AVANAFIL: THE SECOND-GENERATION TREATMENT OF ERECTILE DYSFUNCTION

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ABSTRACT

The main objectives of erectile dysfunction (ED) management are to control and reduce associated organic cardiovascular risk factors and to restore the capacity to obtain and maintain a rigid penile erection.

Since oral phosphodiesterase (PDE)-5 inhibitors have a demonstrated efficiency in the number and duration of erections in patients with ED with a favourable benefit-to-risk ratio, they have been recommended in European guidelines as the first-line medical therapy for ED.

In January 2016, we published a comprehensive review and meta-analysis on the safety and efficacy of avanafil, a novel second-generation PDE-5 inhibitor. This review aims to shed a special spotlight on the key aspects of this meta-analysis and to discuss how avanafil can provide an added value in the management of ED over first-generation agents.

Keywords: Erectile dysfunction (ED), avanafil, phosphodiesterase (PDE)-5 inhibitors.

INTRODUCTION

Erectile dysfunction (ED) is defined by the National Institutes of Health (NIH) as the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual performance. This self-reported condition is the main complaint in male sexual medicine.[1] The incidence of ED is 26 new annual cases per 1,000 men,[2] for a worldwide ED prevalence evaluated at 37–52% of adults aged ≥40 years old and that is projected to increase by 2025 to approximately 322 million.[3] Of note, ED prevalence and severity is strongly associated with age.[4-11]

ED must be considered a multidimensional disorder deriving from a general (or stepwise) perturbation of all the components involved in the erectile response including organic (the body), relational (the couple), and intra-psychic (the mind).[12-18] ED may arise from the alteration of any one of these components (as a precipitating event) but sooner or later it will involve the other components in a redundant way, having negative effects on quality of life, interpersonal relationships, and mood.[9,19-24]

Despite this evidence, it is important to recognise that organic components and in particular cardiovascular risk factors such as smoking,[25,26] hypertension,[27,28] diabetes,[29,30] dyslipidaemia,[27] obesity, and sedentary lifestyle,[31,32] are major contributors to the pathogenesis of ED. In fact, arteriogenic ED, usually assessed through penile

colour Doppler ultrasound, is associated with a relevant increase in cardiovascular disease risk.[33,34]

THE PHARMACOLOGICAL MANAGEMENT OF ERECTILE DYSFUNCTION

The main objectives of ED management are to control and reduce associated organic cardiovascular risk factors and to restore the capacity to obtain and maintain a rigid penile erection. Due to the great variability of underlying aetiologies and the subjective aspects of ED, medical therapy depends on the patients' (and their partners') characteristics and comorbidities.[10,35,36]

Androgens are considered the major hormonal regulator of penile physiology.[37-40] Hypogonadism is a frequent condition in subjects seeking medical care for ED.[41] Testosterone replacement therapy in hypogonadal men (total testosterone <12 nM) is associated with significant increases in self-reported measures of erectile function.[39,40] Hence, according to the 4th International Consultation on Sexual Medicine (ICSM), testosterone assessment must precede any pharmacological intervention of ED subjects.[40]

Oral pharmacological management with phosphodiesterase (PDE)-5 inhibitors is the first-line modality, before other methods, which comprise penile self-injections with vasoactive drugs, intraurethral or intracavernosal alprostadil (a prostaglandin E1), vacuum-assisted erection devices, and penile prosthesis.[10,35,36,42-44] Only oral PDE-5 inhibitors that have been approved in Europe will be discussed in this article. These drugs act with a predominantly peripheral mechanism potentiating the nitric oxide (NO) pathway. Sexual stimulation generates a local production of NO which after binding to its intracellular receptors, activates the enzyme guanylate cyclase, leading to increased levels of cyclic guanosine monophosphate (cGMP). cGMP can engage a number of downstream targets, leading eventually to smooth muscle relaxation and penile erection. PDE-5 inhibition, by blocking cGMP degradation, can therefore increase NO signalling and induce smooth muscle relaxation.[45-47]

Oral PDE-5 inhibitors have a demonstrated efficiency in the number and duration of erections in patients with ED, with a favourable benefit-to-risk ratio, and hence they have been recommended in European guidelines as the first-line medical therapy for ED.[48] In January 2016, we published a comprehensive review and meta-analysis on the safety and efficacy of avanafil, a novel second-generation PDE-5 inhibitor. This review aims to shed a special spotlight on the key aspects of this meta-analysis and to discuss how avanafil can provide an added value in the management of ED over first-generation agents.

FIRST-GENERATION PHOSPHODIESTERASE 5 INHIBITORS

Sildenafil (Viagra®) was approved by the European Medicines Agency (EMA) in 1998 as the first oral PDE-5 inhibitor for ED and has been explored in a plethora of clinical trials.[49,50] Market authorisations for two other agents, vardenafil and tadalafil, were then subsequently granted by the EMA. The main characteristics of PDE-5 inhibitors are summarised in Table 1.[35,46,50-77] Adverse events (AEs) reported with first-generation PDE-5 inhibitors are generally mild, mostly transient, and self-limited; the most commonly-reported being headache, flushing, dyspepsia, nasal congestion, and dizziness with tadalafil also being associated to myalgia and back pain.[35,60,73,78-80]

All PDE-5 inhibitors are contraindicated with the use of nitrates or NO-donor drugs due to the risk of severe hypotension which can sometimes be life-threatening. PDE-5 inhibitors are to be used with caution with non-selective alpha-blockers and potent CYP3A4 inhibitors.[81] In addition, precaution is recommended for vardenafil in patients taking Type 1A anti-arrhythmics (such as quinidine or procainamide) or Type 3 anti-arrhythmics (such as sotalol or amiodarone) due to a possible causal association with QT prolongation.[82]

AVANAFIL: A SECOND-GENERATION PHOSPHODIESTERASE 5 INHIBITOR

Drug Characteristics

Avanafil (Spedra®) is the newest available PDE-5 inhibitor having been approved by the EMA in June 2013. It is a second-generation PDE-5 inhibitor along with lodenafil, mirodenafil, and udenafil (the last two are marketed in South Korea) but is the only one approved in Europe to date.[83,84]

Avanafil has a demonstrated high potency with a 50% inhibitory concentration (4.3–5.2 nM).[55-57] This compound is highly selective for PDE-5 as opposed to other PDE-5 inhibitors. *In vitro* studies evidenced less inhibition of PDE-1 (>10,000-fold;

present in the heart), PDE-6 (120-fold, present in the retina), and PDE-11 (>10,000-fold, present in the testicles). Furthermore, approximately 20,000-fold selectivity for the PDE-5 versus PDE-3 enzyme is found in the heart and blood vessels, which is important because PDE-3 is involved in control of cardiac contractility.[85] This high selectivity may confer and/or contribute to an improved safety profile over other PDE-5 inhibitors (Table 1).[51-54]

Avanafil is available in Europe as 50, 100, or 200 mg oral tablets. The recommended dose is 100 mg, taken as needed approximately 15–30 minutes before sexual activity; sexual stimulation is required for a response to treatment. Based on individual efficacy and tolerability, the dose may be increased to a maximum dose of 200 mg or decreased to 50 mg. The maximum recommended dosing frequency is once per day.[51]

Table 1: Main characteristics and isozyme selectivity of phosphodiesterase 5 inhibitors.

	Sildenafil[50,66-68]	Vardenafil[35,46,69-74]	Vardenafil[75-77]	Tadalafil[35,59-65]	Avanafil[51-58]
Brand name	Viagra®	Levitra®		Cialis®	Spedra®
Generation	First-generation				Second-generation
Galenic form	Film-coated tablets	Film-coated tablets	Orodispersible tablets	Film-coated tablets	Tablets
Year of European market authorisation	1998	2003	2010	2003	2013
Recommended dose	50 mg (may be increased to 100 mg or decreased to 25 mg based on efficacy and tolerability)	10 mg (may be increased to 20 mg or decreased to 5 mg based on efficacy and tolerability)		10–20 mg (also available as doses of 2.5 and 5 mg for once-daily dosing)	100 mg (may be increased to 200 mg or decreased to 50 mg based on efficacy and tolerability)
Maximum recommended dose	100 mg	20 mg		20 mg	200 mg
Onset of action	60 minutes	25–60 minutes	<30 minutes	30 minutes	Approximately 15–30 minutes
Onset of action delayed due to fatty meal or alcohol consumption?	Yes	Yes	No	No	Yes
Duration of action	About 4 hours Some reports of durations of action for up to 12 hours	About 4 hours		Up to 36 hours	>6 hours in some patients
PDE selectivity (fold-difference) 1	375	1,012		10,500	10,192
2	39,375	273,810		>25,000	9,808
3	16,250	26,190		>25,000	>19,231
4	3,125	14,286		14,750	1,096
5	1	1		1	1
6	16	21		550	121
7	13,750	17,857		>25,000	5,192
8	>62,500	1,000,000		>25,000	2,308
9	2,250	16,667		>25,000	>19,231
10	3,375	17,857		8,750	1,192
11	4,875	5,952		25	>19,231

PDE: phosphodiesterase.

Table 2: Efficacy and safety parameters for avanafil 100/200 mg versus placebo.

Parameter	Avanafil 100 mg versus placebo	Avanafil 200 mg versus placebo
Efficacy parameters	**OR (95% CI)**	
Successful intercourse (SEP3)	2.51 (1.85–3.41)	2.87 (2.23–3.69)
Successful intercourse (SEP3) within 15 minutes	4.72 (2.08–10.71)	4.21 (1.44–12.28)
Normalisation of IIEF (>26)	3.54 (2.14–5.87)	3.19 (1.93–5.29)
Successful vaginal penetration (SEP2)	2.20 (1.74–2.84)	2.57 (1.99–3.32)
Safety parameters	**OR (95% CI)**	
Serious AEs	1.99 (0.67–5.93)	1.70 (0.54–5.31)
Any drug-related AEs	2.07 (1.23–3.48)	2.10 (1.35–3.26)
AEs leading to drug discontinuation	1.45 (0.52–4.03)	1.24 (0.44–3.50)
Flushing	6.17 (2.08–18.32)	7.91 (2.71–23.04)
Headache	4.57 (1.91–10.94)	10.21 (4.50–23.17)
Nasal congestion	2.81 (0.99–8.01)	2.63 (0.89–7.73)
Back pain	1.74 (0.53–5.72)	1.24 (0.32–4.83)

SEP3: "Did your erection last long enough for you to have successful intercourse?" and SEP2: "Were you able to insert your penis into your partner's vagina?"
Data are derived and adapted from the meta-analysis of the available randomised placebo-controlled trials. Reproduced with permission from Corona G et al.[88]
SEP: sexual encounter profile; IIEF: International Index of Erectile Function; OR: odds ratio; CI: confidence interval; AEs: adverse events.

Dose adjustments are not required in patients aged 65 years and older. However, the available data on patients aged ≥70 years old is limited.[51] Similarly, dose adjustments are not required in patients with diabetes mellitus or mild-to-moderate renal impairment. It is to be noted that in Phase III studies, decreased efficacy was observed in the latter patient category, as compared with patients with normal renal function.[52,53] In patients with mild-to-moderate hepatic impairment (Child–Pugh Class A or B), treatment should be initiated with the minimum efficacious dose and posology should be adjusted based on tolerance.[52,53] Avanafil is contraindicated in patients with severe renal impairment (defined as creatinine clearance <30 mL/min) and severe hepatic impairment (Child–Pugh Class C) due to lack of specific data in these conditions.[52,53,86,87]

Meta-Analysis of Clinical Efficacy and Safety Data to Date

We conducted a meta-analysis of all available randomised clinical trials to date on the efficacy and safety of avanafil 100 and 200 mg.[88] A comprehensive search was conducted on the MEDLINE, EMBASE, and Cochrane databases. Five placebo-controlled randomised clinical trials of avanafil in ED were included in the analysis, reporting data on a total of 1,379 and 605 patients in the active and placebo arms, respectively.[58,89-92] Since only one study out of five reported on the 50 mg dosage, the authors chose to focus their analyses on the 100 and 200 mg dosages. In the overall cohort, mean ED duration was 65.5 months and the prevalence of severe ED was 42.9%.[88]

Clinical Outcomes

Efficacy: Successful intercourse

In the meta-analysis cited above, according to the evaluation of Sexual Encounter Profile (SEP)-3, avanafil 100 and 200 mg were significantly superior (3-fold increased probability to normalise erectile function) over placebo in improving successful sexual intercourse (Table 2), independently of baseline severity or duration of ED but also of comorbidities (high body mass index, diabetes, and hypertension). Both doses were also significantly superior to placebo with a 4-fold increased likelihood of a successful intercourse within 15 minutes.[88]

Of note, the efficacy of the 100 mg dosage was lower in elderly patients but this effect was not observed with the 200 mg dose. In addition, avanafil 100 and 200 mg were associated with a significantly higher International Index of Erectile Function (IIEF) versus placebo, with a better score for avanafil 200 mg (3.92 [range: 2.68–5.15] and 4.92 [range: 3.66–6.19], respectively, for the 100 and 200 mg doses; both p<0.0001).[88]

Onset and duration of action

Avanafil has a more rapid onset of action than the older PDE-5 inhibitors (within 15 minutes).[53,56,88,93-95] The rapid onset of action was demonstrated during a randomised, double-blind, placebo-controlled registrative clinical trial involving 646 ED patients over 12 weeks (67% and 71% of successful intercourse attempts with 100 and 200 mg avanafil versus 27% with placebo, respectively).[58]

In a newly published randomised, double-blind, placebo controlled, 12-week study, men were either assigned to placebo, avanafil 100 mg, or avanafil 200 mg.[91] Successful intercourse attempts within approximately 15 minutes after dosing were significantly higher with avanafil 100 mg (mean: 25.9%) and 200 mg (mean: 29.1%) than with placebo (mean: 14.9%, p=0.001 and <0.001, respectively). A statistically significant difference between avanafil and placebo was observed for successful intercourse attempts as early as 10 and 12 minutes in the 200 mg and 100 mg groups, respectively. The erectogenic effect of avanafil has been reported beyond 6 hours in some subjects.[51,58]

Safety Profile of Avanafil

Common class-related AEs reported with avanafil include headache, flushing, and nasal congestion.[51,58,89-91,96] Unsurprisingly, In the meta-analysis both avanafil 100 and 200 mg dosage forms were associated with an increased rate of reported drug-related AEs over placebo (especially flushing and headache but no differences for nasal congestion and back pain were observed; Table 2). However, the rate of discontinuations due to AEs for both active doses were similar to those for placebo.[88] An interesting finding was that no difference was observed between the 100 and 200 mg dosages and placebo in terms of serious AEs (odds ratio: 1.99 [0.67–5.93] and 1.70 [0.54–5.31] for avanafil 100 and 200 mg, respectively, both with a non-significant p-value).

Avanafil at its maximum dosage has a comparable efficacy but an improved safety profile over first-generation PDE-5 inhibitors.[53,56,88,93-95] In another meta-analysis published by Chen et al.,[42] the frequency of AEs for each PDE-5 inhibitor when used at their maximum dosage demonstrated a favourable safety profile with avanafil 200 mg versus tadalafil 20 mg (p<0.02), vardenafil 20 mg (p=0.001), and sildenafil (p=0.0001).[88] However head-to-head trials or longer duration studies on the safety of avanafil are needed to ascertain this suggested advantage.[10,88]

CHOICE OF THERAPY AND PRACTICAL CONSIDERATIONS FOR REAL-WORLD PATIENTS: THE ADDED VALUE OF AVANAFIL

The efficacy and safety of PDE-5 inhibitors has been highly documented. However, beyond the first year of therapy with a PDE-5 inhibitor, a substantial proportion of men discontinue treatment prematurely.[10,88,97,98] It therefore appears ineluctable that in order to improve treatment adherence, clinicians should try to better understand patient expectations to help refine the choice of PDE-5 therapy on an individual basis, and tailor therapy according to the patient's/couple's characteristics and expectations.

Although there is no head-to-head data from double-blind randomised trials comparing PDE-5 inhibitors against each other, all four drugs are effective within an acceptable safety profile.[35,99] Guidance from both the American College of Physicians (ACP; 2009) and the European Association of Urology (EAU; 2016) recommend that the choice of PDE-5 inhibitor be based on patient's preferences, costs, ease of use, frequency of intercourse, desired onset, and duration of action as well as AEs.[48,79,100,101]

While the therapeutic armamentarium may seem homogenous, different pharmacokinetic properties and selectivity differences are at the core of the choice for the most appropriate drug.[99,102] Indeed, pharmacokinetic differences translate into different onset and duration of action parameters. Sildenafil, film-coated vardenafil, and tadalafil should be taken 30–60, 25–60, and 30 minutes before desired sexual activity, respectively. Orodispersible vardenafil can be taken only 30 minutes before sexual intercourse; avanafil has the shorter onset of action with a delay of action of only 15 minutes

which is of particular interest for couples seeking a very spontaneous sex life. With this very short onset of action, avanafil is the closest PDE-5 inhibitor to a 'natural' occurrence.[51,59,63,66,69,74]

According to a large online survey (N=1,534) initiated to better understand patients' needs and expectations of sexual activity and ED management, 38% of men considered an ideal onset of action of oral therapies to be of 'about 15 minutes' giving them 'the ability to respond immediately to their partner's sexual wishes and requests' and 'allowing a certain degree of spontaneity'. As we previously commented in our meta-analysis, in the context of ED a drug with a rapid onset can generate better spontaneous sexual interaction.[88] Furthermore, the short delay provided by avanafil could help reduce the psychological impact of ED (couple-related problems, low self-esteem), improve treatment satisfaction, and therefore solidify treatment adherence.

With respect to available dosage forms, avanafil 200 mg could provide an added value in elderly (>65 years old) ED patients in achieving successful sexual encounters. Indeed, in the meta-analysis, while the efficacy of the 100 mg dosage was lower in the elderly than in younger patients, this effect was not observed with the 200 mg dose which was still demonstrated to be as safe as the 100 mg dose.[88] Elderly patients can present several comorbidities and risk factors, and thus the fact that avanafil at its maximum dosage has a comparable efficacy but fewer AEs than first-generation PDE-5 inhibitors, is of particular interest. This safer profile could increase physician confidence in prescribing an on-demand but long-term therapy, as can be the case with elderly ED patients. Likewise, as suggested by some experts and our clinical practice, the maximum dosage of 200 mg could be directly prescribed to complicated subjects in order to obtain the best initial treatment success and generate a strong patient adherence to therapy from the beginning.[88]

CONCLUSION

This new meta-analysis further ascertains the safety and efficacy of avanafil, as evaluated by SEP-3, SEP-2, and IIEF scores in the studied populations. While avanafil has comparable efficacy outcomes with the three older PDE-5 inhibitors, its improved safety profile (due to a higher selectivity) can be of particular interest for clinicians. Furthermore, as a consequence of unique pharmacokinetic properties, this compound provides added value due to its rapid onset of action and reasonable duration of action.

These factors could translate into higher patient compliance and treatment satisfaction thus adherence, and help reduce treatment discontinuations (e.g. due to AEs).[79,103] Second-generation PDE-5 inhibitors are a welcome addition to the therapeutic landscape of ED and can contribute to a more individually-tailored ED therapy.

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