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Review

Sildenafil Citrate Oral Suspension for Managing Erectile Dysfunction: A Systematic Review and a Consensus Report from the Italian Society of Andrology (SIA)

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Abstract: The management of erectile dysfunction (ED) shows several gray zones, especially in terms of patients' satisfaction and adherence to the treatment. The main and first-line treatment for ED is drug therapy, mainly phosphodiesterase-5 inhibitors (PDE5is), but adherence to the therapy is not optimal due to the low patient satisfaction reported in several cases. To address this issue, different administration routes and PDE5i pharmacological formulations have been introduced in the pharmacological market. The pharmaceutical market has recently seen the introduction of a novel sildenafil oral suspension. This device offers access to all therapeutic regimens in one device, releasing 0.5 mL of suspension containing 12.5 mg of sildenafil with each pulse. This formulation enables tailored dosing based on clinical requirements and the demands of ED patients. Here, we aim to give a brief narrative review of the management of this new oral suspension in order to provide readers with some suggestions to use in everyday clinical practice, on the basis of recent evidence, by using an easy and rapid-to-consult question and answer form. Also included are the conclusions of a board meeting of experienced andrologists regarding the most recent developments in this area.

Keywords: erectile dysfunction; phosphodiesterase-5 inhibitors; sildenafil

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1. Introduction

Erectile dysfunction is a common medical disorder estimated to affect 7 million (13%) of the Italian male population [1], but the projections for 2025 show a prevalence of 322 million men that will be affected worldwide [2]. The main and first-line treatment for erectile dysfunction is drug therapy, mainly phosphodiesterase-5 (PDE5) inhibitors [3,4]. These drugs increase the concentration of cyclic guanosine monophosphate (cGMP) in vascular smooth muscle cells by inhibiting PDE5 expression in the corpus cavernosa, reduce the concentration of intracellular calcium, cause smooth muscle relaxation, increase blood flow to the corpus cavernosa and improve erection. Treating ED with a PDE5 inhibitor can improve the International Index of Erectile Function-5 (IIEF-5) scores and sexual success in a significant number of patients. Currently, sildenafil is the most efficient drug, with the most clinical experience and the strongest and most solid scientific evidence since its launch in

1998, independently of age [5,6]. Sildenafil tablets can be administered in fixed doses of 25, 50 or 100 mg. However, patients may need to adjust the dose to their needs, always under medical supervision. In the last 25 years, many steps forward have been accomplished in understanding the management of ED with sildenafil. On the other hand, in the last decade, the Internet has become an easily accessible source of medical information for patients and, in particular, for ED treatment [7]. Patients frequently turn to the Internet in search of treatment recommendations, where they frequently come across ambiguous news and potentially harmful dosage management advice. In this regard, it is imperative that all doctors supervising ED patients be up to date on the most recent research regarding PDE5i care. A bioequivalent of sildenafil in an oral suspension with good bioavailability against Viagra® (Pfizer Inc., 04100 Latina, Italy) has been developed [8], allowing for a more flexible dose adjustment. The new sildenafil oral suspension is a system releasing 0.5 mL of suspension containing 12.5 mg of sildenafil with each pulse, providing access to all therapeutic regimens in a single device. This formulation allows for personalized dosing according to ED severity and patients' needs. Urologists and andrologists were asked to give practical recommendations to patients regarding the management of this new kind of formulation. The aim of this paper is to give a brief narrative review of the management of this new oral suspension in order to provide readers with some suggestions to use in everyday clinical practice, on the basis of recent evidence, by using an easy and rapid-to-consult question and answer form. The conclusions of a board meeting of experienced andrologists conducted on the most recent updates in this field have been also provided.

2. Materials and Methods

2.1. Search Strategy

A literature review using the PubMed, Cochrane CENTRAL and Scopus databases was conducted to retrieve papers written in English on sildenafil use published over the past 25 years. The search strategy involved articles reporting "sildenafil" AND "oral suspension" AND/OR "erectile disfunction" AND/OR "treatment" from up to January 2024. Review articles, editorials, comments and letters to the editor were included if deemed to contain relevant information on the use of the sildenafil oral suspension. References from selected articles were also considered for inclusion. Articles discussing sildenafil citrate oral suspension for the treatment of pulmonary hypertension in children were excluded. Two authors (C.M. and L.B.) performed the initial screening of titles and abstracts independently to determine which papers could potentially meet the inclusion criteria. All authors finally agreed on the articles to include for discussion in the present review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance and the Cochrane Handbook for systematic reviews of interventions have been used for this review, in accordance with our previous paper [9].

2.2. Expert Opinion

The literature findings were presented and discussed in an expert meeting yielded on 6th March 2024 in Milan. Our research identified 712 articles of potential interest. After the first screening round, 143 articles were considered eligible for inclusion in this narrative review, and finally, 37 were discussed during the meeting. All authors discussed all relevant aspects of the sildenafil citrate oral suspension in order to give recommendations for everyday clinical practice. The following questions were posed to each member of the board:

1. Why choose sildenafil?
2. Why choose an oral suspension?
3. What is the best usage strategy?
4. What is the bedtime strategy?
5. What is the strategy for using sildenafil in premature ejaculation (PE)?
6. What is the therapy involvement strategy for a couple to use sildenafil?

7. Why use the sildenafil oral suspension in benign prostatic hypertrophy and interstitial cystitis?
8. Is it safe to use sildenafil for months and years?

3. Evidence Synthesis

This review aims to update the new therapeutic alternatives, focusing on the profile of patients susceptible to their use, the therapeutic strategies for use in everyday clinical practice and the usefulness of the oral suspension. Selecting an oral sildenafil suspension can be broken down into eight main categories for simplicity of explanation.

1—Why choose Sildenafil?

Sildenafil therapy has demonstrated effectiveness across all ages, ED etiologies and ED severities. The availability of an effective therapy has prompted an immediate shift in the setting of ED care. The most important outcome of therapy is the resumption of successful sexual intercourse. In prospective, randomized, placebo-controlled trials in variable patient populations, the rate of successful intercourse has been 65% to 78% [10]. The product insert recommends an interval of 45 min to 1 h between sildenafil ingestion and the maximal penile response to stimulation; however, some patients have reported an adequate response in as little as 15 to 20 min, particularly when the drug is taken on an empty stomach. Older patients and those with delayed gastric emptying (such as diabetic patients) may need a prolonged interval before an effect is achieved. A survey of male sexual habits indicates that the time interval between the respondent's first thought that he might have intercourse and the beginning of intercourse is approximately 1 h and does not vary significantly between men with and without ED.

2—Why choose an Oral suspension?

According to the World Health Organization, patients may not be taking 50% of their medications as prescribed by providers, and this omission of therapy can lead to negative health-related outcomes (including but not limited to treatment failures, hospital admissions and increased costs) [11]. Whether patients are prescribed medications for acute or chronic illnesses, their adherence (or ability to fill prescriptions and then take as directed for the duration of treatment) can be influenced by numerous social, economic and logistic factors [12,13]. One element that can influence adherence is drug formulation [14]. The ability to take oral dosage forms generally varies with age; although most adults are able to swallow whole tablets or capsules, oral suspension is a valid substitute for patients who are elderly, have declining physical or cognitive capacities or are afraid of choking. Other factors need to be taken into account when managing ED. A recent multicenter observational study showed the three factors for which patients chose an oral suspension of the drug over the tablet counterpart: problems of adherence to previous treatment, dose adjustment and convenience of use [15]. A total of 73.3% of patients in that study reported that the oral suspension facilitated the dose adjustment of sildenafil. Not using the right dose is one of the most common causes of incorrect PDE5i use, ranked second in the European Association of Urology (EAU) Guidelines on Sexual and Reproductive Health of 2022. Treatment adherence implies a collaborative approach to decision-making, ideally with mutual agreement between patient and clinician with respect to medication choice, dosing and frequency of administration. We differentiated adherence from compliance, which connotes a passive role for patients in receiving and following medical advice. Oral liquid medications have flexible dosing and can be swallowed more easily. Palatability (i.e., taste and smell) and smaller volumes are also better tolerated. Additional methods to improve adherence and reduce administration errors in patients include providing pre-dosing measurements (i.e., avoiding opening, breaking, crushing, chewing, dissolving another solid pharmacological formulation) These interventions mitigate interruptions in treatment and promote medication adherence. In a recent study [16], urology and/or andrology specialists endorsed the effectiveness of the sildenafil oral suspension. The main reason why sildenafil in the oral suspension was chosen was its formulation, which facilitates dose adjustment, since all commercially available doses are contained in a single

container, in addition to convenience of use and discretion, since it does not require water to be taken. These factors may have an impact on improving adherence and, subsequently, on clinical outcomes.

3—What is the best usage strategy?

During treatment with an on-demand regimen, insufficient medication attempts is a common reason for patients not achieving a response to PDE5is, and the reason may be associated with an insufficient blood concentration. There is no strategic plan for using sildenafil. Continuous inhibition of PDE5 results in a permanently high concentration of cyclic guanosine monophosphate, offering ED patients a higher level of efficacy and flexibility in sexual involvement. It has been shown that the coital success rate was elevated with increased sildenafil frequency but remained stable after eight doses (with a success rate of up to 86%) [17]. Onset and duration of effect depended on dosage, age, medical conditions and other medications. For the most predictable effects in the useful taking of sildenafil 60 min before sex, however, these remain adaptable, as responses vary from person to person. Many patients consider keeping arousal aids like sensual media, lubricants or toys on hand because they can be helpful if they experience occasional delays or changes in erection strength. At all dosage levels, sildenafil enables harder erections for a reliable 4 to 6-h duration in most users. Three hours following intake, half the peak drug amount still circulates sufficiently for sexual response with arousal. The effects do not instantly disappear at the 6-h mark. The efficacy steadily declines as the drug concentration drops, halving every 3–4 h thereafter. Food (heavy meals) delays it up to 2 h and also slows drug fading. Foods that delay sildenafil absorption are fatty red meats, cheeses, high-fat meals and fried and heavily processed items requiring prolonged digestion; sugary drinks; and citrus juices (like grapefruit juice). Drinking too much alcohol can lessen sildenafil's effects. Timing sexual intercourse strategically within the active window can prevent frustration. While sildenafil provides reliable assistance for achieving erections, making positive additions like a balanced diet, more physical activity, lower stress and the quitting of smoking can further boost the effects of sildenafil on erections. Sildenafil (12.5 mg) is delivered with each pump press. Starting at four actuations of suspension, or 50 mg of sildenafil, is the suggested dosage (and is also the most widely used dosage for sildenafil tablets).

4—What is the Bedtime strategy?

Nighttime erections are a normal physiological phenomenon that occurs spontaneously 3–5 times per night, during nighttime sleep, in healthy males at all ages and contributes to the maintenance of the integrity of the smooth muscle cells within the corpora cavernosa. Many studies have shown that the administration of sildenafil at bedtime, regardless of eventual sexual activity, is considered a useful tool in the prevention of morphodynamic deterioration of the cavernosal smooth muscle (a factor that occurs with aging or following exposure to vascular and other risk factors). In a double-blind, crossover, placebo-controlled study [18], the effects of sildenafil and placebo on sleep-related erectile activity were evaluated. Thirty selected patients with erectile dysfunction (vasculogenic etiology, 73%; psychogenic etiology, 27%) were submitted to a polysomnographic recording of nocturnal erections, using a RigiScan device during three consecutive nights after the administration of sildenafil or a placebo taken at bedtime. In total, 77% of patients showed significantly improved nocturnal erectile activity after the administration of sildenafil; the duration of tip rigidity greater than 60% was significantly longer during the night with sildenafil; and also, the number of erectile episodes was greater during the sildenafil night. From this finding, a door was opened to assessing the potential preventive value of sildenafil treatment. Actually, there are many studies that have addressed the potential for "disease modification" or "cure" via chronic PDE5-i therapy. According to Fusco et al. [19], there are data supporting a potential role for daily PDE5-i administration daily that may be beneficial for treating endothelial dysfunction and potentially curing ED. Starting from this scenario and according to the works in the literature [20] on sexual rehabilitation after radical prostatectomy, if we also transfer this idea to patients without surgical treatment, we could say that a regular daily intake of low-dose sildenafil (25 mg at night) leads to

significantly improved erectile function. Furthermore, according to Rochira et al. [21], in normal men, 50 mg of sildenafil at night will lead to better erections and more prolonged action than when administered to awake subjects. In any case, attention must be paid to administration at bedtime, especially in patients suffering from severe obstructive sleep apnea (OSA). In severe OSA, the use of sildenafil, 50 mg at bedtime, plays a detrimental role on respiratory parameters in both non-REM and REM sleep [22].

5—What is the strategy for using Sildenafil in premature ejaculation (PE)?

PE is one of the most common sexual dysfunctions that may affect the quality of sexual intercourse. Various pharmacological agents are used for the clinical treatment of PE. PDE5is are prescribed off-label. Several randomized controlled trials (RCTs) and observational studies have compared PDE5 inhibitors to placebos with no therapy or pharmacological agents. According to systematic review and meta-analysis [23], considering intra-vaginal ejaculatory latency time (IELT), the pooled effect estimate across two RCTs [24,25] comparing sildenafil (50 mg) to a placebo was 2.21 min (95% CI: 1.45 to 2.97; $p < 0.00001$), in favor of sildenafil. Instead, in comparing sildenafil (50 mg) to paroxetine, the pooled effect in IELT across two RCTs was 0.33 min [25,26]. Combination therapy with a selective serotonin reuptake inhibitor (ssri) plus sildenafil demonstrated a better result than the ssri alone. Sildenafil, 50 mg, was significantly more effective than the squeeze technique [26] at increasing IELT (MD: 3.56 min). A high level of heterogeneity was shown in these analyses, which might have resulted from the differences in types of PE, the duration of treatment and the sample sizes. If we analyze primary PE only, the conclusions are insufficient because of the small number of RCTs and patients.

6—What is the therapy involvement strategy for a Couple to use Sildenafil?

Epidemiologic data from multiple countries and groups of women suggest that sexual problems (e.g., arousal disorders, low desire, lack of orgasm) are more prevalent overall in women than men [27]. There are sparse data of the effects of these drugs on female sexual psychophysiology in the management of female sexual arousal disorder (FSAD) or other sexual dysfunctions in women. From the beginning, both laboratory studies and clinical trials were undertaken to evaluate sildenafil's effects in women with FSAD; women with desire disorders (hypoactive sexual desire disorder [HSDD]) were included in some but not all of these early studies. At the state of the art, PDE5is demonstrated significantly improved sexual arousal compared to patients who received placebos, as demonstrated with a double-blind, cross-over, placebo-controlled study [28]. Sexual orgasm and satisfaction improved after PDE5i treatment compared to placebos in pooled data from three studies [29–31]; on the other side, sexual satisfaction, when assessed as the frequency of sexual intercourse, demonstrated no significant difference. In women treated with antidepressants, it is common to observe sexual dysfunction as an adverse effect that frequently results in premature medication treatment discontinuation and for which no treatment has demonstrated efficacy in women. In an 8-week prospective, parallel-group, randomized, double-blind, placebo-controlled clinical trial, patients were assigned to take sildenafil, 50 mg, or a placebo before sexual activity [32]. Sildenafil demonstrates a significant reduction in adverse sexual effects, measured by the Clinical Global Impression of sexual function. Nowadays, the results suggest that PDE5i treatment could be an effective option for improving FSAD and sexual dysfunction. No serious adverse effects have been reported, but, like in men, headache, nausea, flushing and vision changes are frequent.

7—Why use Sildenafil oral suspension in Benign prostatic hypertrophy and Interstitial Cystitis?

Many epidemiological studies have reported a strong correlation between ED and LUTS, which share common pathophysiological pathways. Actually, tadalafil (5 mg once daily) has been licensed for the treatment of male LUTS. The mechanism of action is quite unclear; anyway, the upregulation of NO/cGMP activity is probably the most important pathway. Moreover, chronic treatment with PDE5is seems to increase blood perfusion and oxygenation and also reduce chronic inflammation in the prostate and bladder. A recent randomized, double-blind, placebo-controlled study conducted on men older than 45 years

with clinical diagnosis of LUTS due to BPH proved that sildenafil, 25 mg once/twice a day, improved I-PSS compared to placebos; sildenafil, 50 mg once a day, improved nocturia significantly [33]. Sildenafil, 50 mg/day, in another study, was more effective than tadalafil (5 mg/day) in reducing PVR, the IPSS-QoL index and, although not significantly, IPSS [34]. The use of PDE5is has been proposed to treat chronic inflammatory disease like interstitial cystitis (IC). Up to now, the etiology of IC has been unknown, resulting in controversies over the definition, pathophysiology and treatment. The idea behind the use of PDE5is in this type of pathology is contained in the ability of these molecules to determine relaxation of the smooth muscles, whose pathological contraction derives from the alteration of the permeability of the urothelium and the destruction of the capillaries and lymphatic capillaries, as well as mast cell degranulation. A low dose of sildenafil (25 mg/day) vs. a placebo demonstrated a reduction in frequency of nocturia and, moreover, in VAS scores, maintaining an improvement state for 3 months after treatment [35].

8—Is it safe to use Sildenafil for months and years?

Sildenafil is safe to take for a long time; there do not seem to be any lasting harmful effects from taking it for many months and years. Several studies indicate that, in general terms, sildenafil is well-tolerated and the side effects are few, mild and due to the vasoactivity effect on vascular smooth muscles. The most common reported events are dose-dependent and include headache, flushing, nasal congestion, facial and ocular hyperemia, dyspepsia and, rarely, myalgia and back pain [36]. Visual side effects were reported in 3–11% of men taking 25–100 mg of sildenafil, 50% of men taking 200 mg and 100% of men taking 600 or 800 mg (center for drug evaluation) [36,37]. Sildenafil may induce a reversible increase in intraocular pressure (IOP), and a few case reports suggest it is involved in the development of nonarteritic ischemic optic neuropathy (NAION). Most published reports have not demonstrated an association between sildenafil administration and IOP elevation, considering transient IOP elevations as coincidental [37]. During the postmarketing surveillance phase, US and Canadian health authorities received reports of anterior nonarteritic ischemic optic neuropathy (NAION) occurring in patients taking phosphodiesterase 5 (PDE5) inhibitors for the treatment of erectile dysfunction. NAION is due to a lack of blood supply to the optic nerve and involves a sudden, painless partial or complete loss of vision in one or both eyes. Although in some patients, functional recovery can be achieved over time, in others, the damage is irreversible. Patients who have already had one episode of NAION are at greater risk of experiencing a second episode in the other eye. Among the factors predisposing to the onset of NAION are age over 50, the presence of coronary heart disease, high pressure, high cholesterolemia, diabetes and smoking. These risk factors also play an important role in the onset of erectile dysfunction. Most of the reports of NAION associated with the use of PDE5 inhibitors concerned sildenafil (38 of the 43 cases reported to the FDA and the two reports received by the Canadian authorities), and most patients had one or more vascular risk factors for NAION. The small number of events reported compared to the large number of users of PDE5 inhibitors and the fact that many reports concern patients with risk profiles similar to patients diagnosed with NAION but who do not use these drugs make it difficult. At the moment, we cannot confidently establish a causal link between the use of PDE5 inhibitors and the appearance of this disorder. However, some factors, such as the temporal consequentiality between taking the drug and the appearance of NAION in some of the reported cases and the presence of recurrent ocular symptoms compatible with NAION in other cases, make this association plausible. Among the auditory effects reported in the long-term use of sildenafil, sudden hearing loss (SSHL) with or without vestibular symptoms (tinnitus and dizziness) are reported in the literature. It is important to note that the association between sildenafil (and other PDE5is) and hearing loss is still under investigation; additionally, it is worth mentioning that hearing loss is considered rare, occurring in a small percentage of individuals who take the medication. SSHL has been defined as hearing loss of at least 30 dB in three or more continuous frequencies that occurs within 72 h of symptom onset; it was not until 2007 [38] that a case of SSHL was reported as a potential side effect of sildenafil and its drug class. Its

etiology is controversial: vascular disease, autoimmune conditions, labyrinthine membrane rupture, viral infection and psychosomatic disorders are all contenders as potential causes, but often, it is labeled as idiopathic. The exact mechanism is not fully understood. However, there are a few theories that researchers [39] have proposed to explain this potential link: sildenafil, promoting the congestion of nasal erectile tissue, causes an increases of middle ear pressure, as well as concerns that PDE5is work by blocking cGMP breakdown and their buildup induces gene expression through transcription factor protein phosphorylation by specific kinases, which have been associated with damage to the hair cells of the cochlea.

4. Discussion

Currently, there is unanimous consensus that ED may be successfully treated but cannot be cured with current treatment options (EAU Guidelines 2024). The first-line treatment for ED is phosphodiesterase-5 inhibitors, and sildenafil is the most efficient drug with the most clinical experience and the strongest and most solid scientific evidence since its launch. Dose tailoring is advised, and it is important to know how new therapeutic alternatives are assessed and the profiles of patients susceptible to their use. While ED drugs work in similar ways, they are each made up of different chemicals and different formulations. An oral suspension prevents the patient from being able to crush a tablet or cut an oral film, altering the pharmaceutical form and determining the alteration of the concentration and speed of absorption; in these conditions, underdosing can almost always occur, and, more rarely in others, an overdose. Healthcare professionals are required to improve their knowledge of the use of PDE5is and their formulations because men who have previously failed with sildenafil can become successful with reeducation, dose escalation and a different intake strategy. Scheduling follow-up visits at regular intervals is useful to assess treatment progress. This is essential for the best possible treatment outcome, especially if concomitant diseases are present that could worsen over time, possibly affecting treatment efficacy. Changing the application method by moving from an on-demand strategy to a bedtime strategy may improve the efficacy of therapy. It is also useful to discuss side effects with patients, ensuring that taking sildenafil for a long time is safe. It is known that discontinuation of treatment due to side effects is possible. Healthcare professionals should remember that the most common side effects of sildenafil are headache, hot flashes and dyspepsia. Less commonly and transient, nasal congestion, bluish vision, blurred vision or tenderness to light activity may occur. Sildenafil is not yet approved for the treatment of sexual dysfunction disorders in women. The use in women with sexual dysfunction has arisen from the demonstration that phosphodiesterase type 5 is present in vaginal, clitoral and labial smooth muscles. This would suggest that PDE5 is involved in female sexual functions, particularly genital arousal. Although it can be prescribed off-label, studies on its effectiveness in the female population have had mixed results. In off-label use and in some studies reporting "recreational" use in couples, sildenafil increased blood flow to the genitals' arousal and orgasmic function (indirectly determining an augmented sensitivity). The taking of sildenafil by both partners, in the form of an oral suspension, could be more practical in order to improve a couple's interaction. This would smooth out what it means for each partner to use a medical intervention to restore sexual intercourse and improve the quality of the nonsexual relationship and could bring about new, unconventional patterns of sexual arousal in the male. If we consider males suffering from LUTS/BPH and who also have erectile dysfunction, we know that sildenafil can be a valid alternative to other therapies. Its short duration of action may be more appropriate than long-acting drugs for some particular components of LUTS, such as nocturia. It is one of the most bothersome symptoms of LUTS and is particularly common in men over 70. We know, therefore, how taking sildenafil with the bedtime strategy can lead to two associated positive effects: improving urinary symptoms and improving oxygenation of the corpora cavernosa during the night.

5. Conclusions and Future Perspectives

The treatment of patients affected by sexual disfunctions should be based on patients' and their sexual partners' perspectives [40]. Moreover, in this context, the role of the drug administration route and pharmacological formulation should be taken into account. After more than 25 years, sildenafil has transformed from being a drug for erectile dysfunction to having many other faces. The possibility of taking it in the form of an oral suspension increases compliance, practicality and therapeutic tailoring. The oral suspension has the ability to dissolve more quickly than solid oral dose forms and therefore absorb pharmaceuticals more quickly and is more stable than solutions [16]. New clinical trials involving patients' sexual partners should be planned in order to understand these aspects in depth and improve ED treatment outcomes.

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