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Comparison of Treatment of Emergent Adverse Events in Men With Premature Ejaculation Treated With Dapoxetine and Alternate Oral Treatments: Results From a Large Multinational Observational Trial

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ABSTRACT

Introduction: Dapoxetine (DPX) has a pharmacokinetic profile suggesting a low rate of class-related adverse events (AEs).

Aim: To assess the incidence of treatment emergent AEs (TEAEs) of special interest (known associations with selective serotonin reuptake inhibitors and/or potential clinically relevant AEs), and the related discontinuation rate in patients with premature ejaculation (PE) treated with DPX or alternate oral treatment (AOT), in routine clinical practice.

Methods: In a prospective, 12-week, open-label, postmarketing observational, multinational study (PAUSE), 7545 patients were enrolled and divided into 2 groups: DPX 30–60 mg and AOT.

Main outcome measures: The incidence rate of predefined TEAEs of special interest (mood and related, neurocognitive related, cardiovascular, urogenital and sexual function, accidental injury, and abnormal bleeding) in the DPX and the AOT groups, and the rate of AEs leading to study discontinuation.

Results: The safety analysis was performed on 6128 patients treated with DPX and 1417 with AOT. The incidence of TEAEs of special interest in each AE category was greater for patients treated with AOT than with DPX. The higher differences were observed in the neurocognitive-related category (DPX 1.9% vs AOT 4.7%; $P < .001$), in the mood and related category (DPX 0.4% vs AOT 1.1%; $P < .001$), and in the urogenital system/sexual function (DPX 0.4% vs AOT 0.8%; $P = .04$). Cardiovascular TEAEs were the only AEs numerically greater in the DPX group (1.3 vs 1.6%, $P = .34$). The overall discontinuation rate was 10.9% in the DPX group and 6.9% in the AOT group).

Conclusion: DPX has a favorable safety profile in terms of class-related TEAEs and clinically relevant AEs of special interest. In particular, it shows a significantly better safety profile in mood and related AEs, neurocognitive-related AEs, urogenital system, and sexual function, compared to the AOT group in the study population.

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Key Words: Dapoxetine; Safety; Cardiovascular Events; SSRI; Paroxetine; Fluoxetine

INTRODUCTION

Chronic administration of selective serotonin reuptake inhibitors (SSRIs) has been used off label for the treatment of premature ejaculation (PE) based on the ability of this class of drugs to cause prolonged increases in synaptic cleft serotonin, a key neurotransmitter involved in ejaculatory control in humans.[1] However, although some antidepressant SSRIs are effective in delaying ejaculation, their safety profile has not been comprehensively demonstrated in PE patients and can only be presumed from clinical trials in men with psychiatric disorders.[2–4] In a meta-analysis of studies in patients with major depressive disorder, the incidence of adverse events (AEs) with SSRIs ranged from 8.5% to 16.3%.[5] Furthermore, several class-related effects (mainly affecting the neurocognitive system and mood related) are reported for SSRIs.[6] Finally, abrupt discontinuation of SSRIs may result in SSRI withdrawal syndrome (typically characterized

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by headache, diarrhea, nausea, vomiting, chills, dizziness, or fatigue).[7] DPX, the only SSRI approved in more than 60 countries for PE treatment, differs from other drugs within the SSRI class due to its rapid onset of action and elimination time, enabling an on-demand use, theoretically resulting in a lower rate of AEs commonly observed with antidepressant SSRIs.[8,9]

The safety database for DPX has been recently enriched with the results from the PAUSE study, a large, multinational, postmarketing observational trial conducted in seven European countries between September 2009 and September 2012.[10] The results showed that DPX has a good safety profile, with low incidence of treatment emergent AEs (TEAEs).[10] A comprehensive evaluation of TEAEs of special interest was still lacking. The present analysis was aimed to focus attention only on the incidence of TEAEs of special interest in PE patients treated with DPX or alternate oral treatment (AOT) and to assess the related discontinuation rate.

PATIENTS AND METHODS

Study Design

The analysis was conducted in patients affected by PE enrolled in the PAUSE study.[10] The main criteria for patient enrolment and study design have been previously described.[10] Briefly, 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. Two groups were identified: patients treated with DPX and patients receiving AOT. No specific selection criteria (inclusion or exclusion criteria) were specified, due to the observational nature of the study. Participating healthcare providers (HCPs) determined that either treatment with DPX or AOT was appropriate before enrollment. It was a prospective, 12-week, open-label, postmarketing observational, multinational study (Austria, Finland, Germany, Italy, Portugal, Spain, and Sweden) that enrolled patients between September 2009 and September 2012 (ClinicalTrials.gov identifier NCT01021670). The study design consisted of 3 periods. Preobservational period included prescription of DPX (in accordance with the summary of product characteristics) or AOT after an initial assessment. In the observational period, outcome and safety measures were collected for 12 weeks. In the postobservational period, 1 telephone contact was made 4 weeks after the end of observational period. This study was planned as a new analysis of a previous prospective cohort study, highlighting the need for a new evaluation of TEAE of special interest due to the fact that specific TEAEs may be the reason of a patient's compliance reduction.

Safety and tolerability were evaluated throughout the study by incidence, severity, type of AEs, serious AEs, and AEs of special interest. All AEs were to be described and recorded on the patient's case report form and source document. AEs were followed until resolution or until the AEs were no longer considered to be of clinical significance. Safety was reviewed on a regular basis by an internal safety-working group to detect potential safety signals associated with the use of DPX in the postapproval setting. The list of TEAEs of special interest due to their known associations with the SSRI drug class and/or the potential for clinically relevant effects as predefined in the study design are reported in Table 1. The events of special interest were identified through a search of all AE terms in the clinical database using the same search strings that were developed for previous clinical trials and the summary of clinical safety. Dizziness can originate from either a cardiovascular or neurocognitive source and was thus included in both categories.

Patient Population

All patients who took at least 1 dose of DPX (6128 patients) or AOT (1417 patients) were included in the safety analysis set (SAS; SAS Institute, Cary, North Carolina).

A patient was considered to have completed the study if he reached the end-of-observation assessments period. Baseline information was described using common statistical descriptors for continuous data, count, and percentages for categorical data. All reported TEAEs with onset during the observational period were included in the analysis. The percentage of patients who experienced at least 1 AE was reported by treatment group. The main outcome measures were the rate of TEAEs of special interest in the DPX and the AOT groups during the 12-week observational period and the rate of those TEAEs leading to study discontinuation in the same period.

Statistical and Ethical Considerations

The sample size was presumed to be large enough to potentially observe at least 1 rare AE and to detect any safety issue that had not been observed during the clinical development program. It was determined that the sample size of 6000 patients would yield a precision (half width) of 0.17%, thus constructing a 95% confidence interval (CI) for an AE where the AE rate is assumed to be 0.50% (ie, the 95% CI would extend from 0.33% to 0.67%) as observed in phase 3 trials.[11] In addition, this sample size would result in an 80% of probability to observe at least 1 infrequent AE (0.027%). The 95% CI for serious and AEs of special interest was provided. Due to the potential for systematic patient channeling, a direct comparison of safety event rates between patients treated with DPX and patients treated with AOT was considered likely to be biased. To minimize this bias, the difference in the incidence of AEs of special interest between

Table 1. Treatment of Emergent Adverse Events of Special Interest Included in the Safety Analysis of the PAUSE Study*

Mood and related
Neurocognitive related
Cardiovascular system
Urogenital system and sexual function
Accidental injury
Abnormal bleeding
Others

*Appendix A — Supplementary data — Supplemental Table 3.[7]