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Results from a Prospective Observational Study of Men with Premature Ejaculation Treated with Dapoxetine or Alternative Care: The PAUSE Study

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Abstract

Background: Dapoxetine hydrochloride is a selective serotonin reuptake inhibitor and the first drug approved for the on-demand treatment of premature ejaculation (PE). Its safety was established in a thorough clinical development program.
Objective: To characterize the safety profile of dapoxetine in PE treatment and to report the incidence, severity, and type of adverse events.
Design, setting, and participants: We conducted a 12-wk, open-label, observational study with a 4-wk, postobservational contact. A total of 10 028 patients were enrolled, with 6712 patients (67.6%) treated with dapoxetine 30–60 mg (group A)and 3316 (32.4%) treated with alternative care/nondapoxetine (group B).
Interventions: Treatment with dapoxetine or alternative care/nondapoxetine.
Outcome measurements and statistical analysis: Treatment-emergent adverse events (TEAEs) and concomitant therapy use during the 12-wk observational and the post-observational period were reported.
Results and limitations: The mean age for all patients was 40.5 yr. In group A, 93.0% of the patients were initially prescribed dapoxetine 30 mg. Treatment options for group B patients included clomipramine, paroxetine, fluoxetine, sertraline, topical drugs, condoms, and behavioral counseling. Both treatment regimens were well tolerated. TEAEs were reported by 12.0% and 8.9% of group A and group B, respectively, with the highest incidence observed in patients aged >65 yr for group A (21.4%) and 30–39 yr (9.8%) for group B. The most commonly reported TEAEs were nausea, headache, and vertigo, with a higher incidence in group A (3.1%, 2.6%, and 1.0%, respectively) than in group B (oral drugs: 2.3%, 1.3%, and 0.9%, respectively). There were no cases of syncope in group A and one case in group B. A major limitation is that this was a nonrandomized, open-label, short-term study lacking efficacy data.
Conclusions: The results of this postmarketing observational study demonstrated that dapoxetine for treatment of PE has a good safety profile and low prevalence of TEAEs. Syncope and major cardiovascular adverse events were not reported. The high level of adherence by healthcare providers to the contraindications, special warnings, and precautions for dapoxetine minimizes the risk for its use in routine clinical practice. The current risk minimization measures for its identified and potential risks are effective.

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1. Introduction

Dapoxetine hydrochloride (Priligy; Janssen Pharmaceutica NV, Beerse, Belgium), a selective serotonin reuptake inhibitor (SSRI), was the first drug originally approved for the on-demand treatment of premature ejaculation (PE) by seven European countries (Austria, Finland, Germany, Italy, Portugal, Spain, and Sweden) in 2008 [1]. Since then, it has received marketing authorization in 59 countries worldwide.

An integrated analysis from five phase 3 trials concluded that dapoxetine 30 mg and 60 mg significantly improved all aspects of PE compared to placebo, including intravaginal ejaculatory latency time, PE profile questionnaire items, and Clinical Global Impression of Change in PE [2]. The geometric mean fold increases were 2.5, 3.0, and 1.6 with dapoxetine 30 mg, 60 mg, and placebo, respectively.

The safety profile of antidepressant SSRIs has never been comprehensively studied in men with PE. It consists only of safety data from clinical studies and spontaneously reported adverse events in men with psychiatric disorders. Although dapoxetine differs from other drugs within the SSRI class, due to its rapid onset of action and elimination profile enabling on-demand use, its mechanism of action theoretically could result in adverse events similar to other available SSRIs. The safety assessment currently available for dapoxetine is based on data from the clinical development program that included >6000 patients [3]. In phase 3 studies, several well-recognized side effects of SSRIs (ie, akathisia, withdrawal syndrome, and mood-related changes) were not reported for dapoxetine use [2]. A low rate of vasovagal syncope was reported in phase 3 studies, and the premarketing safety profile did not show evidence of serious cardiovascular (CV) events or arrhythmias [4,5]. The primary objectives of this study were to characterize the safety profile of dapoxetine when used to treat men with PE in routine clinical practice, and to report the incidence, severity, and type of adverse events (serious adverse events and/or adverse events of special clinical interest).

2. Patients and methods

2.1. Subjects

Patients with a current diagnosis of PE or who were newly diagnosed with PE and who received therapy for this condition were enrolled in the study. Group A included all patients treated with dapoxetine; group B patients had alternative care/nondapoxetine treatment. The alternative care/nondapoxetine treatment was defined as any treatment other than dapoxetine (Table 1). No specific selection criteria (inclusion or exclusion criteria) were specified to select patients, due to the observational nature of the study. Patients were considered for enrollment only after the participating healthcare providers (HCPs) had determined that either treatment with dapoxetine or alternative care/nondapoxetine was appropriate. All patients were informed about the observational nature of the study and gave their written consent.

2.2. Study design

This prospective, 12-wk, open-label, postmarketing observational study was conducted at 414 sites in seven European countries (Austria, Finland, Germany, Italy, Portugal, Spain, and Sweden) with an enrollment period ranging from September 2009 to September 2012 (ClinicalTrials.gov identifier NCT01021670). The study design consisted of three periods, as shown in Figure 1. The participating HCP prescribed either dapoxetine or alternative care/nondapoxetine treatment after an initial assessment of the patient during the preobservational period. The study protocol and amendments were approved by local ethics committees at every site, and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was consistent with good clinical practice guidelines. After an initial evaluation was performed, the participating HCP instructed the patient to take dapoxetine in accordance with the summary of product characteristics [6].

Table 1 – Alternative care/nondapoxetine group (safety analysis set, *n* = 3315)

Oral drug*	No. (%)
Clomipramine	98 (6.5)
Paroxetine	629 (41.5)
Fluoxetine	27 (1.8)
Sertraline	91 (6.0)
Other	680 (44.9)
Total	**1515**
Other treatment†	
Topical drug	952 (32.5)
Condoms	432 (14.8)
Behavioral counseling	1182 (40.4)
Other	362 (12.4)
Total	**2928**

* In the alternative care/nondapoxetine group components, number counts the patients prescribed the component at any visit. Percentages are calculated with the total number of the alternative care/nondapoxetine oral drug as the denominator.

† Percentages are calculated with the total number of the alternative care/nondapoxetine other treatment as the denominator.

2.3. Outcome measures

Study-related data were collected and safety evaluations carried out to monitor treatment-emergent adverse events (TEAEs) and concomitant therapy use during the 12-wk observational period and at the postobservational telephone contact. Some adverse events (ie, syncope, mood and related, neurocognitive related, CV system, urogenital system and sexual function, accidental injury, abnormal bleeding) were considered of special clinical interest compared with commonly reported TEAEs and were analyzed separately in this study. Orthostatic vital signs (blood pressure and heart rate) were measured during the preobservational period for patients who were dapoxetine candidates. The first measurement was recorded with the patient in the supine position for at least 2 min. The second measurement was taken with the patient in the standing or the erect position for at least 2 min following the supine measurements but before 3 min had elapsed.

2.4. Sample size determination

The sample size was presumed to be large enough to potentially observe at least one rare adverse event and to detect any safety issue that had not been observed during the clinical development program. The sample size of 6000 patients (per group) would yield a precision (half width) of 0.17%, thus constructing a 95% confidence interval (CI) for an adverse event where the adverse event rate is assumed to be 0.50% (ie, the 95% CI would extend from 0.33% to 0.67%), which is similar to the rate of

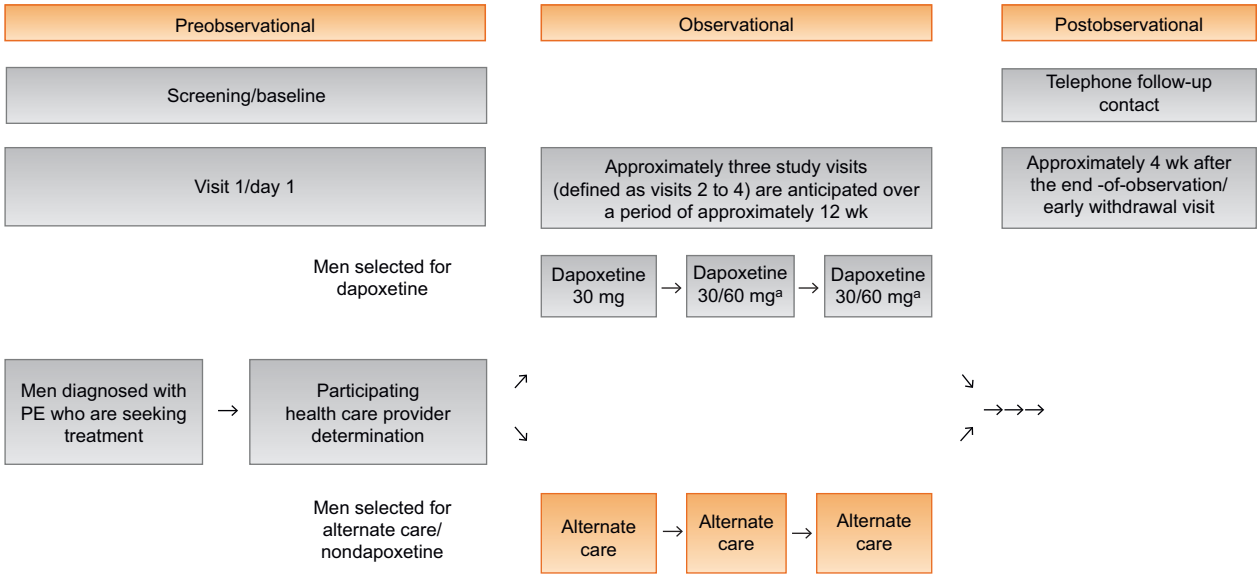

Fig. 1 – Study diagram.
PE = premature ejaculation.
[a]The dose of dapoxetine might be modified (eg, might be increased from 30 mg to 60 mg or decreased from 60 mg to 30 mg) at the discretion of the participating healthcare provider, in accordance with the SPC.

syncope observed in phase 3 studies (0.23%) [2]. In addition, this sample size would result in an 80% probability of observing at least one infrequent adverse event (0.027%).

2.5. *Statistical analyses*

The enrolled patient analysis set (PAS) was defined as all patients whose information was entered into the database. All patients who took at least one dose of dapoxetine were included in the safety analysis set (SAS) associated with dapoxetine treatment (group A). All patients not using dapoxetine at visit 1 and using alternative care/nondapoxetine treatment were included in the alternative care/nondapoxetine treatment group B. A patient was considered to have completed the study if he finished the end-of-observation assessments. Baseline information was described using common statistical descriptors for continuous data, count, and percentages for categorical data. All reported adverse events with onset during the observational period were included in the analysis. The percentage of patients who experienced at least one adverse event was summarized by treatment group. We performed a multivariate logistic regression analysis for predicting the outcome of dichotomous dependent variables, with a statistically significant p value set at <0.05.

3. Results

A total of 10 028 patients were included in the PAS, with 6712 patients (67.6%) selected for group A and 3316 (32.4%) for group B. Among all the enrolled patients, 9443 (94.2%) were included in the SAS, of whom 6128 (91.3%) and 3315 (>99.9%) belonged to groups A and B, respectively.

There were no significant differences in demographic or baseline characteristics or in duration of the treatment period between the two groups (Table 2). The mean age for all patients was 40.5 yr, with most patients included in the 30- to 39-yr age group (28.0%) and the 40- to 49-yr age group (27.0%). Most of the patients in group A were aged <65 yr and had no history of orthostatic reactions (98.1% and >99.9%, respectively).

Evaluation for orthostatic reaction at baseline for the dapoxetine-only treatment candidates revealed the reaction in 70 patients (1.0%). Overall, 60 of the 70 patients were included in the SAS; 6 patients took no dapoxetine, and the remaining 4 patients underwent only a first visit. A total of 5697 patients (93.0%) were initially prescribed dapoxetine 30 mg; 431 patients (7.0%) were initially prescribed the 60-mg dose.

Most of the patients continued with the 30-mg dose at visits 2, 3, and 4 (82.4%, 77.8%, and 76.9%, respectively) (Table 3). An increase to the 60-mg dose occurred most frequently at visit 2 (10.6%). For 36 (8.3%) of the 431 patients taking 60 mg at visit 2, the dosage was decreased from 60 mg to 30 mg. The main reason for the dose increase from 30 mg to 60 mg at visits 2, 3, and 4 (82.8%, 79.4%, and 77.9%, respectively) was insufficient response. For most of the patients whose dosage was decreased from 60 mg to 30 mg at visits 2, 3, and 4 (50.0%, 47.4%, and 53.6%, respectively), the main reason was patient preference.

The total number of dapoxetine doses per patient during the entire study ranged from 1 to 54. Most of the patients (61.8%) took no more than 10 doses during the treatment period; the mean number taken during the treatment period was 10.2. The mean duration of treatment was similar between groups A and B (88.2 d vs 87.0 d, respectively).

A total of 58 patients (0.9%) treated with dapoxetine were prescribed a contraindicated concomitant therapy during the course of the study. Antidepressants were the most frequently used class of drugs.

A total of 540 patients (8.8%) treated with dapoxetine used a concomitant medication with special warnings and

Table 2 – Demographics and baseline characteristics

	Dapoxetine	Alternative care/nondapoxetine	Total
No. of patients	6712	3316	10 028
Age, yr			
Mean (SD)	40.6 (11.78)	40.2 (12.35)	40.5 (11.97)
Median	40.0	39.0	40.0
Range	17–79	17–81	17–81
Race, no. (%)			
White	6437 (95.9)	3189 (96.2)	9626 (96.0)
Black	79 (1.2)	41 (1.2)	120 (1.2)
Asian	62 (0.9)	51 (1.5)	113 (1.1)
Unknown	6 (0.1)	6 (0.2)	12 (0.1)
Multiple	2 (<0.1)	2 (0.1)	4 (<0.1)
Not reported	1 (<0.1)	1 (<0.1)	2 (<0.1)
Other	125 (1.9)	26 (0.8)	151 (1.5)
PE diagnosis, no. (%)			
Lifelong	3133 (46.7)	1292 (39.0)	4425 (44.1)
Acquired	2951 (44.0)	1596 (48.1)	4547 (45.3)
Unsure	628 (9.4)	426 (12.8)	1054 (10.5)
Missing	0	2 (0.1)	2 (<0.1)

SD = standard deviation; PE = premature ejaculation.
For continuous variables, mean and median are rounded to one decimal point, and standard deviations are rounded to two decimal points.

Table 3 – Dose adjustments over time

Visit	Dapoxetine treatment group				
	Total no. (%)	Dose increase, 30 mg to 60 mg	Dose decrease, 60 mg to 30 mg	No change, 30 mg	No change, 60 mg
Visit 1*	6128 (100)	0	0	5697 (93.0)	431 (7.0)
Visit 2	5869 (95.8)	621 (10.6)	36 (0.6)	4837 (82.4)	375 (6.4)
Visit 3	5518 (90.0)	315 (5.7)	57 (1.0)	4295 (77.8)	851 (15.4)
Visit 4**	5126 (83.6)	149 (2.9)	28 (0.5)	3942 (76.9)	1006 (19.6)

* Number of patients who started with dapoxetine 30/60 mg.
** One patient receiving dapoxetine stopped at Visit 3, but dapoxetine was still prescribed at Visit 4. This patient is included in the Total column for Visit 4.

precautions for use, namely, phosphodiesterase type 5 inhibitors (PDE5-Is; 5.5%) and α-blockers (3.3%).

TEAEs were reported by 12.0% and 8.9% of patients in groups A and B, respectively, with the highest incidence observed in patients >65 yr of age for the dapoxetine group (21.4%) and between 30 yr and 39 yr of age (9.8%) for the alternative care/nondapoxetine group (Supplemental Table 1).

The most commonly reported TEAEs (>1% in any group) were nausea (2.4%), headache (1.9%), and vertigo (0.8%), with a higher incidence in group A (3.1%, 2.6%, and 1.0%, respectively) than in group B (oral drugs 2.3%, 1.3%, and 0.9%, respectively; nonoral treatments: 0.1%, 0.3%, and 0%, respectively).

The overall number of patients experiencing at least one TEAE was greater in patients who were titrated from the 30-mg to the 60-mg dose than in those who remained on the 30-mg dose for the duration of the study (15.0% vs 10.9%, respectively). TEAE incidence was greater in those who were titrated to dapoxetine 60 mg at visit 2 than in those who remained on dapoxetine 30 mg for the duration of the study (12.9% vs 4.8%, respectively), although for patients remaining on dapoxetine 60 mg at visits 3 and 4, the incidence of TEAEs was lower than at visit 2 (10.5% and 8.7%, respectively). Nausea was the most commonly reported TEAE (Table 4) in the dapoxetine group.

A total of 22 patients included in the SAS reported severe TEAEs during the study: 12 (0.2%) treated with dapoxetine and 10 (0.3%) treated with alternative care/nondapoxetine; however, none were considered related to the treatment. No deaths were reported in either treatment group.

The incidence of patients who discontinued the study due to a TEAE was greater in group A than in group B (1.5% vs 0.2%, respectively), although no TEAE led to the discontinuation of >0.3% of patients in either treatment group (Supplemental Table 2).

Overall, the total incidence in each category of special adverse events was low (Supplemental Table 3). The number of patients reporting adverse events was higher in the neurocognitive-related adverse event category (2.0%). With the exception of the CV system (dapoxetine, 1.6%; alternative care [oral drug], 1.3%) and accidental injury (0.1% for both), the incidence of TEAEs of special interest in each category was greater in group B (oral drug) than in those treated with dapoxetine. There were no associations between TEAEs of syncope and the orthostatic test results. One event of syncope was reported as a serious adverse event in a group B patient treated with paroxetine; no event

Table 4 – Dapoxetine: treatment-emergent adverse events in ≥1% of patients by preferred term, dose, and study visit

Study visit	Visit 1–Visit 2 (n = 5869)		Visit 2–Visit 3 (n = 5518)		Visit 3–Visit 4 (n = 5125)		Visit 1–Visit 4 (Visit 1, n = 6128)		Total (N = 9443)				
									Dapoxetine	Nondapoxetine			Total
										Total	Nonoral	Oral drug	
Dapoxetine dose, mg	30	60	30	60	30	60	30	60					
No. of patients*	5458	411	4610	908	4091	1034	5697	431	6128	3315	1898	1417	**9443**
Patients with at least one AE, no. (%)	281 (5.1)	39 (9.5)	161 (3.5)	84 (9.3)	125 (3.1)	47 (4.5)	567 (10.0)	170 (39.4)	737 (12.0)	294 (8.9)	66 (3.5)	228 (16.1)	**1031** (10.9)
Nausea, no. (%)	64 (1.2)	9 (2.2)	39 (0.8)	25 (2.8)	41 (1.0)	14 (1.4)	144 (2.5)	48 (11.1)	192 (3.1)	34 (1.0)	1 (0.1)	33 (2.3)	**226** (2.4)
Headache, no. (%)	72 (1.3)	10 (2.4)	28 (0.6)	14 (1.5)	22 (0.5)	11 (1.1)	122 (2.1)	35 (8.1)	157 (2.6)	24 (0.7)	5 (0.3)	19 (1.3)	**181** (1.9)
Vertigo, no. (%)	23 (0.4)	4 (1.0)	17 (0.4)	3 (0.3)	11 (0.3)	6 (0.6)	51 (0.9)	13 (3.0)	64 (1.0)	13 (0.4)	0	13 (0.9)	**77** (0.8)
Fatigue, no. (%)	12 (0.2)	0	4 (0.1)	3 (0.3)	3 (0.1)	0	19 (0.3)	3 (0.7)	22 (0.4)	40 (1.2)	0	40 (2.8)	**62** (0.7)
Diarrhea, no. (%)	13 (0.2)	2 (0.5)	7 (0.2)	4 (0.4)	5 (0.1)	3 (0.3)	25 (0.4)	9 (2.1)	34 (0.6)	24 (0.7)	1 (0.1)	23 (1.6)	**58** (0.6)

AE = adverse event.
Incidence is based on the number of patients experiencing at least one adverse event, not the number of events.
* Percentages were calculated with the number of patients (safety analysis set) in each group as the denominator.

of syncope was reported in any patient treated with dapoxetine.

Table 5 summarizes the independent predictor of any grade TEAEs. Presence of CV disorders at baseline (odds ratio [OR]: 0.619; $p < 0.001$), presence of metabolic disorders at baseline (OR: 0.711; $p = 0.004$), alcohol assumption (OR: 1.372; $p < 0.0001$), PE diagnosis (OR: 0.681; $p < 0.0001$), and treatment modality (p for trend < 0.0001) were independent predictors of TEAE, once adjusted for the other covariates. The low number of severe TEAEs prevented us from an analysis of predictors.

4. Discussion

The data from this postmarketing observational study demonstrate that dapoxetine for treatment of PE has a good safety profile and low prevalence of TEAEs in routine clinical practice. Key study design features that differed from previous phase 3 studies [7–11] in the clinical development program were a lack of strict patient-exclusion criteria (eg, age <18 yr, comorbid erectile dysfunction, psychiatric or CV disorders) and the ability of participating physicians to select the starting dose of dapoxetine and adjust the dosage during the course of the study.

An important strength of this study was the thorough and comprehensive collection of adverse event data. Compared with former studies, fewer patients were lost to follow-up (6.2% vs 3.9%, respectively) and fewer patients prematurely withdrew from the study because of the onset of a side effect induced by the drug (approximately 31% vs approximately 11%, respectively) [2].

The overall demographics of the enrolled population were similar among treatment groups and to those reported in the phase 3 study population except for a greater proportion of men with acquired PE (44% vs 35%, respectively). The higher prevalence of acquired PE in the postmarketing setting may, in part, be related to the 5.5% of patients reporting the concomitant use of a PDE5-I who were excluded from phase 3 trials.

The overall incidence of adverse events in patients treated with dapoxetine was lower in this study (12.0%) compared with phase 3 studies. Most adverse events were mild to moderate and related to the gastrointestinal or nervous systems. Similarly, the proportion of patients who discontinued use due to adverse events (1.5%) was lower in this study than in the pooled phase 3 data (3.5% of dapoxetine 30 mg and 8.8% of dapoxetine 60 mg).

Although the incidence of TEAEs in patients treated with dapoxetine was lower than those treated with alternative care (oral drug) (12.0% vs 16.1%, respectively), it was greater than in those patients treated with alternative care (nonoral) treatment (3.5%). This is plausible considering that topical and behavioral treatments are associated with minimal and no systemic exposure, respectively. Similarly, it is not surprising that the rate of discontinuation due to adverse events was lower in those patients treated with alternative care/nondapoxetine therapies than with those reported with dapoxetine (0.2% vs 1.5%, respectively).

Table 5 – Multivariable analysis for predictors of any grade treatment-emergent adverse events

Variables	OR	95% CI	*p* value
Age, continuous	1.001	0.995–1.008	0.681
Race	–	–	0.416
Black vs white	1.501	0.821–2.744	0.187
Asian vs white	0.965	0.457–2.038	0.925
Presence of cardiovascular disorders (no vs yes)	0.619	0.495–0.774	<0.0001
Presence of psychiatric disorders (no vs yes)	0.566	0.304–1.053	0.072
Presence of metabolic disorders (no vs yes)	0.711	0.562–0.898	0.004
Alcohol assumption			<0.0001
1–7 drinks per week vs none	1.372	1.178–1.598	<0.0001
8–14 drinks per week vs none	1.250	0.974–1.605	0.079
≥15 drinks per week vs none	1.508	1.054–2.159	0.025
PE diagnosis			<0.0001
Acquired vs lifelong	0.681	0.585–0.793	<0.0001
Unsure vs lifelong	1.118	0.870–1.436	0.382
Treatment			<0.0001
Dapoxetine vs nondapoxetine (oral)	0.750	0.629–0.894	0.001
Dapoxetine vs nondapoxetine (nonoral)	3.990	2.972–5.357	<0.0001

OR = odds ratio; CI = confidence interval; PE = premature ejaculation.

Considering that adverse events among dapoxetine-treated patients tend to be dose dependent, a greater incidence of TEAEs in patients treated with the 60-mg dose was expected. A trend of a lower incidence and severity of adverse events at visit 2 on the 30-mg dose among patients titrated to 60 mg at visit 2 compared with those who remained on 30 mg for the duration of the study was observed. Subsequently, adverse events were the most frequently reported reason for a reduction from the 60-mg to the 30-mg dose.

Among a total of 6081 subjects in the phase 3 studies, of whom 4224 subjects were treated with dapoxetine, the incidence of syncope was similar in patients receiving placebo and in those treated with dapoxetine 30 mg (0.05% vs 0.06%, respectively), although greater in subjects treated with the 60-mg dose (0.23%) [2]. In comparison, based on this large observational study of 6128 patients treated with dapoxetine, it was observed that the incidence of syncope was zero, with the upper bound of the 95% confidence limit around 2.0 per 1000 person-years. One syncope case (alternative care/nondapoxetine) occurred in the context of 3315 patients (<0.1%) and was generally consistent with the literature reports of a background rate of vasovagal syncope of 1.31–6 per 1000 person-years [12] and 0.13% per patient [13].

The incidence of other serious adverse events was similar between patients treated with dapoxetine and those treated with alternative care/nondapoxetine and consistent with the previous phase 3 studies [2].

Multivariate logistic regression analysis assessed the variables predicting incidence of any grade TEAEs. It is interesting to note that among predictors, CV disorders (the absence of CV disorders at baseline decreased TEAE hazard by 38%), metabolic disorders (the absence of metabolic disorders at baseline decreased TEAE hazard by 29%), alcohol assumption (>15 drinks/wk increased TEAE hazard 1.5 times), PE diagnosis (lifelong diagnosis increased TEAE hazard by 32% related to acquired diagnosis) were found to be statistically significant. Furthermore, dapoxetine, relative to oral alternative cares, decreased TEAE hazard by 25 times.

Finally, the results of the present study suggest the high adherence of HCPs to the contraindications, special warnings, and precautions for the use of dapoxetine. These include a medical history including the presence of orthostatic reaction and/or the use of concomitant therapies that are contraindicated (antidepressants, potent CYP3A4 inhibitor, triptans) or have precautions and warnings when used with dapoxetine (α-blockers, moderate CYP3A4 inhibitor, nitrates, PDE5inhibitors, potent CYP2D6 inhibitors). This was confirmed by the adequate identification of patients at risk for orthostatic reaction by medical history evaluation and orthostatic testing, the prescription of a 30-mg starting dose in >90% of PE patients, and the concomitant use of drugs with special warnings and vasodilatory properties in <10% of the patients.

Major limitations of the study are the nonrandomized, open-label, short-term design and the lack of efficacy data.

5. Conclusions

The results of the present postmarketing observational study demonstrate that dapoxetine for treatment of PE has a good safety profile, with low prevalence of TEAE. The lack of any syncope or other major CV events in dapoxetine-treated patients in this large, diverse population of men with PE supports the positive safety and tolerability profile of dapoxetine when prescribed in routine clinical practice. The high adherence of HCPs to the contraindications, special warnings, and precautions for the use of dapoxetine minimizes the risk for its use.

Author contributions: Vincenzo Mirone had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Mirone, Rivas, Bull, Aquilina.
Acquisition of data: Rivas, Bull, Aquilina.

Analysis and interpretation of data: Mirone, Verze, Arcaniolo.
Drafting of the manuscript: Verze, Arcaniolo.
Critical revision of the manuscript for important intellectual content: Mirone, Rivas.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2013.08.018.

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