PATIENT INSIGHT AND TREATMENT EXPECTATIONS IN ERECTILE DYSFUNCTION

***Hartmut Porst**

Private Institute of Urology, Andrology and Sexual Medicine, Hamburg, Germany.
**Correspondence to Porst20354@aol.com*

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ABSTRACT

In the literature, a strong preference towards pharmacological management with oral phosphodiesterase type 5 (PDE5) inhibitors has been demonstrated in men with erectile dysfunction (ED) versus other methods. However, following pharmacological management, a large proportion of men with ED discontinue treatment prematurely. Therefore, a better understanding of the expectations from, and demands on modern ED management from both the patients and their partners is needed in order to identify factors that may improve outcomes, patient adherence, and patient satisfaction with therapy. Thus, we will present new findings on patient and partner satisfaction and preferences, and discuss how the current pharmacological armamentarium can answer these needs.

Keywords: Erectile dysfunction (ED), patient preference, treatment adherence, quality of life, sildenafil, vardenafil, tadalafil, avanafil, oral phosphodiesterase type 5 (PDE5) inhibitors.

INTRODUCTION

Erectile dysfunction (ED) is a self-reported condition that is defined as the persistent 'inability to achieve or maintain an erection sufficient for satisfactory sexual performance'; it is the main complaint in male sexual medicine.[1] While sexual performance and overall evaluation of sex life satisfaction are highly subjective, partner-related, multi-factorial, and subject to a high inter-individual variability, ED may affect physical and psychosocial health, and therefore may result in poorer sexual intimacy and a lower quality of life.[2-5]

Both ED incidence (26 new cases per 1,000 men each year)[6] and prevalence, as well as ED severity are strongly correlated with age, with a worldwide prevalence of 37–52% in adults aged ≥40 years.[3,7-12] As the pathophysiology and aetiological factors contributing to ED are widely documented in the literature and well known in the medical domain, this review will focus on the insights and treatment expectations of patients alone. Pharmacological management with oral agents is the first-line therapeutic modality, as opposed to other methods, such as vacuum erection devices, intraurethral alprostadil, or intracavernous self-injection therapy with vasoactive drugs.[12-16]

Following pharmacological management however, a large proportion of men with ED discontinue treatment prematurely. Therefore, a better understanding of the expectations from, and demands on modern ED management both from the patients and their partners is needed in order to identify factors that may improve patient outcomes, adherence, and satisfaction with therapy.

This review will present new findings on patient and partner satisfaction and preferences, and discuss how the current pharmacological armamentarium can comply with these needs.

PATIENT INSIGHTS AND TREATMENT EXPECTATIONS: RESULTS FROM A LARGE ONLINE SURVEY

Burri and Porst[17] recently conducted a large online survey to better understand patients' needs and expectations regarding sexual activity and ED management. The study was conducted within an online consumer panel contacted via email.

The aim was to collect data via recruitment of sexually active heterosexual individuals aged 30–75 years, who were either healthy or suffering from ED.

Diagnosis of ED was based on the abbreviated form of the International Index of Erectile Function (IIEF-5), which is a validated global assessment questionnaire, commonly used to evaluate male sexual function in clinical research.[18,19] The ideal cohort for the study would have included 80% of individuals with ED, with one-third from each treatment group (treatment-naïve patients [NGs], previously-treated patients [PTGs], and currently-treated patients [CTGs]), and 20% healthy men (HG). While reporting bias may have affected the results given the sensitive nature of the topic, this survey still provides a large-scale picture of ED patient expectations.

Patient Population

The final patient population was composed of 1,534 men with a mean age of 46±10.9 years (range 30–75), of which 73% (n=1,124) had a history of ED (47%, n=529 NG).[17] In most ED patients (53%, n=590), the condition was of mild severity according to the IIEF-5, with an average disease duration of 49±42.5 months.

Importance of Sexual Activity

Sexual activity was evaluated as important (41%, n=622) or very important (37%, n=575) in the majority of patients, regardless of age.[17] However, NG patients considered sexual activity significantly less important, as compared with CTG patients (chi-square, χ^2=10.15, p=0.02). To put these findings into perspective, the FEMALES study focussed on the sexual experiences and perceptions of the female partners of men with ED (n=293).[20] Significantly fewer women reported satisfaction with their sexual relationship after their partner developed ED, compared with before (85% versus 39%, p<0.001).

Importance of Erectile Function

Within the cohort, men considered 'maintaining an erection until the partner reaches orgasm' to be most important aspect of sexual intercourse.[17] The importance of the occurrence of multiple episodes within one sexual encounter seemed to be correlated with age, with younger men shifting towards this aspect, while older men considered 'maintaining an erection until the partner reaches orgasm' to be a higher priority (r=0.08, p=0.006).

Aspects Related to a Fulfilled Sex Life

The most frequently described aspects contributing to a fulfilled sex life were 'being able to please their partner', 'feeling pleasure', and 'partner involvement'. Similar to erectile function, the level of importance of all the aspects was highest in the HG, then in the CTG, and lowest in the NG groups.[17] In the FEMALES study, decreases in the frequency of orgasms were significantly related to the severity of their male partner's ED (p<0.01).[20]

Spontaneity and Naturalness of the Encounter

The 'not having to plan' and 'engaging in sex whenever he wants' aspects were considered as less important than the previously mentioned aspects in the overall sample, but were considered more important by younger men (Pearson correlation [r_p]=−0.06, p<0.05; r_p=−0.61, p<0.05, respectively).

Not having to plan the exact timing of intercourse is nevertheless a relevant aspect of a couple's sex life. In the FEMALES study, the latter aspect was a relevant topic, with 34% of the females and 30% of the males stating that they did not have a set pattern regarding predictability of sexual activity.[20] Similarly, 61% of females and 52% of males denied advance aspiration of sexual activities, underlining the importance of spontaneity in their sex life (Figure 1).

Ideal Onset of Action

Thirty-eight percent of men (n=584) considered an ideal onset of action to be of 'about 15 min', giving them 'the ability to respond immediately to the partner's sexual wishes and requests' and 'allowing a certain degree of spontaneity'. This finding was observed across all ED treatment groups (Figure 2). A further 28% of men (n=423) considered that an ideal onset of action was somewhere 'between 15 and 30 min', and for 34% of the sample (n=527) 'between 30 and 60 min'. None of the respondents considered an onset of 'more than 60 min' to be adequate or desirable.

Ideal Duration of Effect

Most men with ED (96%, n=1,078) considered a duration of up to 4 hours to be desirable, and 48% (n=536) of men considered 6–12 hours to be adequate. Conversely, approximately 71% of men in the ED groups (n=798) considered a duration of >12 hours to be too long.

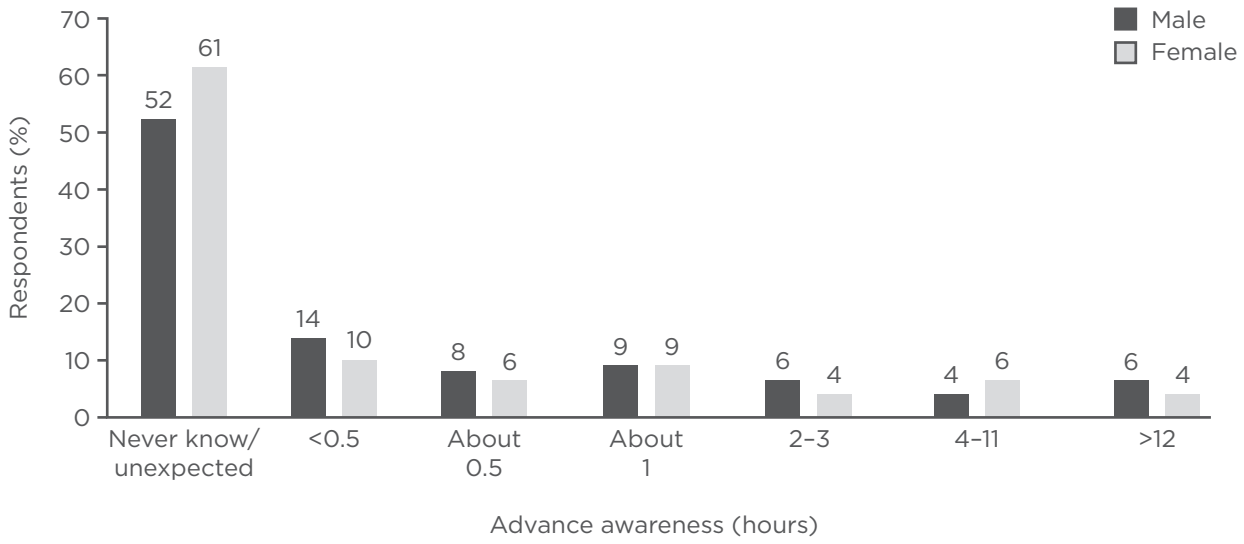


Figure 1: Male–female reports of advance awareness of sexual activity.[20]

Ideal Erectile Dysfunction Therapy Characteristics

The findings from this survey could reflect the key pharmacokinetic features to aim for in an ideal ED drug according to each patient's expectations. Oral therapy for ED is generally expected by patients to boast a high efficacy, with a fast onset of action and a desirable window of efficacy. In this survey, results showed that once the basic aspects of ED management are satisfied, namely achieving and sustaining an erection, patients look for qualitative versus quantitative factors associated with a fulfilled sex life, such as spontaneity and being able to please their partner. The corresponding pharmacokinetic features that patients prioritised to meet their wishes and expectations to improve their satisfaction in sexual life were a fast onset of action of approximately 15 min and a reasonably long duration of efficacy between 6 and 12 hours.

OVERVIEW OF THE CURRENT MANAGEMENT OF ERECTILE DYSFUNCTION

ED management is aimed at restoring the capacity to initiate and maintain a rigid penile erection, enabling the patient to perform satisfactorily during sexual intercourse. It comprises pharmacological management with oral phosphodiesterase type 5 (PDE5) inhibitors, penile self-injection programmes with vasoactive drugs, intraurethral therapy, vacuum erection devices, and penile prostheses for men.[12,21] Because of the great variety of underlying aetiologies for ED, a successful initiation of medical therapy is highly dependent on the patient's characteristics and comorbidities.[12,21]

ORAL PHARMACOLOGICAL MANAGEMENT OF ERECTILE DYSFUNCTION

PDE5 inhibitors inhibit the PDE5 enzyme involved in the catabolism of cyclic guanosine monophosphate, which is in turn responsible for the vasodilation mechanisms of penile erection.[22] PDE5 inhibitors are easy to use and have a demonstrated efficacy in the number and duration of erections in patients with ED, with a favourable benefit-to-risk ratio and a low rate of side-effects. As such, oral PDE5 inhibitors have been established as the first-line medical therapy for ED.[16]

In the FEMALES study, the proportion of women who experienced sexual desire, arousal, and orgasm 'almost always' or 'most times' was significantly higher when their partner was currently treated with a PDE5 inhibitor ($p<0.05$).[20]

Sildenafil

Sildenafil (Viagra®, approved by the European Medicines Agency [EMA] in 1998) was the first oral PDE5 inhibitor approved to treat ED and has been the subject of many clinical trials.[23] The recommended dose is 50 mg, taken as needed approximately 1 hour before sexual activity. Based on efficacy and tolerability, the dose may be increased to 100 mg or decreased to 25 mg. The maximum recommended dose is 100 mg.[24]

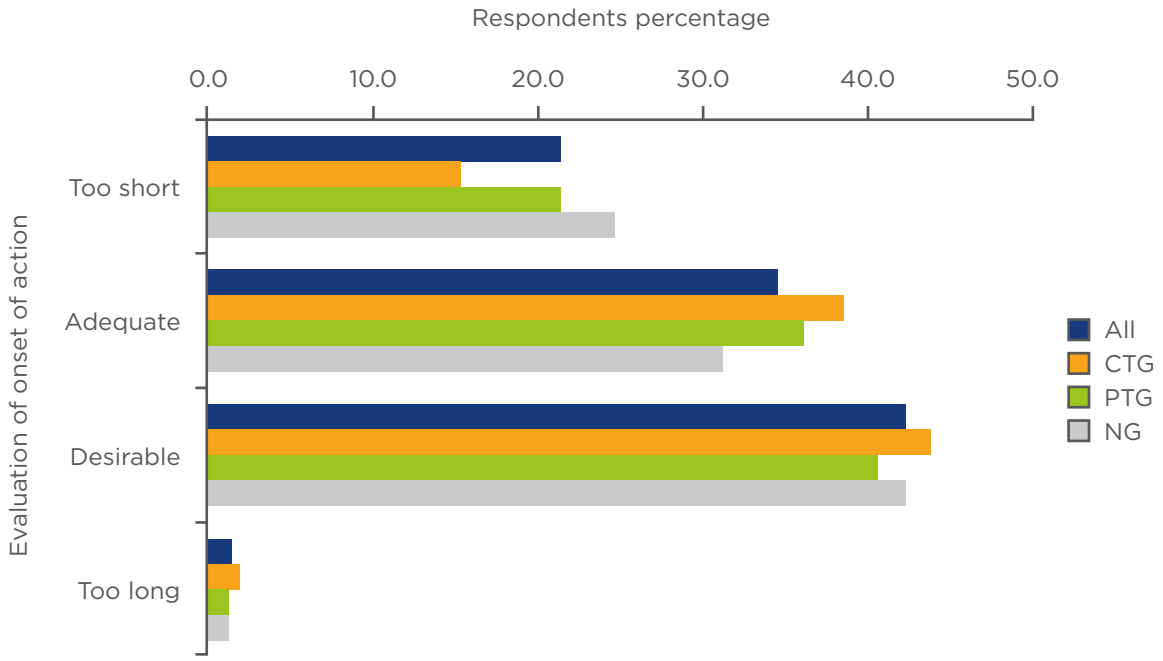


Figure 2: Evaluation of onset of action of about 15 minutes by currently-treated (CTG, n=298), previously-treated (PTG, n=297), and naïve erectile dysfunction (ED) patients (NG, n=529).[17]

Adverse events (AEs) include flushing (12%), headache (11%), dyspepsia (5%), and visual disturbances (3%), but sildenafil is not significantly associated with serious cardiovascular events or death.[25] It should be noted that the onset of action can be delayed after a heavy, fatty meal or alcohol intake due to prolonged absorption. Co-administration with non-selective alpha-1 blockers may cause symptomatic hypotension in patients using sildenafil intermittently.

Vardenafil

While no head-to-head studies have been conducted to compare the efficacy of vardenafil (Levitra®, approved by the EMA in March 2003) with sildenafil, it seems the former presents a similar onset, duration of action (up to 4 hours), and safety profile compared to that of sildenafil.[21,26-30]

The recommended dose of vardenafil is 10 mg, taken as needed approximately 25–60 minutes before sexual activity. Based on efficacy and tolerability, the dose may be increased to 20 mg or decreased to 5 mg.[31] Vardenafil is available as a film-coated tablet or in a new formulation as a orodispersible tablet, which could generate a more rapid onset (≤30 minutes) of action.[32-34] As with sildenafil, administration with a high-fat meal or alcohol consumption may delay the absorption with the film-coated formulations.

Tadalafil

Tadalafil (Cialis®, approved by the EMA in February 2003) has a completely different chemical structure than the first two drugs, providing similar efficacy outcomes and a well-tolerated safety profile, but a longer duration of action.[35] With a plasma half-life of 17 hours, tadalafil has the longest window of opportunity of up to 36 hours.[36-38]

The recommended dosing is of 10–20 mg prior to anticipated sexual activity, with or without food. In those patients in whom tadalafil 10 mg does not produce an adequate effect, 20 mg might be tried. It may be taken at least 30 minutes prior to sexual activity. A lower dose of 5 mg is available for once-daily dosing and has been approved both for the treatment of ED and benign prostatic hyperplasia/lower urinary tract symptoms.[39-41] Tadalafil absorption is not affected by food intake (namely, fatty meals) or alcohol consumption. AEs reported with tadalafil are comparable to the other two PDE5 inhibitors with the exception of myalgia and back pain, which are observed more often.[16,21]

Avanafil

Avanafil (Spedra®, approved by the EMA in June 2013) is the newest available PDE5 inhibitor and is considered a second-generation agent due to its enhanced PDE5 selectivity as compared with the

first three compounds.[42] Avanafil has a more rapid onset of action (≤15 minutes) with a similar efficacy, but the main advantage of avanafil in comparison to the first-generation PDE5 inhibitors is its improved safety profile, due to its high selectivity for PDE5.[43-49] The recommended dose is 100 mg taken as needed approximately 15–30 minutes before sexual activity. Based on individual efficacy and tolerability, the dose may be increased to a maximum dose of 200 mg or decreased to 50 mg.[50]

The rapid onset of action has been evidenced by a randomised, double-blind, placebo-controlled registered clinical trial involving 646 patients with ED over a 12-week treatment period (67% and 71% successful intercourse attempts with 100 mg and 200 mg avanafil compared with 27% with placebo, respectively; Figure 3).[51]

In a newly-published, randomised, double-blind, placebo-controlled, 12-week study (4-week run-in and 8-week treatment), 145 men were assigned to placebo, 147 to avanafil 100 mg, and 148 to avanafil 200 mg on demand.[52] Successful intercourse attempts within approximately 15 minutes of dosing were significantly higher with avanafil 100 mg (mean 25.9%) and 200 mg (mean 29.1%) versus placebo (mean 14.9%, p=0.001 and p<0.001, respectively). A statistically significant difference between avanafil and placebo was observed in the average per-subject proportion of successful intercourse attempts as early as 10 minutes in the 200 mg group and 12 minutes in the 100 mg group (Figure 4).

The average duration of action of avanafil has been reported as beyond 6 hours in some subjects.[51] Treatment-emergent AEs were similar but generally lower compared with the other PDE5 inhibitors. AEs reported with avanafil include headache, flushing, and nasal congestion. Although avanafil clinical trials have been conducted without any kind of restrictions on food and alcohol, high-fat meals could delay its rate of absorption into the plasma.[49,50]

Safety Profiles of PDE5 Inhibitors

AEs occurring with PDE5 inhibitors are generally mild or at best modest, and are mostly transient and self-limited.[16,21,30,36,53-55] As stated previously, the most commonly reported AEs are headache, flushing, dyspepsia, nasal congestion, and dizziness. All PDE5 inhibitors are contraindicated with the use of nitrates or nitric oxide donors of any form due to the risk of severe and sometimes life-threatening hypotension. Moreover, PDE5 inhibitors are to be used with caution with non-selective alpha-blockers and potent CYP3A4 inhibitors.[56]

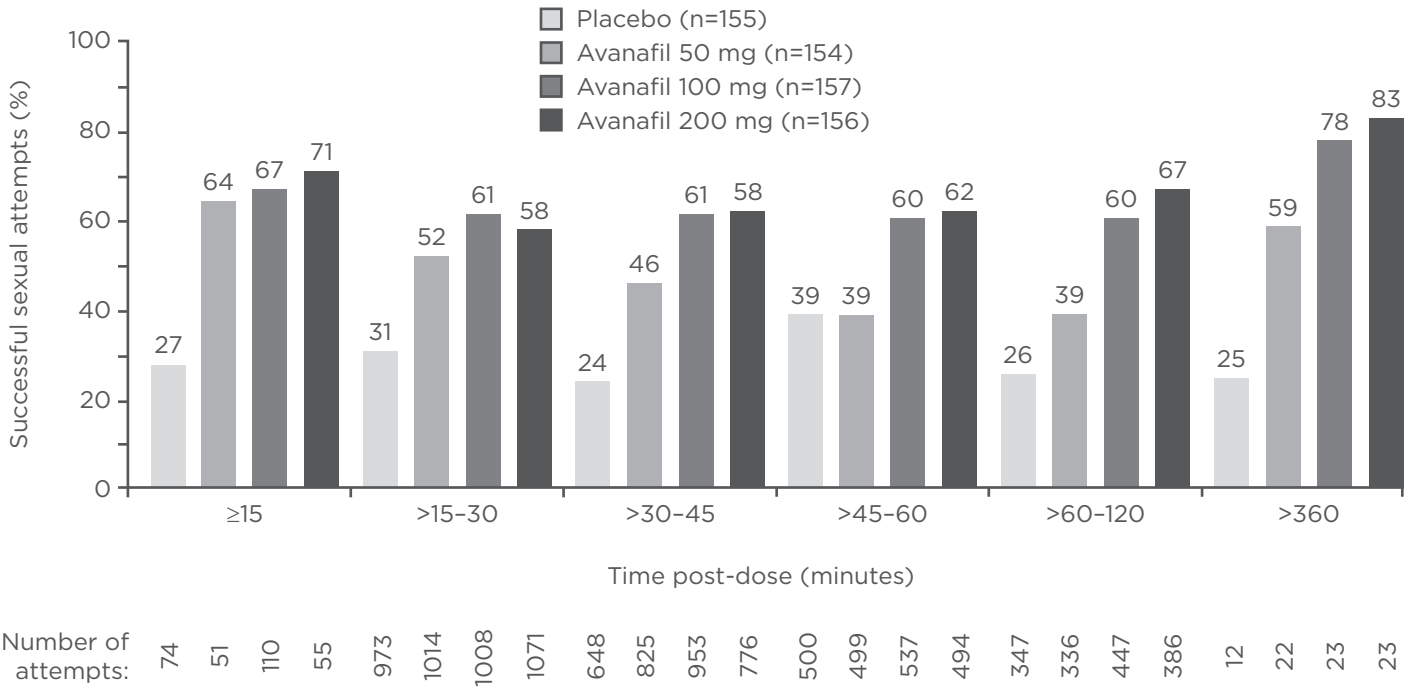
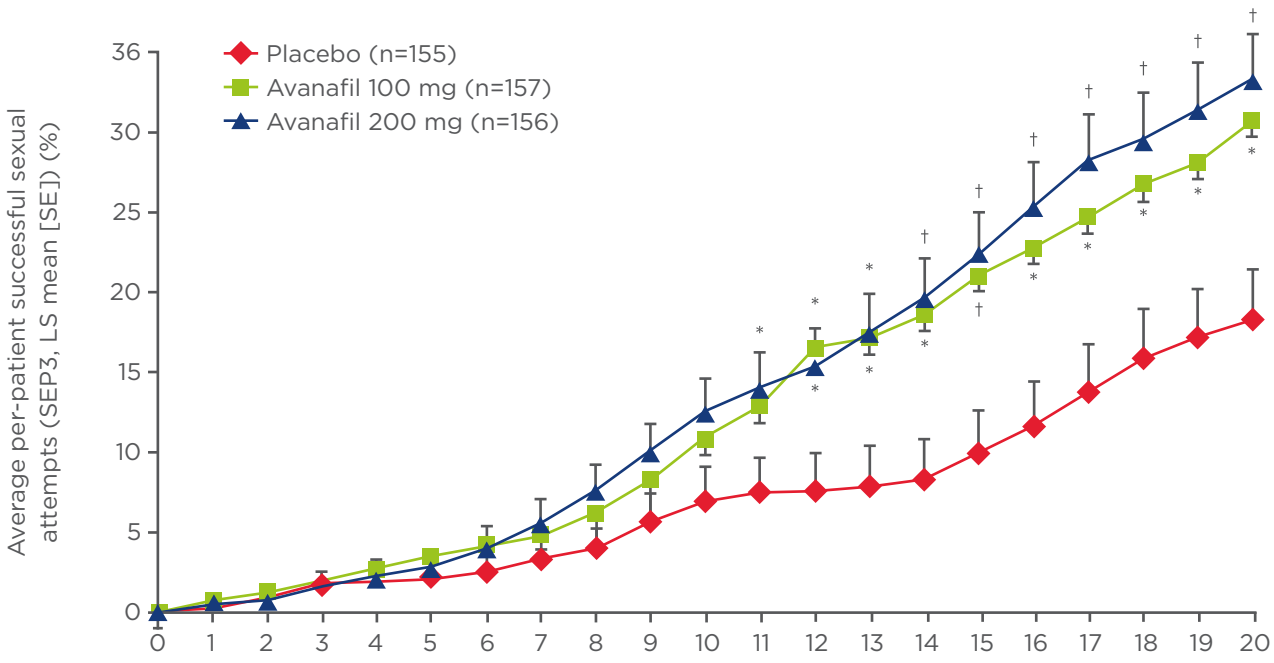


Figure 3: Successful intercourse by time interval, from dose to attempt. Sexual attempts in which subjects were able to maintain an erection of sufficient duration to have successful intercourse by post-dose time interval.[51]



Number of subjects with at least one success at the timepoint:

Placebo	2	5	8	8	10	14	17	21	30	33	34	36	37	42	5	51	55	56	59	62
Avanafil 100 mg	7	11	14	16	22	23	28	36	42	53	56	65	66	70	74	76	80	84	85	90
Avanafil 200 mg	4	6	12	16	20	23	29	36	40	49	56	59	63	68	79	83	83	85	88	90

Figure 4: Sexual attempts during the 8-week treatment period in which intent-to-treat subjects maintained erection of sufficient duration for successful intercourse by time since dose administration.[52]
*p<0.05 versus placebo. †ANCOVA p<0.001 versus placebo.
LS: least squares; SE: standard error.

Avanafil seems to be associated with reduced incidence of common AEs as compared with the other agents, but head-to-head trials or longer duration studies on the safety of avanafil are needed to confirm this perceived advantage.[12,49]

RATIONALE FOR CHOICE OF THERAPY: ADDRESSING PATIENT EXPECTATIONS WITH THE CURRENT ARMAMENTARIUM

Sildenafil, vardenafil, tadalafil, and avanafil are mostly equivalent in terms of efficacy profiles, but different pharmacokinetic properties can allow physicians to choose the most appropriate drug according to the patient's/couple's characteristics and expectations.[16,46,57] While all four compounds provide a similar efficacy in regards to the rates of successfully completed intercourse (SEP 3 data) in men with ED, there is no direct head-to-head data from double-blind multicentre studies comparing the efficacy or tolerability of PDE5 inhibitors.[21,57]

In 2009, the American College of Physicians recommended that the choice of PDE5 inhibitor be based on patient's preferences, costs, ease of use, and desired onset and duration of action, as well as AEs.[58] The 2015 guidelines on male sexual dysfunction published by the European Association of Urology recommend that the choice of drug should be based on the frequency of intercourse and the short or long-acting properties of the options, while highlighting that patients should be aware of these characteristics and how to use them.[12]

The differences in pharmacological characteristics and pharmacokinetic profiles, with different onset and duration of action parameters, differentiate PDE5 inhibitors and contribute to ED therapy more 'individually tailored' to the couple's needs. While sildenafil, film-coated vardenafil, and tadalafil should be taken 1 hour before sex, orodispersible vardenafil and avanafil can be taken only 30 and 15 minutes before sex, respectively, which is of particular interest for those couples who have a spontaneous sex life.

Moreover, daily low-dose tadalafil can be recommended in men seeking to eliminate

concerns regarding the preservation of spontaneity in their sex life and in this context the onset or duration of action of a drug. However, this represents a costlier treatment option compared with on-demand regimens.

CONCLUSIONS

There is no doubt that avanafil is not only an interesting addition to, but a real enrichment of the class of PDE5 inhibitors, due to its rapid onset, reasonably long duration of action, and superior safety profile thanks to its high selectivity. These pharmacokinetic and pharmacodynamic advantages will likely improve patient compliance and couples' treatment satisfaction, with fewer treatment discontinuations. Therefore, avanafil may represent a valid option for all those patients who are not satisfied with the pharmacokinetic properties and the rate of side effects associated with the three older PDE5 inhibitors.[12,16]

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