Premature Ejaculation and Pharmaceutical Company-Based Medicine: The Dapoxetine Case

Marcel D. Waldinger, MD, PhD,*† and Dave H. Schweitzer, MD, PhD‡

*Department of Psychiatry and Neurosexology, HagaHospital Leyenburg, The Hague, the Netherlands; †Department of Psychopharmacology, Utrecht Institute for Pharmaceutical Sciences and Rudolf Magnus Institute for Neurosciences, Utrecht University, Utrecht, the Netherlands; ‡Department of Internal Medicine and Endocrinology, Reinier de Graaf Groep Hospital, Delft-Voorburg, the Netherlands

DOI: 10.1111/j.1743-6109.2008.00633.x

ABSTRACT

Introduction. The manufacturer of dapoxetine funded randomized clinical trials to study its effect in premature ejaculation (PE). Financial support by pharmaceutical companies, however, may jeopardize the neutrality of clinical research.

Aim. To investigate the scientific process that has been followed in dapoxetine treatment trials and reviews as compared to daily drug treatment trials and reviews with selective serotonin reuptake inhibitors (SSRIs) in men with PE.

Methods. A search of Medline and Embase was conducted using the search terms "dapoxetine" or "SSRI." References of retrieved articles were searched. Only studies describing the use of these drugs in men with PE were included.

Main Outcome Measures. Compared fold-increase intravaginal ejaculation latency time (IELT), geometric mean IELT, and adverse effect profiles between dapoxetine and SSRIs in PE.

Results. Preclinical studies on dapoxetine, including a multicenter study (category A) and reviews (category B), were compared with clinical studies with daily conventional SSRIs in PE (category C). Categories A/B focused on patient-reported outcomes with less attention for the IELT. The ejaculation-delaying effect of dapoxetine was expressed as natural mean IELT rather than as geometrical mean IELT. Dapoxetine side effects were monthly scored. In contrast, a significant part of category C articles focused on IELT data, used geometric mean IELT outcomes, and one study reported the side effects measured 24–48 hours after drug intake using a validated questionnaire. Without the Food and Drug Administration approval, dapoxetine, as well as other SSRIs in PE, is an off-label drug for PE. However, the off-label use of dapoxetine has never been criticized by clinical investigators in contrast to commentaries against the off-label use of daily SSRI treatment in PE.

Conclusions. Manufacturer-funded drug treatment research (categories A and B) is advantageously treated by some authors as compared with nonfunded trials with daily conventional SSRIs (category C). PE drug treatment research is a young and dynamic field, and its development deserves transparency to its development. **Waldinger MD, and Schweitzer DH. Premature ejaculation and pharmaceutical company-based medicine: The dapoxetine case. J Sex Med 2008;5:966–997.**

Key Words. Adverse Effects; Dapoxetine; Geometric Mean IELT; Premature Ejaculation; SSRIs

Introduction

Since its first publication in the medical literature in 1887 [1], various and sometimes opposing views on premature ejaculation (PE) have been debated among psychiatrists, psychologists, urologists, and endocrinologists [2,3]. However, for just a few years, another party has joined the PE debate, i.e., *the pharmaceutical industry*.

In the new millennium, two multinational pharmaceutical companies decided to develop pipeline selective serotonine reuptake inhibitors (SSRIs)

with a short half-life for the treatment of PE. In 2005, Pfizer Int. decided to withdraw their compound UK-390,957 from further clinical studies. However, ALZA Inc., currently part of Johnson & Johnson Inc., pioneered "dapoxetine" in men with complaints of PE [4,5]. The situation today is that the Food and Drug Administration (FDA) has decided critically to turn down all registration files on dapoxetine, while a final decision of the European registration authorities (EMEA) is still pending.

As marketing and commercial interests are also part of pharmaceutical strategies, complete transparency over the involvement of pharmaceutical companies in medicine is urgently needed. It is comprehensible that marketing strategies interfere with scientific research, which need careful unraveling about what is exactly pharmaceutical company-based medicine and what is evidence-based medicine. In case of PE research, it remains a question what the manufacturer influence was or still is regarding several aspects of the scientific process of ongoing dapoxetine research. Yet, there are no systematic analyses or comparative studies published, which confirm or reject the hypothesis that financial interference of firms may influence the outcomes of drug treatment trials.

The aim of the current review was to compare several aspects of clinical trials and reviews about dapoxetine with that of previously published scientific work on SSRIs in men with PE. Because of the lack of other studies about the role of the pharmaceutical industry in drug treatment trials, studying dapoxetine in men with PE may serve as "index case" for other new drugs.

Methods

Articles on PE, published between January 2005 and May 2007, were retrieved through a MEDLINE and EMBASE search and cross-referencing. Search terms included dapoxetine, SSRI, and premature ejaculation. The literature search was limited to articles published in the English language. In addition, all available articles reviewing the pharmacotherapy of PE in that period were evaluated. Single abstracts were excluded from analysis. All articles were compared regarding the style of information, objectivity of data information, interpretation of existent knowledge, textual consistencies, conflicting methodologies, and the use of appropriate statistics. These criteria were formulated prior to the analysis by the authors, but are obviously debatable because standard audit protocols for the purpose of this study are not available.

Results

Four major categories of articles were distinguished (Tables 1–3). Category A: five articles on the pharmacokinetics of dapoxetine, funded mainly by ALZA Inc. (Johnson & Johnson), including a clinical multicenter trial of dapoxetine [6–11] (Table 1). Category B: five articles reviewing the drug treatment of PE with a major focus on dapoxetine, a drug for on-demand treatment of PE [12–16] (Table 2). Category C: 14 reviews on the drug treatment of PE but without a specific focus on dapoxetine [17–31] (Table 3); and category D: miscellaneous articles, e.g., animal studies on neuropharmacology and neurophysiology of ejaculation [32–45], one clinical study of dapoxetine that was not funded by ALZA Inc. [46], and many abstracts. For the purpose of the current study, published works of A, B, and C were categorized and compared.

Historical Information

The dapoxetine program, aiming at investigating an on-demand oral treatment of PE, has been mentioned in the articles of categories A and B by noting that dapoxetine has specifically been developed for the on-demand treatment of PE [8].

Dapoxetine was originally developed as a drug for the treatment of depression [4,5]. The chemical formula of dapoxetine (LY210448) was originally produced by Eli Lilly, and aimed to be an antidepressant (SSRI) [4,5]. The compound is structurally related to fluoxetine from the same manufacturer. Because fluoxetine is an SSRI with a long half-life (the longest half-life of all licensed SSRIs), Eli Lilly became interested in "developing" an SSRI with a short half-life for the treatment of depression [4,5]. Their program with dapoxetine initially started with phase I clinical trials in the United States [4,5]. However, in 2000, PPD GenuPro, which was established from a collaboration between Eli Lilly and Pharmaceutical Product Development (PPD), granted a license for dapoxetine to ALZA Corporation, a completely owned subsidiary of Johnson & Johnson. In December 2004, ALZA Inc. submitted a new drug application to the FDA for dapoxetine hydrochloride as a drug to treat PE [4,5].

Assessment of Side Effects

The authors of categories A and B rely on the reported side effects as reported from the