Global Journal of Medical Research: B
Pharma, Drug Discovery, Toxicology & Medicine
Volume 17 Issue 1 Version 1.0 Year 2017
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals Inc. (USA)
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Relationship between the Wording of the Instructions and the Efficacy of Dapoxetine in the Therapy of Lifelong Premature Ejaculation: A Pilot Study

By Giorgio Cavallini & Carlo Maretti

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All PE patients received dapoxetine 60 mg. Sixty patients (Group 1) were given the following instructions “Take one tablet two hours before sexual intercourse; dapoxetine will delay your ejaculation” and 64 patients (Group 2) were given the following instructions “Take one tablet two hours before sexual intercourse; do not try to delay or to hold back ejaculation because dapoxetine is doing it for you. Dapoxetine will delay/improve your ejaculation within 3 months from the first assumption”. Before, and during the course of dapoxetine assumption, the stopwatch-measured intravaginal ejaculatory latency time, the Clinical Global Impression of Change and the side effects were measured in both groups.

Results: The baseline intravaginal ejaculatory latency time and the Clinical Global Impression of Change values did not significantly differ in Groups 1 and 2; however, during the course of dapoxetine administration, they were significantly more improved in Group 2 than in Group 1. The side effects were negligible and did not significantly differ between the groups.

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GJMR-B Classification: NLMC Code: QV 752

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Conclusions: Dapoxetine efficacy for the treatment of lifelong PE might be improved by the wording used in the instructions.

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I. Introduction

Premature ejaculation (PE) can be a debilitating male sexual impairment. A series of studies has suggested a prevalence of 4–39% (1, 2, 3). This wide range can be partly attributed to variations in the way PE is defined, but may also reflect differences between populations and differences in the degree of annoyance. Furthermore, due to the intimate nature of the problem, PE tends to be under-reported by patients who do not typically seek medical help (1).

Premature ejaculation can be divided into two distinct entities: acquired or lifelong (4). Anxiety and genetic factors are regarded as the most likely causes of lifelong PE (5). We explored the hypothesis that medical instructions (which the Authors consider soothing) might improve the efficacy of a drug.

Dapoxetine is a drug specifically developed for the on-demand treatment of PE. It has been extensively evaluated in five randomized, placebo-controlled phase III clinical trials involving more than 6000 men. There is evidence of its efficacy, its relatively mundane side effect profile and its validity as an on-demand medication. Sixty mg dapoxetine users had their intravaginal ejaculatory latency time (IELT) increased by 3-4 minutes with respect to baseline, and 55-60% were satisfied with its efficacy (6).

This open label, crossover, multicenter, fixed dose, prospective trial explored the hypothesis as to whether medical instructions for the assumption of dapoxetine might improve its efficacy.

II. Materials and Methods

This study was reviewed by the appropriate ethics committee, and all patients gave informed consent prior to their inclusion in the study. This open label, crossover, multicenter, fixed dose, pilot study began on January 2nd 2015 and ended on July 2nd 2016, and was conducted in two centers: Bologna (1st center, Giorgio Cavallini) and Piacenza (2nd center, Carlo Maretti). All patients meeting lifelong PE criteria were considered. Premature ejaculation was defined according to the International Society of Sexual Medicine (7).

1. Ejaculation which always or nearly always occurs prior to or within approximately 1 minute of vaginal penetration;
2. The inability to delay ejaculation during all or nearly all vaginal penetrations;
3. Negative personal consequences, such as distress, annoyance, frustration and/or the avoidance of sexual encounters.

Medical history was collected and a semi-structured interview was carried out; objective examination of the patient involved a general examination as well as a more focused examination of

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the genitalia, namely the scrotal contents and the penis in detail. A digital rectal examination to palpate the prostate gland and a Stamey test were also performed. Endocrine assessment involved thyroid function: total tyroxine (reference range: 60 - 150 nmol/L), free tyroxine (reference range 10 - 25 pmoli/L), total triiodothyronine (reference range 1.1 – 2.6 nmol/L), free triiodothyronine (reference range 3.0 – 8.0 pmol/L) and thyreotropin (reference range 0.15 – 3.5 mU/L) (Wespes et al, 2013).

The exclusion criteria were: congenital penile curvature (3 cases), phymosis (6 cases), short frenum (6 cases), painful prostate at digital rectal examination and/or a positive Stamey test to detect the presence of any level of urinary infection/inflammation (2 cases), thyroid endocrine alterations (no cases), drug and/or alcohol consumption (6 cases) (8), previous or concurrent sexual dysfunction of the patient or of his female partner (0 cases).

The inclusion criteria were: stable heterosexual relationship > 1 year, cohabitation > 1 year and age > 18 years.

The patients were all instructed to take one 60 mg tablet of dapoxetine (Priligy®, Menarini) two hours before sexual intercourse. Two different sets of instructions were given to the patients. The first set of instructions was: "Take one tablet two hours before sexual intercourse; dapoxetine will delay your ejaculation"; the second set of instructions was: "Take one tablet two hours before sexual intercourse; do not try to delay or to hold ejaculation because dapoxetine is doing it for you. Dapoxetine will delay/improve your IELT within 3 months from the first assumption". Instructions were given to each new patient enrolled in the study, and dapoxetine was administered for six m,onths. The first author gave the first set of instructions to all new patients enrolled from January 2nd 2015 to July 2nd 2015, and gave the second set of instructions to all patients enrolled from July 3rd 2015 to January 2nd 2016. The second Author gave the second set of instructions from January 2nd 2015 to July 2nd 2015 and gave the first set of instructions from July 3rd 2015 to January 2nd 2016. The patients who received set 1 made up Group 1, the patients who received set 2 made up Group 2.

The following variables were assessed before and during the course of dapoxetine assumption: stopwatch-measured average IELT; the clinical global impression of change (CGIC) in PE. The IELT was defined as the time elapsed between penetration and ejaculation; an ejaculation which occurred before penetration was assigned an IELT of 0 min. The mean IELT is intended an entire one-month measurement after 3 months of use and was measured with a partner-operated stopwatch. The CGIC is a subjective answer to the following 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?' (7). The side effects of dapoxetine were recorded as well. The differences in side effects and the differences between the number of patients studied in each center and belonging to Group 1 or Group 2 were assessed using the chi^2 test; the differences between paired data were assessed using the Wilcoxon test while the differences between the independent data were assessed using the Mann-Whitney test. The levels of significance maintained an overall P value of 0.05 and were calculated according to the O'Brien-Fleming stopping boundary for endpoints (9, 10).

III. Results

One hundred and eighty-one people were evaluated for potential enrollment; 21 did not satisfy the inclusion criteria. Thirty-six were lost to follow up due to insufficient therapeutic effect (25 cases), side effects (6 cases) and protocol violations (incorrect assumption of dapoxetine) (5 cases). One hundred and twenty-four patients were studied.

The clinical and demographic data of each population studied are presented in Table 1. No significant differences emerged between Group 1 and Group 2 patients.

The stopwatch-measured average IELT, the CGIC and the side effects in Groups 1 and 2 are reported in Table 2. There were no significant differences among the baseline values of IELT and PEP which, however, significantly improved after dapoxetine assumption; Group 2 patients achieved a greater improvement in IELT and CGIC than Group 1. No significant differences occurred between the data obtained in Piacenza and the data obtained in Ferrara. The side effects were similar in both groups.

IV. Discussion and Conclusions

Our data showed that medical instructions influence dapoxetine efficacy for lifelong PE. The fact that operator-dependent variability in terms of efficacy is mundane confirms that the physician's instructions are critical for dapoxetine efficacy. It is likely that no operator-dependent variability occurred since the researchers have approximately thirty years of experience in the field, and they are truly skilled in giving instructions as to the assumption of medications.

From a psychological point of view, lifelong PE can be regarded as anxiety which manifests itself as a sexual dysfunction (11). Thus, we sought to develop a set of instruction with the aim of overcoming the anxiety of the patients. We decided a prior to develop (at least in part) a set of instructions for Group 2 based on the instructions given in the course of integrated task couple therapy for psychogenic sexual dysfunctions where the technique used by the therapist to instruct the couple regarding sexual homework is critical for success (12). The physician's tone was compelling and was used to

stress the efficacy of the drug and the power of the medical prescription (12). The patients were instructed not to try to delay or to hold back ejaculation (a psychological tactic regarded as stressing (11); other physicians indicated that the time required to improve their ejaculation was long in order to avoid any expectancy (and consequent anxiety) on the part of the patient regarding the interval between the first assumption of the drug and its taking effect. To further overcome patient anxiety as much as possible, we chose to carry out a fixed dose study using the highest available dapoxetine dosage (60 mg) in order to be able to achieve the highest drug efficacy and to reassure the patients regarding dapoxetine efficacy as soon as possible.

The patients belonging to the first group received dapoxetine without any explanation regarding drug activity and the interval between the first assumption and when the drug takes effect; thus, it may be presumed that their anxiety regarding when and if dapoxetine functions may still have been present.

The Authors felt that it was not possible to take into account all the other variables involved in the patient-physician relationship and sexual and other relationships of a couple; thus a multicenter cross-over study was adopted. The fact that no operator dependent variability could be found indicated that our data could be regarded as reliable.

This paper has some limitations, because it is very difficult to produce perfectly balanced results when the subjects of study are men with an anxiety-based disease such as PE. In this regard, we chose to examine only couples who cohabitated > 1 year to avoid any differences regardingt marital status as much as possible. The first potential limitation of this study was that the Authors could only presume that the instructions for Group 2 were more soothing than those for Group 1 since direct proof of the influence of the physicians' instructions regarding the anxiety of the patients could not be achieved. In any case, a study in which two different sets of instructions were administered to the same group of patients is confounding. Furthermore, any medical instructions for the use of a drug which might resolve a lifelong disease could be perceived by the patient as soothing "per se" (13); however, the more detailed the instructions, the more soothing they are (14). The instructions for Group 2 were more detailed than those for Group 1; however, in the literature, we could not find a statement that soothing and detailed instructions might improve the efficacy of a drug, even for a psychogenic disease. In this regard, this paper might represent a true novelty. A second limitation of the present study was the absence of a placebo branch; however, a preliminary attempt to use a placebo induced the vast majority of the patients (80%) to refuse to participate in the present study, further a number of placebo controlled studies were conducted using Dapoxetine, which showed to be more efficient for resolving lifelong PE than placebo (15) . When the patients were asked the reason for their refusal, they all answered that they were impatient to resolve their symptoms. Impatience is actually a characteristic of PE patients (11). Thus the Authors were compelled not to use a placebo branch because this percentage of refusals to participate would induce sampling errors (9). A third limitation was that it was very difficult to fully evaluate the distress, annoyance or interpersonal difficulty of each patient before and after dapoxetine assumption, mainly in the absence of a validated questionnaire (in fact, the premature ejaculation profile (PEP), used to evaluate ejaculatory capacity and satisfaction with the treatment, could not be used because it has not been translated into Italian and validated in Italy (16). In any case, it ws thought that stopwatch-measured average IELT and the CGIC might be sufficient for evaluating results.

Although the characteristics of premature ejaculation have been established, the exact etiology is largely unknown. Genetic, neurobiological, pharmacological, psychological, urological and endocrine factors have all been proposed. In lifelong PE, there are convincing data to support roles for genetic and psychological factors, either causal, or secondary to PE for the latter (17); however, our data seem to support the hypothesis that lifelong PE could depend, at least in part, on psychological factors.

Genetic polymorphisms located on the SLC6A4 gene codifying for the 5-HT transporter (5-HTT), the major regulator of serotonic neurotransmission, have been linked to the pathogenesis and risk of PE. A recent meta-analysis has shown that the *5-HTTLPR* gene polymorphism was associated with a significantly decreased risk for lifelong PE risk in Caucasians (18). As a matter of fact, the 5-HTTLPR gene is associated with prosocial behavior due to its effects on anxiety in social situations (19). Thus, even in the case that lifelong PE has a genetic etiology, it is not surprising that medical instructions of a soothing nature improve dapoxetine efficacy, because of the effects on anxiety of the gene involved.

In conclusion, since the main cause of dropping out of the study was the poor efficacy of dapoxetine in improving ejaculation (six months after the beginning of the study, approximately 38% of the patients autonomously stopped dapoxetine assumption (20), it is likely that soothing and/or detailed instructions for taking the drug could improve patient compliance to dapoxetine treatment.

List of abbreviations

Premature ejaculation = PE;
Intravaginal ejaculatory latency time = IELT;
Clinical global impression of change = CGIC;
Premature ejaculation profile = PEP.

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Table 1: Clinical and demographical data of the population studied. Data are presented as medians and as ranges (min-max). Group 1 was made up of patients who received dapoxetine 60 mg with the following instructions: "Take one tablet two hours before sexual intercourse; dapoxetine will delay your IELT beginning with the first sexual intercourse". Group 2 was made up of patients the second was: "You will assume one tablet two hours before sexual intercourse; do not try to delay or to hold back ejaculation because dapoxetine is doing it for you. Dapoxetine will delay/improve your intravaginal ejaculatory latency time (IELT) within 3 months from the first assumption".

			Patients examined in Ferrara	Patients examined in Piacenza
Group 1	Number		32	28
	Age (in years)		28 (21-34)	29 (21-36)
	Age at first sexual intercourse (in years)		18 (16-20)	17 (14-20)
	Duration of premature ejaculation (in years)		10 (7-13)	11 (9-13)
	Social status	Workmen	11	12
		Artisans	5	3
		Employees	4	3
		Graduates	6	5
		Businessmen	2	1
		Undergraduates	4	4
Group 2	Number		28	36
	Age (in years)		29 (21-36)	29 (21-36)
	Age at first sexual intercourse (in years)		17 (14-20)	18 (16-20)

	Duration of premature ejacula		12 (9-15)	12 (10-15)
	Social status	Workmen	10	12
		Artisans	4	6
		Employees	4	5
		Graduates	5	6
		Businessmen	1	2
		Undergraduat	4	5

Table 2: Results of a prospective multicenter study where the patients were all instructed to take dapoxetine 60 mg, one tablet, two hours before sexual intercourse. Data are presented as medians and as ranges (min-max). Two different sets of instructions were given to the patients. The first set of instructions was given to Group 1 : "Take one tablet two hours before sexual intercourse; dapoxetine will delay your ejaculation beginning with the first sexual intercourse"; the second set of instructions was given to Group 2: "Take one tablet two hours before sexual intercourse; do not try to delay or to hold back ejaculation because dapoxetine is is doing it for you. Dapoxetine will delay/improve your intravaginal ejaculatory latency time (IELT) within 3 months from the first assumption".

Key: * headache; **one case of headache and one case of nausea; ***one case of nervousness + nausea, one case of headache and one case of nausea; ****one case of nervousness + headache + nausea, one case of headache + nausea, vs. = versus.

Comparisons:

a1 vs. a2, a3 vs. a4, a1 vs. a3, a2 vs. a4, b1 vs. b2, b3 vs. b4, c1vs. c2, c3 vs. c4, c1 vs. c3, c2 vs. c4, d1 vs. d2, e1 vs. e2, e2 vs. e3, f1 vs. f2, f3 vs. f4, f1 vs. f3, and f2 vs. f4: p not significant.
a1 vs. b1, a2 vs. b2, a3 vs. b3, a4 vs. b4, c1 vs. d1, c2 vs. d2, c3 vs. d3, d4 vs. d4: $p<0.01$.
b1 vs. b3, b2 vs. b4, d1 vs. d3, d2 vs. d4, e1 vs. e3, e2 vs. e 4: $p<0.01$.

	Group 1					
	Stopwatch-measured average intravaginal ejaculatory latency time (IELT) in minutes		Premature Ejaculation Profile (PEP) score		Number (percentage) of patients who described their premature ejaculation as slightly better, better, or much better after dapoxetine assumption (e)	Number (percentage) of patients who suffered from side effects (f)
	Before dapoxetine assumption (a)	After dapoxetine assumption (b)	Before dapoxetine assumption (c)	After dapoxetine assumption (d)		
Patients examined in Ferrara(1)	0.8 (0.5 -1.1)	2.6 (0.8-3.2)	15 (11-19)	10 (5-17)	17 (53.1%)	1* (3.1%)
Patients examined in Piacenza(2)	0.8 (0-1)	2.5 (0.9-3.1)	16 (11-19)	11 (6-16)	15 (53.6%)	2** (7.1%)
Group 2						
Patients examined in Ferrara(3)	0.8 (0.2-1)	5.4 (1.7-9.8)	16 (11-20)	7 (2-13)	22 (78.6%)	2*** (7.1%)
Patients examined in Piacenza (4)	0.8 (0.1± 1.1)	6.0 (1.8-10.0)	16 (11-20)	7 (3-14)	30 (83.3%)	2**** (5.6%)