INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Erectile Dysfunction***
-November 2022-

Background:

The Indian Health Service National Pharmacy and Therapeutics Committee (NPTC) provided a drug class review of phosphodiesterase 5 inhibitors (PDE5i) for Erectile Dysfunction (ED) in August 2018 and as a result, the NPTC added "any PDE5i" to the National Core Formulary (NCF) at that time. Since that review, tadalafil has become available as a generic drug along with sildenafil. A new review of ED agents was performed at the Fall 2022 NPTC meeting and following the clinical review and analysis, the NPTC voted to **remove the designation of "any PDE5 inhibitor"** and **add both (1) sildenafil and (2) tadalafil** to the NCF.

Discussion:

Male sexual dysfunction consists of erectile dysfunction, diminished libido and ejaculatory disorders. Erectile dysfunction is the inability to acquire or maintain an erection of sufficient rigidity and duration for sexual intercourse. While it is present in young men, it emerges as a common problem for men in their 40s and increases with advancing age. An estimated 30 million men in the United States and 150 million men worldwide have some degree of ED.[1] ED etiologies are generally broken down into six categories: vascular, neurogenic, local penile factors, hormonal, drug induced, and psychogenic. ED etiology is most frequently multi-factorial. The best predictors for ED include age, cardiovascular disease (CVD), diabetes mellitus, hypertension, obesity, dyslipidemia, depression, hypogonadism, smoking, and medication use.[2] While no specific studies detail ED prevalence in the American Indian/Alaska Native (AI/AN) male population, given the high incidence of the listed risk factors above, it can be assumed that ED is a proportionately significant problem for this group of men.

An ED evaluation should consist of a medical, psychosocial and sexual history that includes a validated sexual assessment tool (e.g., the International Index of Erectile Function [IIEF]) and a physical exam to rule out penile abnormalities and other possible causes for ED. Laboratory studies include a glycated hemoglobin, a lipid panel and a morning testosterone level, plus additional tests as clinically indicated. Lower urinary tract symptoms (LUTS) due to benign prostatic hypertrophy (BPH) are present in up to 72% of men with ED. Medications such as SSRIs, thiazides and antiandrogens are frequently implicated. Most patients benefit from a combination of disease/lifestyle modification, psychological or sexual counseling, and treatment with medications. ED is considered a sentinel marker for occult CVD and may precede a male's first CVD event by 5 years.

The American Urological Association (AUA) ED guidelines include PDE5i as an initial drug treatment option. The AUA encourages discussion of all other interventions at the onset of treatment and to include the partner along with the patient in treatment decisions. The Princeton Consensus III[3] recommendations offer guidance for patients needing cardiac evaluation prior to starting PDE5i medication. Men who have no known cardiac disease and are able to exercise with no to minimal cardiac symptoms, cardiac disease with successful revascularization, controlled asymptomatic hypertension, low grade heart failure (NYHA Class I and II), and mild cardiac valve disease are at low risk and can be treated for ED without a cardiology evaluation. All others require an evaluation before starting treatment. The FDA approved non-PDE5i treatments include intracavernosal injections (ICI) with alprostadil, intraurethral alprostadil, vacuum erection devices, and penile prostheses. Treatments with alprostadil must be initiated in an office setting.

There are four FDA approved PDE5i: sildenafil (Viagra®), tadalafil (Cialis®), vardenafil (Levitra®, Staxyn®), and avanafil (Stendra®) which have similarly high rates of successful sexual intercourse (68 to 69 percent compared with 33 to 35 percent for placebo) and similar side-effect profiles.[4] Treatment decisions are based on patient preference with attention to ease of use, duration of action and adverse events. Sildenafil, vardenafil, and tadalafil should be taken 60 minutes before sexual activity. Avanafil and the orally disintegrating tablet (ODT) form of vardenafil (Staxyn®) are more rapid acting and can be taken 30 minutes before sexual activity. Duration of action for sildenafil, vardenafil, and avanafil is up to four to five hours and tadalafil is effective for up to 36 hours after dosing. Daily, low-dose tadalafil administration eliminates the concern about onset and duration of action. Sildenafil and vardenafil must be taken on an empty stomach (high-fat meals and alcohol delay absorption). Food does not interfere with absorption of tadalafil, and has a minimal effect on avanafil or ODT vardenafil. PDE5i are contraindicated in patients taking nitrates (any form or frequency). Common adverse effects include headaches, flushing, dyspepsia, nasal congestion or runny nose, and visual changes. Sildenafil can cause reversible "blue vision" and tadalafil is more commonly associated with back pain and myalgia. Nonarteritic anterior ischemic optic neuropathy causing sudden unilateral vision loss, and sudden unilateral hearing loss, are rare reported events. Patients should be advised of these risks along with the small risk of priapism.

Studies reveal discontinuation rates for ED treatments range from 4 to 76% for PDE5i compared to 18 to 79% for intracavernosal injections, 32 to 69% for urethral suppositories, and penile prosthesis rates of 30%, generally due to device complications or loss of libido. Barriers are treatment ineffectiveness (30 to 35%), side effects, quality of men's intimate relationships, and treatment costs. The most important treatment enabler is reporting side effects to the provider, which emphasizes the importance of close follow up after initiating therapy.[5]

Numerous studies compare PDE5i medications to placebo, but quality head-to-head medication studies are lacking. An overview of systematic reviews examining PDE5i medications published in 2021 included 563 primary studies with 154,796 participants. It looked at changes in the general population using the erectile function questionnaire, IIEF or the short form version IIEF-5[6]. The review also evaluated specific group changes in erectile function and adverse events and dropouts in both the general population and specific groups such as diabetics. Three prior network meta-analyses included in this review had made the following conclusions. Yuan et al. (2013) suggested tadalafil was most effective followed by vardenafil, when all available dosages of the individual PDE5Is were combined.[7] Chen et al. (2015) found sildenafil 50mg followed by sildenafil 100mg were best when compared to placebo[8], and Madeira et al. (2021) found sildenafil 25mg appeared statistically superior to all interventions in improved IIEF versus placebo (WMD: 13.08, 95% CI: 10.1-16.06), but only 2 randomized control trials were available.[9] Pyrgidis et al. (2021) determined sildenafil 50mg and 100mg were most effective in the general population compared to other PDE5i (predominantly by indirect comparison). When looking at specific groups, all PDE5i are superior to placebo. In patients with diabetes, vardenafil and sildenafil on-demand display the highest efficacy. Psychogenic ED appears equally responsive to PDE5i monotherapy versus psychological interventions. Patients with hypogonadism and ED have improved erectile function with the addition of testosterone to PDE5i therapy. On-demand sildenafil 50mg or 100mg, and tadalafil 5mg daily have safe and effective profiles. Daily low dose tadalafil appears better than high dose, on-demand tadalafil. Daily tadalafil and on-demand sildenafil may be more effective with severe ED.

Findings:

ED is a common disease likely affecting many AI/AN males based on the high prevalence of risk factors for this condition such as CVD, diabetes, hypertension and hyperlipidemia. Any person diagnosed with ED needs an assessment for possible CVD prior to initiating treatment. PDE5i are a first line treatment that are frequently prescribed by primary care providers due to their relative safety and effectiveness when administered appropriately. Current systematic reviews and meta-analyses suggest that sildenafil prescribed for on-demand use in the 25-50mg dose range is effective and has a very low adverse event profile. Daily treatment with lower dose tadalafil appears better than on-demand higher dose tadalafil and courtesy of its longer half-life, may be a more appropriate alternative for men willing to take a medication daily. In addition, for men with BPH in addition to ED, this may provide a single drug treatment for both conditions. Short-term follow up for all patients initiated on PDE5i is necessary to ensure adequate treatment of ED, with appropriate medication titration and monitoring for potential adverse events. Based on current literature, agency prescribing patterns, and the desire to have both on-demand and daily PDE5i treatment options available for our patients, the NPTC voted to remove "any PDE5i" and add both sildenafil and tadalafil to the NCF.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov . For more information about the NPTC, please visit the NPTC website.

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