

## ORIGINAL RESEARCH—ED PHARMACOTHERAPY

## Adherence to Phosphodiesterase Type 5 Inhibitors in the Treatment of Erectile Dysfunction in Long-Term Users: How Do Men Use the Inhibitors?

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### ABSTRACT

**Introduction.** The high effectiveness of phosphodiesterase type 5 inhibitors (PDE5-i) in the treatment of erectile dysfunction (ED) has been demonstrated. However, previous research shows that PDE5-i treatments have high discontinuation rates.

**Aim.** The main goals of this study were to (i) characterize the way men use PDE5-i and (ii) analyze the adherence to treatment, identifying the factors that influence PDE5-i use.

**Methods.** A total of 148 men with clinical diagnosis for ED who maintained the treatment with PDE5-i for over 3 years were interviewed. Interviews concerning their ongoing treatment were carried out using a standardized questionnaire with quantitative and qualitative items.

**Main Outcome Measures.** Physiological measures included the intracavernous alprostadil injection test, associated with penile rigidometry and penile Doppler ultrasound. The qualitative measure included two questions: “Do you use the drug in every sexual intercourse?” and “How do you use the inhibitor?”

**Results.** ED causes were classified as venogenic (31%), arteriogenic (23%), psychogenic (18%), iatrogenic (13%), neurogenic (8%), and diabetic (7%). Participation rate was 71.8%. Of the 148 patients studied, 75% claimed not to use PDE5-i in every intercourse. Most used tadalafil (66%), followed by sildenafil (20%), vardenafil (10%), and 4% alternated the type of medicine. Four main categories emerged concerning the factors that determine the intake of PDE5-i in some intercourse situations and not in others: (i) psychological factors; (ii) medication-related factors; (iii) circumstantial factors; and (iv) relational factors.

**Conclusion.** The analysis of men’s narratives revealed a combination of factors that influence the adherence to PDE5-i. The psychological and medication-related factors were the most prevalent. This study highlighted the importance of taking these factors into account, both at the time of prescription and during the follow-up in order to improve adherence. **Carvalheira A, Forjaz V, and Pereira NM. Adherence to phosphodiesterase type 5 inhibitors in the treatment of erectile dysfunction in long-term users: How do men use the inhibitors? Sex Med 2014;2:96–102.**

**Key Words.** Erectile Dysfunction; PDE5 Inhibitors; Adherence; ED Causes

## Introduction

The oral agents for treatment of erectile dysfunction (ED) belonging to the group of phosphodiesterase type-5 inhibitors (PDE5-is) are described in the literature as effective, safe, and easy to administer [1–4]. However, their use is often described by clinicians as involving a pattern of repeated medication intake, often followed by abandonment of the treatment, even when it is effective [5]. These data suggest that the improvement of erectile function is not the only, or even the most important, factor involved in the success of the treatment [6].

Research reveals high discontinuation rates [7–14], suggesting that some of these men may have characteristics specific to their sexual attitude and perception of sexual relationships [6]. A recent study [13] with a sample of 327 men with ED who undertook PDE5-i revealed a discontinuation rate of 48.9%. A qualitative analysis of the reasons for dropout revealed as main reasons the insufficient effectiveness of PDE5-i (36.8%) and psychological factors (e.g., anxiety, negative emotions, fears, concerns, dysfunctional beliefs). It is also known that treatment with PDE5-i among men may follow very irregular patterns [15]. Several studies have attempted to clarify the process of adherence to treatment [5,16–18]. In a qualitative study with 33 men and 27 women [16] evaluating the impact of sildenafil use, the results demonstrated that some participants used a dose lower than prescribed or used the medication intermittently.

Some studies have also shown that a significant percentage of men alternate between several available drugs [19,20]. The spontaneity and naturalness of sexual intercourse, the acceptance of the treatment by the partner, and the speed/duration of the action seem to be decisive in the choice of medication [21]. Variables such as the cost and rationing of medication have also been described as influential in treatment adherence, especially in patients with lower incomes [18,21]. However, these different studies do not address systematically the patients' adherence to PDE5-i and are not consensual regarding the reasons that may influence the medication intake in men.

## Aim

Two main research questions emerged: "Which factors are responsible for patients' adherence to PDE5-i?" and "How do patients use these drugs?" We sought to (i) characterize the way men use

PDE5-i (inhibitor type, frequency of use, side effects) and (ii) analyze the adherence to treatment, identifying the factors that influence PDE5-i use.

## Method

### Participants

The study sample consisted of 148 adult male patients at an andrological outpatient's clinic, aged 25–81 years, with clinical diagnosis of ED who initiated and maintained the treatment with PDE5-i for over 3 years, in a regular basis of at least every 3 months. Exclusion criteria included: taking antidepressants, history of alcohol and substance abuse, hypogonadism, Peyronie's disease, and presence of a severe psychopathological disorder.

Although these exclusion criteria would be interesting to include in the sample, they could also contribute to hide the main reasons why patients are not adhering to PDE5-i treatment. Also, antidepressants intake could interfere with sexual desire and arousal, which ultimately could lead the results into inaccurate analysis.

### Instrument

A comprehensive, detailed questionnaire was developed and piloted for this study, based on the literature review and on the researcher's clinical experience. This was a 29-item questionnaire (see Appendix), which included quantitative and qualitative variables (incorporating sociodemographic, clinical, and adherence-related items). Quantitative variables include demographics, type of PDE5-i and frequency of use, other previous treatments, side effects, expectations regarding the treatment, and partner involvement. Regarding qualitative variables, men were asked if they used the PDE5-i in every intercourse. When the answer was "No", an open-ended question was presented: "How do you take the inhibitor?" When the participants' answers were not clear, the question was reformulated: "Why don't you take the PDE5-i in every single sexual intercourse?"

We chose a phenomenological approach, given our interest in the meanings given by individual men regarding this phenomenon [22].

### Procedure

Patients were contacted by telephone and, after their authorization, they received an informed consent by mail at the discharge address; at this

point, full written information about the project and its aims were provided. Subjects were contacted for a second time after 1 week. Once confirmation had been received from the potential participants, a telephone interview was scheduled. Interviews lasted between 30 and 50 minutes. A neutral research assistant conducted interviews using the standardized questionnaire form in a Google Docs online research database. Complete qualitative and quantitative data from the interviews were introduced directly through the live form and stored in the study database. This study received ethical approval from the Ethics Committees of ISPA-University Institute and Lusófona University.

## Results

### Study Population

A total 148 men were interviewed (participation rate = 71.8%). The average age of participants was 55.8 years (standard deviation 11.11, range 25–81). Most were in a committed relationship (87.8%) and reported heterosexual behavior (98%). A total of 22.9% were smokers. Data on educational level, religion, marital status, and relationship status are summarized in Table 1.

### Characterization of the Use of PDE5-i

Of the 148 patients studied, the vast majority of participants (75.2%) claimed not to use the PDE5-i in every intercourse. Most used tadalafil (65.8%), followed by sildenafil (19.9%) and vardenafil (10.3%). The remaining patients alternated the type of drug (42%).

**Table 1** Participants' characteristics

|                             |       |
|-----------------------------|-------|
| Educational level           |       |
| Undergraduate               | 58.1% |
| Graduate                    | 33.8% |
| Postgraduate                | 8.1%  |
| Religion                    |       |
| Catholic (observant)        | 58.1% |
| Catholic (practicing)       | 19.6% |
| Other religion (practicing) | 1.4%  |
| No religion                 | 20.9% |
| Marital status              |       |
| Married                     | 61.5% |
| Divorced/separated          | 20.3% |
| Single                      | 12.2% |
| Common law                  | 4.1%  |
| Widowed                     | 2.0%  |
| Relationship status         |       |
| In a committed relationship | 87.8% |
| Occasional partner          | 6.1%  |
| Regular sexual partner      | 3.4%  |
| Without sexual partner      | 2.7%  |

Mean age 55.8 (standard deviation 11.11, range 25–81)

The daily use of a PDE5-i was only for tadalafil 5 mg, which was used by 9.1% of total patients. Most men used the drug once or twice a week (42%), followed by patients who used the inhibitor once or twice per month (25.2%), and those using less than once per month (23.7%).

Of the total respondents, 51.2% tried at least one other treatment, before or during the use of PDE5-i, particularly other oral agents (e.g., nicergoline, yohimbine) intracavernous injections, natural products, and sex therapy. However, this did not lead to the abandonment of PDE5-i.

Of the respondents, 54.5% reported side effects (e.g., dyspepsia, nasal congestion, and headaches) but always with mild intensity, so there were no cases of definitive discontinuation of therapy.

Despite maintaining therapy, 19.3% of patients considered that the results of PDE5-i treatment did not meet their needs and expectations.

### The Partner of Patients Taking PDE5-i

Of the 148 men in the sample, 42.5% described their partner as "sexually active," 35% answered "more or less sexually active," and 22.5% reported the partner as "a little" or "not sexually active." A total of 27.9% of men considered that their partner was not important in solving the problem, and 18.8% of men reported that their partner was unaware that they were taking a PDE5-i. Only 18.5% of men had attended the first consultation with their partner.

### Adherence to PDE5-i: Factors Influencing Use

The analysis of the factors reported by the 148 patients was made from the responses to the following two questions: "Do you use the drug in every sexual intercourse?" and "How do you use the inhibitor?" Based on the content analysis performed, the responses were organized into four main categories: (i) psychological factors; (ii) factors associated with the drug; (iii) circumstantial factors; and (iv) relational factors.

Table 2 characterizes these categories, each divided into factors, which were frequently detected as weighing on the patient's decision to use or abstain from the drug.

### Psychological Factors

Despite taking medication consistently for over 3 years, 44% of respondents reported psychological factors influencing their intake patterns.

**Table 2** Factors determining the intake of PDE5-i intake in some intercourse situations and not in others (N = 148)

|   |  |                        |
|---|--|------------------------|
| Psychological factors   | Self-confidence  | 11.4%                  |
|   | To avoid a bad performance                             | 10.1%                  |
|   | Psychological and emotional state                      | 8.1%                   |
|   | Fear of the side effects                               | 5.4%                   |
|   | Be averse to taking medication                         | 4.7%                   |
|   | Fear that it is harmful for the heart                  | 4.0%                   |
|   | Total  | 44.0%                  |
| Medication-related factors  | Efficacy not complete (organicity)                     | 15.5%                  |
|   | High price   | 5.4%                   |
|   | Prolonged effect                                       | 4.7%                   |
|   | Side effects   | 4.7%                   |
|   | Total  | 30.3%                  |
| Relational factors  | Extramarital relations                                 | 8.7%                   |
|   | Lack of emotional and physical stimulus by the partner | 6.0%                   |
|   | Lack of communication and conflicts                    | 3.3%                   |
|   | Partner's difficulty in accepting PDE5-i use           | 3.3%                   |
|   | Not having sexual intercourse or stable partner        | 2.0%                   |
|   | Total  | 23.6%                  |
|   | Circumstantial factors                                 | To improve performance |
| Difficulty in programming the inhibitor intake and geographical distance from the partner |  | 8.7%                   |
| Alternating between different PDE5-i  |  | 2.7%                   |
| Alternating between PDE5-i and a natural product or another drug                          |  | 2.0%                   |
| Forgetting to buy or to get medical prescription  |  | 2.0%                   |
| Total   |  | 22.2%                  |

PDE5-i = phosphodiesterase type-5 inhibitor

Other men (n = 15) reported taking the inhibitor to guarantee they would not to fail sexually:

I'm a bit young. This gets into a man's head . . . thinking "I will falter", then it really falters. The Cialis helps—it was good for the head. I no longer think much about it. (33 years old, divorced, has casual partners)

Sometimes (n = 12), the intake of the inhibitor was dependent on negative emotional states:

It depends on the emotional state. Sometimes my head is free from hassles and problems and things just happen. When a person has his head full, we notice it for sure. When I feel that I am like that, I take half a tablet. (50 years old)

Some qualitative accounts translated fear in relation to the medication, although patients have never felt any significant side effects. Eight men reported fear of side effects, which they could not define, and six showed concern about the cardiovascular safety of the drug. Seven patients justified their intermittent intake with the fact that they avoid taking any type of medication, including PDE5-i.

The average age of the men, in whose narratives we detected psychological factors, was 50 years, ranging between 30 and 81 years.

### Factors Associated with the Medication

These factors include a set of patients (n = 30) who stated not taking PDE5-i in every intercourse. Eight patients stated that the price of the drug prevented them from taking the inhibitor more frequently:

I do not take [it] more often because they are expensive. I buy the 20 mg and cut [them] in half. As sexual activity is not much, the 8 bits are enough for two months. (64 years old)

The presence of side effects as a barrier was reported by seven men, which implied that they would only take the drug in an intermittent and infrequent manner. The average age of men who pointed out factors associated with the drug was 65 years old, ranging between ages 40 and 78.

### Relationship Factors

In this category, we find the patients (n = 35) who stated that taking the PDE5-i is mediated or hindered by relational factors.

The exclusive use of a PDE5-i in extramarital affairs was reported by 13 participants:

I cannot have erections outside of matrimony. I have a regular sex life within the marriage. Outside of matrimony I could not, and resorted to the doctor. (48 years old, taking tadalafil 20 mg for 5 years, less than once a month)

Nine patients were dependent on sexual activity and the physical and emotional stimulation by their partner:

It is not necessary to use it more often because I adjust my doses according to my wife's needs. I take the pills according to my wife's psychological and physical availability to have sex. (64 years old)

Five patients reported the lack of communication or conflict with their partner disturbed the use of the PDE5-i:

I do not take it all of the time because there is little dialogue between the couple, about the best and worst days, about all that . . . it is because of the lack of dialogue. And there is a certain complacency. (55 years old, intermittently taking tadalafil 10 mg for around 6 years)

Five patients stated that their partners did not always accept the inhibitor. The average age of the

men who indicated relational factors was 54, with ages ranging between 33 and 66 years old.

### Circumstantial Factors

The circumstantial factors reported by 33 patients included situations where the intake of PDE5-i was mediated by a punctual situation, not very stable in time, whether it was recurrent or not.

Ten men claimed taking the inhibitor only in special moments to prolong the pleasure or to improve their performance:

When there is more availability and we want things to last longer, we use it—on a weekend, when the kids are at their grandparents, or when there is another available moment for each other. (42 years old)

The difficulty in scheduling the medication intake was another situation reported by nine men:

In the sexuality things, we do not choose a day or an hour. Generally, there is a certain impossibility of programming—the situation arises by itself and sometimes it would make sense to have taken [it] and other times reveals not to have been necessary. (53 years old)

Four men stated that they switch between the different PDE5-is according to the circumstances and objectives. Moreover, three participants said they alternate the inhibitor with certain foods or other natural products purchased at the pharmacy.

The average age of the men who indicated circumstantial factors was 54 years, ranging between 33 and 71 years of age.

### Discussion

The aim of this study was to analyze the factors influencing patients' adherence to, and use of, PDE5-i in a sample of 148 patients who used the inhibitor for a 3-year period.

The results showed that although most men do not take the medication in every intercourse, most use it one to two times a week, similar to the findings of other comparable studies [5,16–18].

The fact that most men used tadalafil (65.8%) can suggest that the duration of the drug's action and preserving the spontaneity are important factors in the choice of an inhibitor. Only a minority of subjects alternated between several inhibitors, unlike the results found in other studies [19,20] where this was more frequent. Furthermore, we did not confirm that the side effects of the continued use of PDE5-i were rare, as described by numerous studies, as around 55% of men reported having noticed these effects, particu-

larly complaining of headaches, dyspepsia, and nasal and ocular congestions. However, these were reported in all cases with low intensity and do not appear to be a reason to abandon treatment. In an earlier study [13], only 12% of the men who stopped the treatment had mentioned side effects as the reason to abandon treatment.

Less than half of the male patients classified their partners as “sexually active,” and a quarter reported that their partner was “not important to the resolution” of their ED problem. Equally interesting is the finding that 19% of men reported that their partner was unaware that they were taking PDE5-i, which shows that the relational dimension and the role of the partner is not taken into account by a quarter of these participants.

The main goal of this study was to identify the factors that influence the adherence to treatment. A qualitative analysis revealed four main groups of factors that influence the use of PDE5-i. Psychological factors—the most frequently reported—are related to self-confidence, emotional states, and fear (of drug side effects or regarding the cardiovascular safety). The second most reported by subjects were medication-related factors. In some occasions, participants do not take the drug because they do not find its efficacy or because it is expensive or because of the side effects. Relational factors were the third most reported and are related to the unavailability of partner (nonexistence, disinterest, or lack of stimuli) and also include those men who use the inhibitor only with an extramarital sex partner. The last group of variables that influence the intake of the PDE5-i is the circumstantial factors. These factors include situations where the intake of PDE5-i was mediated by a punctual situation, e.g., to improve performance or enhance pleasure. Moreover, other circumstantial variables prevent men from taking the drug such as the difficulty in scheduling the medication intake or trying a natural product.

There are limitations to this study that must be considered. The research was developed with a sample of male participants attending a private clinic for ED, which cannot be assumed to be representative of all men suffering from ED due to the fact that the clinic is highly specialized. Owing to the private health care setting, the study population is not fully representative of all social and demographic variables. We also assume that patients of higher socioeconomic status were over-represented. Also, the frequency and patterns of PDE5-i use were based on recall rather than on

medication use log. Moreover, the instrument is not a validated measure, and we did not address the severity of ED.

### Conclusion

This study highlighted the importance of taking psychological, relational, and circumstantial factors into account in improving adherence, both at the time of prescription and during the patient post-prescription stage. Moreover, it is necessary to assess issues of low confidence and related fears, as well as the involvement of respective patients' partners in the treatment, where agreed possible.

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### Appendix

- Number of the clinical file:
- What is your age?
- Complete educational level:
- Do you have a religion?
- What is your marital status?
- What is your relationship situation?
- What is your sexual orientation?
- Are you currently taking any pill for erectile dysfunction?
- Which pills for erectile dysfunction are you currently taking?
- What is the dosage?
- What other pills did you take before?
- Does your partner know you take those pills?
- Do you consider your partner is involved in the resolution of your problem?
- Does your partner go with you and assist at the consultation?
- Do you currently consider your partner to be sexually active?
- For how long have you been taking these pills?
- Do you use the pills in every intercourse?
- How frequently do you use these pills?
- How do you use the inhibitor?
- Was the treatment with these pills according to your expectations?

21. Did you notice any side effect or something that did not please you?
22. Besides this treatment, what other treatments have you done for erectile dysfunction?
23. How frequently do you go to the follow-up consultation?
24. To what degree are you satisfied with your doctor?
25. Do you think this medication should be reimbursed?
26. Do you take antidepressants?
27. Do you take any other medication?
28. Are you a smoker? How many cigarettes do you smoke per day?
29. Do you use other substances (drugs)?