mean difference *vs* placebo (95% CI)	..	0·84 (0·17–1·52)	1·53 (0·85–2·20)
Distribution of IELT at study endpoint	n=787	n=801	n=763
0 to <1 min	342 (44%)	203 (25%)	157 (21%)
1 to <2 min	251 (32%)	250 (31%)	216 (28%)
2 to <3 min	85 (11%)	116 (15%)	129 (17%)
3 to <4 min	42 (5%)	90 (11%)	59 (8%)
≥4 min	67 (9%)	142 (18%)	202 (27%)
Missing	17	21	38

Data are minutes (SD) or number (%), unless otherwise indicated. All percentages rounded. *p<0·0001 *vs* placebo. †p=0·0007 *vs* 30 mg. ‡p=0·018 *vs* 30 mg. §p=0·0094 *vs* 30 mg. ||p=0·014 *vs* placebo. ¶p=0·056 *vs* 30 mg.

Table 2: **IELT at baseline and end of study**

Results

Figure 1 shows the trial profile, and table 1 the demographic and baseline characteristics of the patients. Mean age was 40·5 years (range, 18–77 years), and mean duration of premature ejaculation was 16·0 years.

Figure 2 shows mean IELT by time. At baseline, 1623 men (62%) had IELT of 1 minute or less, with mean IELT values much the same across groups (table 2). 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; figure 2). Overall, IELT increased in all three groups, but the increase was greatest in those on dapoxetine (table 2). At the study endpoint, 109 (14%) of 787 of 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 minutes or more (table 2). The p values for the tests of difference of proportions between placebo and the 30 mg group, as well as between placebo and the 60 mg group, were both p<0·0001.

The patient global impression of change in condition at study endpoint is informative with respect to men's perception to minor detectable changes in IELT. For example, participants with patient global impression of change ratings of slightly better and no change across all treatment groups combined had corresponding mean change in IELT values of 1·46 (median 0·92) minutes and 0·39 (0·78) minute, respectively. Thus, the minimum important change in IELT for this study population seems to be about 1 minute. The proportions of individuals with a 1-minute change from baseline to study endpoint in IELT were 22% (173/787) for placebo, 47% (377/801) for 30 mg dapoxetine, and 51% (388/762) for 60 mg dapoxetine. The p values for the tests of difference of proportions between placebo and the 30 mg group, as well as between placebo and the 60 mg group, were both p<0·0001.

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) minutes with placebo, 2·05 (3·02) minutes with 30 mg dapoxetine, and 2·41 (3·82) minutes with 60 mg dapoxetine. Both dapoxetine doses were also better than placebo at weeks 4, 8, and 12, and study endpoint (p<0·0001, overall comparison of treatments at each time point; figure 2). IELT was also significantly increased for the 60-mg versus the 30-mg dose at each time point.

Table 2 shows subgroup analyses for patients with baseline IELTs of more than 1–2 minutes and 1 minute or less. In both these subgroups, both dapoxetine doses were better than placebo at the end of study (p<0·0001). IELT was significantly longer with 60 mg dapoxetine than with 30 mg dapoxetine in both subgroups (p=0·0180 for IELT of >1–2 minutes and p=0·0094 for IELT of 1 minute or less).

Although patients were to take dapoxetine 1–3 h before anticipated sexual intercourse, not all reported events were within this window. However, significant increases in IELT were seen when dapoxetine was taken 30 minutes to 1 h, 3–4 h, and 4 h or more before sexual activity (table 3).

	Placebo	30 mg dapoxetine	60 mg dapoxetine
Drug taken 30 min to 1 h before sexual activity			
Number of patients	182	182	185
IELT (min)	1·66 (1·59)	3·03 (5·25)*	3·15 (3·16)†
Drug taken 3–4 h before sexual activity			
Number of patients	287	269	259
IELT (min)	1·79 (2·26)	3·06 (3·89)†	3·97 (4·10)†
Drug taken more than 4 h before sexual activity			
Number of patients	157	169	160
IELT (min)	1·77 (1·94)	2·56 (2·71)‡	3·92 (4·79)†

IELT expressed as mean (SD). *p=0·0009 *vs* placebo †p<0·0001 *vs* placebo ‡p=0·065 *vs* placebo.

Table 3: **IELT at baseline and end of study by dosing interval relative to sexual activity**

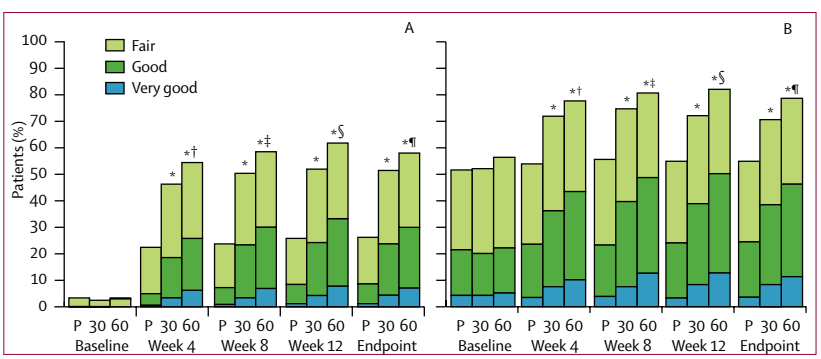

Figure 3: **Control over ejaculation and satisfaction with sexual intercourse**
(A) Percentage of patients reporting fair, good, or very good control over ejaculation over the course of the study. Study endpoint represents final visit values (week 12 or last visit). *p<0·0001 *vs* placebo; †p=0·0013 *vs* 30 mg; ‡p=0·0025 *vs* 30 mg; §p=0·0004 *vs* 30 mg; ||p=0·0082 *vs* 30 mg. (B) Percentage of patients reporting fair, good, or very good satisfaction with sexual intercourse over the course of the study. *p<0·0001 *vs* placebo; †p=0·009 *vs* 30 mg; ‡p=0·007 *vs* 30 mg; §p<0·0001 *vs* 30 mg; ||p=0·0001 *vs* 30 mg. P=placebo. 30=30 mg dapoxetine. 60=60 mg dapoxetine.

The study-specified secondary endpoints also showed that both dapoxetine doses were better than placebo (p<0·0001, each dose *vs* placebo). Improvements in patient perception of control over ejaculation and satisfaction with sexual intercourse were achieved with both doses of dapoxetine at all time points (figure 3 and table 4). Patients who received dapoxetine perceived an overall improvement in symptoms of premature ejaculation, and partners of patients with premature ejaculation had a significant increase in satisfaction with sexual intercourse (table 4). A significant improvement in patient ratings of severity of premature ejaculation was also seen in patients who received dapoxetine (table 4).

The most common adverse events were related to the gastrointestinal and central nervous systems—nausea, diarrhoea, and headache—and seemed to be dose related, but led to treatment discontinuation in only a few patients

(table 5). Most discontinuations were for reasons other than adverse events (figure 1); 5% of all enrolled patients discontinued treatment because of adverse events, although a difference in rates and a dose relation were noted. Sexual side-effects—eg, erectile dysfunction, abnormal ejaculation, decreased libido, and abnormal sexual function—were reported in fewer than 1·5% (n=13) of patients on placebo and in fewer than 3·8% (33) of patients on either dose of dapoxetine (table 5).

Accidental injuries—eg, sprained ankle, car accident—were reported in 17 (1·9%) patients receiving placebo, in 28 (3·2%) patients receiving 30 mg dapoxetine, and in 26 (3·0%) on 60 mg dapoxetine. Dizziness and somnolence were the most common neurocognitive adverse events reported (table 5). Individual categories of cardiovascular adverse events each occurred in less than 2% of patients; the most clinically significant event reported was syncope. Syncope was reported in two individuals (0·2%) receiving placebo, three (0·3%) receiving 30 mg dapoxetine, and two (0·2%) receiving 60 mg dapoxetine. Mean blood pressure and heart rate throughout the study were much the same for active treatment and placebo.

The incidence of severe adverse events was low—2·9% (n=25) for placebo, 2·3% (20) for 30 mg dapoxetine, and 4·3% (37) for 60 mg dapoxetine. The incidence of serious adverse events was also low—0·9% (8) for placebo, 0·3% (3) for 30 mg dapoxetine, and 0·6% (16) for 60 mg dapoxetine. No deaths, suicides, suicide attempts, suicidal ideations, or SSRI withdrawal syndromes were reported.

	Placebo	30 mg dapoxetine	60 mg dapoxetine
Patient perception of control over ejaculation			
Score at baseline	0·44 (0·57)	0·44 (0·55)	0·46 (0·57)
Score at end of study	1·05 (0·95)	1·65 (1·09)	1·82 (1·14)
Patient satisfaction with sexual intercourse			
Score at baseline	1·66 (1·03)	1·65 (1·02)	1·72 (1·05)
Score at end of study	1·70 (1·06)	2·21 (1·05)	2·31 (1·05)
Patient global impression of change			
"Slightly better, better, or much better"	200 (26%)	467 (58%)*	515 (67%)*
Partner satisfaction with sexual intercourse			
"Fair, good, very good" at baseline	445 (58%)	457 (53%)	489 (58%)
"Fair, good, very good" at end of study	429 (56%)	561 (72%)*	576 (78%)*
Score at baseline	1·59 (1·07)	1·62 (1·08)	1·74 (1·08)
Score at end of study	1·69 (1·09)	2·11 (1·05)	2·32 (1·06)
Patient rating of severity of premature ejaculation			
"None/mild" at end of study	90 (12%)	217 (27%)	258 (34%)
Score at baseline	2·73 (0·45)	2·71 (0·45)	2·73 (0·45)
Score at end of study	2·38 (0·72)	1·98 (0·86)*	1·84 (0·91)*

Data presented as mean (SD) or number (%). Percentages are rounded. *p<0·0001 *vs* placebo.

Table 4: **Secondary endpoints**

	Placebo (n=872)*	30 mg dapoxetine (n=876)*	60 mg dapoxetine (n=870)
Occurred more frequently on dapoxetine than placebo			
Nausea	17 (1·9%)	76 (8·7%)	175 (20·1%)
Diarrhoea	12 (1·4%)	34 (3·9%)	59 (6·8%)
Headache	35 (4·0%)	52 (5·9%)	59 (6·8%)
Dizziness	7 (0·8%)	26 (3·0%)	54 (6·2%)
Somnolence	2 (0·2%)	28 (3·2%)	32 (3·7%)
Reasons for study discontinuation			
Nausea	1 (0·1%)	11 (1·3%)	33 (3·8%)
Dizziness	0	8 (0·9%)	13 (1·5%)
Diarrhoea	1 (0·1%)	6 (0·7%)	10 (1·1%)
Headache	2 (0·2%)	4 (0·5%)	9 (1·0%)
Erectile dysfunction	1 (0·1%)	5 (0·6%)	8 (0·9%)
Insomnia	0	4 (0·5%)	6 (0·7%)
Vomiting	0	3 (0·3%)	6 (0·7%)
Anxiety	0	1 (0·1%)	6 (0·7%)
Nervousness	0	3 (0·3%)	5 (0·6%)
Sweating	0	1 (0·1%)	5 (0·6%)
Sexual function			
Erectile dysfunction	13 (1·5%)	25 (2·9%)	33 (3·8%)
Abnormal ejaculation	2 (0·2%)	6 (0·7%)	7 (0·8%)
Libido decreased	0	6 (0·7%)	3 (0·3%)
Sexual function abnormal	2 (0·2%)	2 (0·2%)	4 (0·5%)

AE=adverse event. All data are number (%). *Four patients who were inadvertently treated with both placebo and 30 mg dapoxetine counted in both treatment groups, and their AEs summarised by treatment at onset.

Table 5: **Adverse events**

Discussion

Our analyses show that dapoxetine, given 1–3 h before intercourse, increased IELT significantly, even after administration of the first dose. Dapoxetine also improved patients' perception of control over ejaculation, satisfaction with sexual intercourse, and overall impression of change in condition. Partners benefited through improved satisfaction with sexual intercourse. Thus, dapoxetine seems to lead to improvements in ejaculatory function that have meaning for men with premature ejaculation and their partners. For many men, premature ejaculation is associated with substantial psychological effects—eg, interpersonal distress,[1,2,4,5,26] decreased self-confidence, and relationship difficulties.[2,4] Thus, an effective treatment that can be used as needed will offer an important new option for men with premature ejaculation and their partners.

In the absence of an approved treatment for premature ejaculation, conventional SSRIs are increasingly used to treat premature ejaculation. Such agents could also delay ejaculation when taken on a daily basis. Waldinger's meta-analysis[32] of pharmacological agents that delay ejaculation reported IELT delays ranging from two-fold to nine-fold above baseline when the drugs were taken on a daily basis. He also described IELT delays for on-demand agents in the two-fold to eight-fold range, but noted that these studies were difficult to interpret because of methodological difficulties. Dapoxetine, given on-demand, delays ejaculation roughly three-fold to four-fold in the overall population, with greater increases seen in men with lower baseline IELTs (eg, baseline IELT

<30 s, 5-fold increase with 30 mg dapoxetine and 6·7-fold increase with 60 mg dapoxetine), which is consistent with previously reported studies.[32]

With the baseline IELTs of the population studied (mean of 0·90–0·92 minute and all ≤2 minutes), the overall 2-minutes or more (3-fold to 3·7-fold) improvement in IELT with dapoxetine is clinically meaningful, as evidenced by other more subjective measures of the condition. Improvements in control over ejaculation, satisfaction with sexual intercourse, and self-reported severity in this population of more severely affected individuals are highly relevant to confirming the clinical benefit of treatment. An observational study showed that patient ratings of the severity of premature ejaculation had a strong positive correlation with distress (r=0·61).[26]

The effect of dapoxetine on the single-item patient-reported outcome measures also showed clinically important differences. At baseline, 3% of patients reported fair or better than fair control over ejaculation. By the end of study, only about a quarter of placebo-treated individuals achieved fair or better control over ejaculation. By contrast, at least twice as many achieved that level with dapoxetine. Moreover, although about half of individuals in all groups had fair or better satisfaction with sexual intercourse at baseline, placebo treatment yielded negligible change—about half of individuals who received placebo achieved fair or better than fair satisfaction, compared with about three-quarters of individuals on dapoxetine. The finding that satisfaction with sexual intercourse was not as severely impaired as IELT or control over ejaculation at baseline is unsurprising, since IELT and control over ejaculation are more direct symptoms of premature ejaculation, whereas satisfaction with sexual intercourse is a broader notion that incorporates other aspects of the sexual encounter. Although a placebo effect was apparent for IELT and control over ejaculation, a corresponding improvement in satisfaction with sexual intercourse with placebo treatment was not.

One should note that the study population was restricted to patients with IELT consistently 2 minutes or less and who described their premature ejaculation as moderate to severe. Therefore, the results cannot be generalised to men with milder forms of premature ejaculation. Additionally, the effects of dapoxetine on patient types excluded from these trials—those with coexisting erectile dysfunction or premature ejaculation of other cause—are not known. Finally, because of the predominance of caucasian and young patients, robust conclusions in other ethnic groups and older men could not be established.

Generally, a chronic daily dosing schedule has been used when conventional SSRI antidepressants have been prescribed for premature ejaculation.[5,8–12,33] However, in addition to the inconvenience of such a schedule, long-term daily dosing with conventional SSRIs could be a contributing factor to the increased frequency of sexual side-effects in individuals receiving such treatment—eg, erectile dysfunction (5·9%), decreased libido (2·5–5·0%), and high incidences of problems with orgasm (4·9%) and non-ejaculation (2·5–8·2%).[34] In the trials analysed here, sexual side-effects were reported in 1·5% or less of patients on placebo, 2·9% of those on 30 mg dapoxetine, and 3·8% of those on 60 mg dapoxetine. Thus, dapoxetine on-demand is effective in delaying ejaculation when used as needed and is well tolerated, with a low incidence of sexual side-effects.

Non-sexual side-effects with dapoxetine were transient and characteristic of compounds with serotoninergic effects.[5,8–12] Some of the side-effects—nausea, diarrhoea, and dizziness—seemed dependent on dose. The most commonly reported side-effect was nausea. Most of these events were mild and transient, and resulted in study discontinuation in only a few cases. Cardiovascular and central nervous system side-effects were reported at a low incidence. The most clinically important cardiovascular adverse event reported was syncope, which occurred at a low incidence that was much the same in all groups of patients in this combined analysis, but at a higher rate than placebo in other studies. The occurrence of syncope is not unexpected and is likely to be drug related, since syncope is reported as an infrequent adverse event (1 in 100–1000) with SSRIs approved for the treatment of depression;[35] much the same rate that has been noted with dapoxetine in other, as yet unpublished studies.

Accidental injury is a recognised adverse event reported with many drug classes, especially with agents that modulate the central nervous system. Accidental injury is reported with some SSRIs[36] and phosphodiesterase-5 inhibitors.[37,38] Events should be examined qualitatively for details of circumstances surrounding the reported accidental injury. Such an assessment of the accidental injuries in these trials showed that there was no clinical signal to suggest that the accidental injuries were masking any other important adverse events—eg, syncope and suicidality. Neurocognitive adverse events—eg, dizziness and somnolence—seemed to be dose dependent. Both accidental injuries and neurocognitive adverse events could be drug related. The relation between the occurrence of these two types of adverse events needs further investigation. The discontinuation rate due to adverse events with dapoxetine (about 7%) was much the same as or less than that of other SSRI compounds when used in men with premature ejaculation.[12]

These trials have shown that dapoxetine is effective and generally well tolerated for the treatment of premature ejaculation when given on demand. Dapoxetine improves multiple patient-reported and partner-reported variables as well as the rigorous objective assessment of IELT. In view of the distress and interpersonal difficulties generally associated with this condition, availability of an effective treatment, especially for those with the most severe premature ejaculation, might encourage men with premature ejaculation to

seek a physician diagnosis, and could provide a substantial benefit for men and their partners.

Contributors

All authors took part in the interpretation of the findings and the preparation of the manuscript.

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Conflict of interest statement

S E Althof, R C Rosen, W J G Hellstrom, and R Shabsigh have served as consultants for Johnson & Johnson. R Shabsigh has also received grant/research support from Johnson & Johnson. M Miloslavsky and S Kell are employees of ALZA Corporation. J L Pryor and C Steidle have served on advisory boards for ALZA Corporation.

References

1 Rowland DL, Perelman MA, Althof SE, et al. Self-reported premature ejaculation and aspects of sexual functioning and satisfaction. *J Sex Med* 2004; **1:** 225–32.

2 Rosen RC. The premature ejaculation prevalence and attitudes (PEPA) survey: a multi-national survey. *J Sex Med* 2004; **1** (suppl 1)**:** 57–58.

3 Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA* 1999; **281:** 537–44.

4 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.

5 Montague DK, Jarow J, Broderick GA, et al. AUA guideline on the pharmacologic management of premature ejaculation. *J Urol* 2004; **172:** 290–94.

6 McCabe MP. Intimacy and quality of life among sexually dysfunctional men and women. *J Sex Marital Ther* 1997; **23:** 276–90.

7 Byers ES, Grenier G. Premature or rapid ejaculation: heterosexual couples' perceptions of men's ejaculatory behavior. *Arch Sex Behav* 2003; **32:** 261–70.

8 McMahon CG. Treatment of premature ejaculation with sertraline hydrochloride: a single-blind placebo controlled crossover study. *J Urol* 1998; **159:** 1935–38.

9 McMahon CG, Touma K. Treatment of premature ejaculation with paroxetine hydrochloride. *Int J Impot Res* 1999; **11:** 241–46.

10 McMahon CG, Touma K. Treatment of premature ejaculation with paroxetine hydrochloride as needed: 2 single-blind placebo controlled crossover studies. *J Urol* 1999; **161:** 1826–30.

11 Waldinger MD, Hengeveld MW, Zwinderman AH, Olivier B. Effect of SSRI antidepressants on ejaculation: a double-blind, randomized, placebo-controlled study with fluoxetine, fluvoxamine, paroxetine, and sertraline. *J Clin Psychopharmacol* 1998; **18:** 275–81.

12 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:** 1631–32.

13 Hiemke C, Härtter S. Pharmacokinetics of selective serotonin reuptake inhibitors. *Pharmacol Ther* 2000; **85:** 11–28.

14 Rosen RC, Lane RM, Menza M. Effects of SSRIs on sexual function: a critical review. *J Clin Psychopharmacol* 1999; **19:** 67–85.

15 Montejo-Gonzales AL, Llorca G, Izquierdo JA, et al. SSRI-induced sexual dysfunction: fluoxetine, paroxetine, sertraline, and fluvoxamine in a prospective, multicenter, and descriptive clinical study of 344 patients. *J Sex Marital Ther* 1997; **23:** 176–94.

16 Williams VS, Baldwin DS, Hogue SL, Fehnel SE, Hollis KA, Edin HM. Estimating the prevalence and impact of antidepressant-induced sexual dysfunction in 2 European countries: a cross-sectional patient survey. *J Clin Psychiatry*. 2006; **67:** 204–10.

17 Hu XH, Bull SA, Hunkeler EM, et al. Incidence and duration of side effects and those rated as bothersome with selective serotonin reuptake inhibitor treatment for depression: patient report versus physician estimate. *J Clin Psychiatry* 2004; **65:** 959–65.

18 Goldstein BJ, Goodnick PJ. Selective serotonin reuptake inhibitors in the treatment of affective disorders—III. Tolerability, safety and pharmacoeconomics. *J Psychopharmacol* 1998; **12** (3 suppl B)**:** S55–87.

19 Spigset O. Adverse reactions of selective serotonin reuptake inhibitors: reports from a spontaneous reporting system. *Drug Saf* 1999; **20:** 277–87.

20 Lane R, Baldwin D. Selective serotonin reuptake inhibitor-induced serotonin syndrome: review. *J Clin Psychopharmacol* 1997; **17:** 208–21.

21 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:** 111–18.

22 Waldinger MD. The neurobiological approach to premature ejaculation. *J Urol* 2002; **168:** 2359–67.

23 Gengo PJ, Giuliano F, McKenna K, et al. Monoaminergic transporter binding and inhibition profile of dapoxetine, a medication for the treatment of premature ejaculation. *J Urol* 2005; **173** (suppl 4)**:** 239.

24 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:** 301–09.

25 Diagnostic and Statistical Manual of Mental Disorders, 4th ed., text revision. Washington, DC: American Psychiatric Association, 2000.

26 Patrick DL, Althof SE, Pryor JL, et al. Premature ejaculation: an observational study of men and their partners. *J Sex Med* 2005; **2:** 358–67.

27 Hellstrom W, Althof S, Gittelman M, et al. Dapoxetine for the treatment of men with premature ejaculation (PE): dose-finding analysis. *J Urol* 2005; **173** (suppl 4)**:** 238.

28 Rowland DL, deGouvea Brazao C, Strassberg D, Slob AK. Ejaculatory latency and control in men with premature ejaculation: a detailed analysis across sexual activities using multiple sources of information. *J Psychosom Res* 2000; **48:** 69–77.

29 Grenier G, Byers ES. Rapid ejaculation: a review of conceptual, etiological, and treatment issues. *Arch Sex Behav* 1995; **24:** 447–72.

30 Guyatt G, Osoba D, Wu A, Wyrwich KW, Norman GR, Clinical Significance Consensus Meeting Group. Methods to explain the clinical significance of health status measures. *Mayo Clin Proc* 2002; **77:** 371–83.

31 Patrick DL, Martin ML, Bushnell DM, Yalcin I, Hawner H, Buesching DP. Quality of life of women with urinary incontinence: further development of the incontinence quality of life instrument (I-QOL). *Urology* 1999; **53:** 71–76.

32 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.

33 Waldinger MD. Lifelong premature ejaculation: definition, serotonergic neurotransmission and drug treatment. *World J Urol* 2005; **23:** 102–08.

34 American Urological Association. Pharmacologic treatment of premature ejaculation (PE) appendices. http://www.auanet.org/timssnet/products/guidelines/main_reports/pme/appendices.pdf (accessed Jul 7, 2006).

35 Anon. Physician's desk reference. 58th ed. Montvale, NJ: Thomson Healthcare, 2004.

36 Anon. Paxil (paroxetine hydrochloride) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline, 2005.

37 Anon. Viagra (sildenafil citrate) [prescribing information]. New York, NY: Pfizer Inc, 2005.

38 Anon. Levitra (vardenafil HCl) [prescribing information]. West Haven, CT: Bayer Pharmaceuticals Corporation, 2005.