Clinical and preclinical treatment of urologic diseases with phosphodiesterase isoenzymes 5 inhibitors: an update

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Phosphodiesterase isoenzymes 5 inhibitors (PDE5-Is) are the first-line therapy for erectile dysfunction (ED). The constant discoveries of nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) cell-signaling pathway for smooth muscle (SM) control in other urogenital tracts (UGTs) make PDE5-Is promising pharmacologic agents against other benign urological diseases. This article reviews the literature and contains some previously unpublished data about characterizations and activities of PDE5 and its inhibitors in treating urological disorders. Scientific discoveries have improved our understanding of cell-signaling pathway in NO/cGMP-mediated SM relaxation in UGTs. Moreover, the clinical applications of PDE5-Is have been widely recognized. On-demand PDE5-Is are efficacious for most cases of ED, while daily-dosing and combination with testosterone are recommended for refractory cases. Soluble guanylate cyclase (sGC) stimulators also have promising role in the management of severe ED conditions. PDE5-Is are also the first rehabilitation strategy for postoperation or postradiotherapy ED for prostate cancer patients. PDE5-Is, especially combined with α-adrenoceptor antagonists, are very effective for benign prostatic hyperplasia (BPH) except on maximum urinary flow rate (Q\text{max}) with tadalafil recently proved for BPH with/without ED. Furthermore, PDE5-Is are currently under various phases of clinical or preclinical researches with promising potential for other urinary and genital illnesses, such as priapism, premature ejaculation, urinary tract calculi, overactive bladder, Peyronie's disease, and female sexual dysfunction. Inhibition of PDE5 is expected to be an effective strategy in treating benign urological diseases. However, further clinical studies and basic researches investigating mechanisms of PDE5-Is in disorders of UGTs are required.

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INTRODUCTION

The cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) are important second messengers that play a central role in signal transduction and regulation of physiologic responses, such as smooth muscle (SM) contraction and relaxation, blood pressure control, neurotransmission, platelet aggregation, and disaggregation.1,2 cAMP and cGMP are degraded by phosphodiesterase (PDE) isoenzymes, a heterogeneous group of hydrolytic enzymes. Today, 11 different PDE families have been identified with each family typically having several different isoforms and splice variants. Some types of PDE are specific for either cAMP or cGMP, and some degrade both. PDE11, for example, degrades both cAMP and cGMP, whereas PDE4 is specific for cAMP, and PDE5 is specific for cGMP.1 Importantly, some PDE isoenzymes have been proven to be of pharmacological relevance with PDE5 inhibitors (PDE5-Is) widely studied and used. Sildenafil citrate was the first effective oral treatment for erectile dysfunction (ED). Its advent marked the milestone in the ED history.2 Until now, there are six oral PDE5-Is commercially available, which are sildenafil (Viagra; Pfizer, New York, USA), vardenafil (Levitra, Staxyn; Bayer, West Haven, CT, USA), tadalafil (Cialis; Lilly, Indianapolis, USA), avanafil (Stendra; VIVUS Inc., CA, USA), udenafil (Zydena; Dong-A PharmTech, South Korea), and mirodenafil (Mvix; SK Chemical, South Korea) with mirodenafil and udenafil, and are only approved in Korea.3,4 There are still several PDE5-Is under development, including JNJ-10280205, JNJ-10287069, lodenafil, and SLx-2101 with the purpose of offering safer and more effective options for ED suffers. All six PDE5-Is have an appropriate onset of action, duration and a success rate at least 65% for ED (Table 1) and newly developed compounds may contain certain advantages over sildenafil, such as higher selectivity for PDE5 compared with other isozymes, faster onset, longer duration of effect, and absence of food effect on absorption, which consequently, allowing more flexibility in sexual activity.3,4 Besides corpus cavernosum (CC), PDE5 is also expressed in urinary tract and mediated relaxation of related SM. Inhibition of this enzyme would have a clinical benefit in the management of many benign urological diseases other than ED, such as lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH), priapism, premature ejaculation (PE), urinary tract

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Erectile dysfunctions are common in men and can have a significant impact on their quality of life. Some of the most common causes of erectile dysfunction include cardiovascular disease, diabetes, and neurological disorders. In some cases, the treatment of the underlying cause can improve erectile function. In other cases, medications such as phosphodiesterase type 5 (PDE5) inhibitors can be effective in improving erectile function.

Phosphodiesterase type 5 inhibitors are the first-line therapy for erectile dysfunction. They work by inhibiting the degradation of cyclic guanosine monophosphate (cGMP) and increasing the levels of cGMP in the corpora cavernosa, leading to relaxation of smooth muscle and increased blood flow to the penis. There are several PDE5 inhibitors available, including sildenafil, vardenafil, tadalafil, and avanafil. Each of these medications has different dosing regimens and side effects.

Table 1: Characteristics of commercially available phosphodiesterase type 5 inhibitors

| PDE5 Inhibitor | Dosage (mg) | Time to maximum plasma concentration (Tmax, min) | Efficacy (Tmax, h) | Side-effects | Food and alcohol interaction |
|---------------|-------------|-----------------------------------------------|-------------------|--------------|------------------------------|
| Sildenafil    | 25, 50, and 100 | 30–60                                       | >65               | Headache, flushing, and dyspepsia | Interacts with food. No alcohol interaction |
| Vardenafil   | 2.5, 5, 10, and 20 | 30–60                                       | >65               | Flushing, back pain, and general maligya | As for sildenafil |
| Tadalafil    | 50, 100, 200 daily | 60–90                                       | >65               | Flushing, nasal congestion, ocular hyperemia, and headache | No food or alcohol interaction |
| Mirodenafil  | 50, 100, 200 daily | 75                                           | >65               | Flushing, headache, nausea, and eye redness | No food or alcohol interaction |
| Avanafil     | 2.5, 5, 10, and 20 | 30–45                                       | >65               | Headache, flushing, nasal congestion, nasopharyngitis, and back pain | Interacts with food |

Other treatment options for erectile dysfunction include penile rehabilitation, which involves exercises to strengthen the erectile tissues. Other options include vacuum constriction devices (VCDs), neuromodulatory therapy, and a combination of these treatments. Some men may also benefit from psychological counseling or medication to help with anxiety or depression.

In conclusion, erectile dysfunction is a common and treatable condition. Treatment options include PDE5 inhibitors, penile rehabilitation, and other medical and psychological treatments. Patients should work with their healthcare provider to find the best treatment plan for their individual needs.
Post radical prostatectomy

In different trials, the response rate to sildenafil treatment ranged from 50% to 75% among patients underwent nerve-sparing surgery. An RCT conducted in Europe and the USA showed that 71% of the patients treated with tadalafil 20 mg had an improvement of their EF after bilateral NSRP, compared to 24% of that in placebo group. Also, patients taking tadalafil had 52% rate of successful intercourse attempts, which was significantly higher than the 26% rate obtained with placebo. Results from another RCT with PCa men who underwent NSRP at 50 international centers showed that both daily tadalafil and on-demand tadalafil could improve post-NSRP ED, with daily dosing more effective in ameliorating EF, maintaining penile length and protecting against structural changes due to neuropaxia. However, the unassisted erection was not enhanced during drug-free washout period. However, another study reported that men using vardenafil on a regular rehabilitation schedule showed no better effect than men who used PDE5-Is on-demand. This contrasting result could be attributed to the different pharmacokinetic characteristics of these two PDE-Is. The half-life time of tadalafil is approximately 4-fold longer than vardenafil, which may contribute to the better effectiveness of tadalafil on penile rehabilitation. Many factors influence the severity of postoperative ED and rehabilitative efficacy of PDE5-Is, including patient age, tumor stage, preoperative potency, length of time following surgery, surgical types, and the experience of surgeon. The integrity of cavernosal nerve after surgery is also extremely important since PDE5-Is improve EF depending on the peripheral release of NO from cavernosal nerve terminals. Controversies still exist in a number of other clinical trials on the rehabilitative efficacy of PDE5-Is. The meta-analysis from Candy et al. showed oral PDE5-Is were effective in the medium term (up to 4 months) when used to treat ED subsequent to EBRT and bilateral or unilateral NSRP for PCa. However, no significant differences were found in their comparisons of the PDE5-Is dose, or between patients with unilateral and bilateral NSRP. They attributed these observations to too few patients in each subgroup. Recently, we performed a meta-analysis and confirmed the efficacy and safety of PDE5-Is in treating post bilateral NSRP ED in subjects suffering PCa. In our subgroup comparisons, there was a trend that higher dose, longer course of treatment, on-demand dosing and sildenafil were associated with more efficacy of PDE5-Is, but these trends were not sufficient to demonstrate statistical differences. The lack of statistical significance could also be accounted for insufficient patient numbers in the trials included.

Post radiotherapy

Besides surgical treatment, radiotherapy that includes EBRT and brachytherapy is common treatment modalities. Even with brachytherapy, the irradiation affects only a very precise and localized area, 24%–50% of the patients complained ED according to different literature. A double-blind, placebo-controlled, cross-over study confirmed the efficacy and safety of tadalafil in treating three-dimensional conformal external beam radiotherapy (3D-CRT) induced ED. Similar effect was observed for brachytherapy. An open-label, nonrandomized study showed that brachytherapy induced ED is as amenable to sildenafil treatment as ED from other causes. However, as far as the short-term follow-up and limited patients involved, more large-scale and long-term clinical trials should be done to further clarify the efficiency and safety of PDE5-Is in treating radiotherapy-related ED.

In general, early penile rehabilitation can increase the arterial flow and tissue oxygenation that interrupt the gradual apoptotic loss of corpus cavernosum smooth muscle (CCSM) and endothelial cell. However, the advantage of PDE5-Is over placebo in these clinical data may not reflect the real rehabilitative effect of PDE5-Is, as the majority of patients after post-PCa treatment experience severe ED. The efficacy of PDE5-Is in this population would not be expected to be high as in the general ED subjects. In Brock’s study, only 28% severe ED patients had successful intercourse at the end of treatment. As for providing sound practical advice for the use of PDE5-Is for post PCa-treatment ED, such as when to initiate, what dosage, duration of treatment, selection criteria, and which drug is most efficacious, more clinical trials are required.

Combined therapy

PDE5-Is plus testosterone

Despite the efficiency of PDE5-Is, 30%–35% of the patients do not respond to PDE5-Is alone. Given the important role of testosterone (T) in the sexual activity and decreased plasma level of T in unresponsive subjects, interest in T plus PDE5-Is therapy has increased in recent years. SM cell degeneration (apoptosis), adipose tissue and collagen fibers deposition in CC, and reduced expression of eNOS and neural nitric oxide synthase (nNOS) were confirmed in hypogonadism subjects by previous studies. Upregulation of Ccsm contractility was also found in castrated or diabetic animal models. Also, we and others found that PDE5 in CC is T-dependent, which has an important clinical significance: when the unresponsiveness to PDE5-Is in an ED subject happens, androgen deficiency should be considered, and supplement of T may be an effective solution. Indeed, a lot of clinical trials have demonstrated that T replacement therapy (TRT) can improve EF and the response to PDE5-Is in patients with ED and hypogonadism. Furthermore, other studies have confirmed the beneficial effects of combination therapy in patients with comorbid conditions, like type II diabetes and obesity. During clinical practice, all patients with ED should be evaluated for T levels before any therapy. If hypogonadism can be diagnosed, TRT should be prescribed first. Many patients may achieve successful erection with TRT alone. Moreover, other disorders related to hypogonadism, such as osteoporosis, dyslipidemia, obesity, and cardiovascular mortality, could be benefited from TRT. If necessary, PDE5-Is could be added for patients whose hypogonadism is resolved but ED remains. However, sometimes blood T level is not low enough for the diagnosis of hypogonadism and determination of bioactive T level is not available. For those ED sufferers, EF should be restored with PDE5-Is first, and TRT could be combined when PDE5-Is alone is ineffective.

Soluble guanylate cyclase (sGC) stimulators/activators plus PDE5-Is

In addition to PDE5-Is, soluble guanylate cyclase (sGC) stimulators and sGC activators have been developed to target sGC directly and increase cGMP formation. sGC stimulators, such as BAY 60-4552, can bind to sGC and enhance the catalytic activity of sGC to increase cGMP formation NO-independently. With using a cavernous nerve crush induced ED rat model, Oudot et al. showed the combination of intravenous injection of BAY 60-4552 and vardenafil produced synergistic beneficial effects on the erectile response to cavernosal nerve stimulation. In the situation of the failure of sGC stimulators, the sGC activator, such as BAY 60-2770 can be helpful. Unlike sGC stimulators, the sGC activators increase the catalytic activity of sGC directly when the enzyme is inactivated. In a rat model treated with 1H[1,2,4]oxadiazolo-[4,3-a] quinoxalin-1-one (ODQ), which inhibited sGC and made it insensitive to NO, the intracavernosal pressure (ICP) rise in response to intracavernosal injection of BAY 60-2770 were enhanced significantly while this ICP increase induced
by intracavernosal injection of the sGC stimulator BAY 41-8543 or NO-donor were not found.62,63 These data suggest that sGC stimulators will potentially be useful when NO is inactivated, while sGC activators can be used as a salvage therapy when sGC is inactivated or oxidized and not responsive to NO or sGC stimulators. The combination of these agents with PDE5-Is would have a promising future in the management of severe ED conditions. A clinical trial on the treatment of ED using a combination of the sGC stimulator BAY 60-4552 and vardenafil has been completed by Bayer HealthCare, but the results are still not published.

**Benign Prostatic Hyperplasia**

Current oral therapies recommended by guidelines include α-adrenoceptor antagonists (α-blockers, ABs), 5α-reductase inhibitors (5ARIs), muscarinic receptor antagonists (MRAs) and a "new emerging treatment" PDE5-Is.64,65 Recently, numerous clinical trials have investigated the efficacy of PDE5-Is for LUTS/BPH, while tadalafil was licensed in the USA and in European Union for treating LUTS/BPH with or without ED.64,65 Recent studies suggested the potential significance of the NO/cGMP and adenylyl cyclase (AC)/cAMP pathway in the control of prostate SM.66,67 The presence of PDE5 in prostate has been confirmed by Ückert et al but controversy exists regarding the precise location of PDE5 within prostate.68,69 We most recently showed that PDE5 distributed mainly in fibromuscular stroma cell as well as in endothelial and SM cells of blood vessels both in rat and human prostate (Figure 1, Zhang et al, unpublished data). Differences in the polyclonal antibodies and tissue source employed could explain the disparity. Using organ bath technique, we and others showed that exposure of isolated rat or human prostatic tissue to PDE5-Is could produce a relaxation of the precontracted prostatic strips.70–72 These preclinical studies support the use of inhibitors of PDE5 for treating LUTS/BPH.

**Clinical evidence**

The first clinical trial was conducted by Sairam et al in 2002 with sildenafil for treating LUTS/BPH/ED patients. After 3 months of treatment, there was a significant inverse relationship between international prostate symptom score (IPSS) and IIEF score suggesting that sildenafil both improved LUTS and ED. Since then, the effects of PDE5-Is on LUTS/BPH were extensively investigated, especially tadalafil, a long-acting PDE5-Is. Different doses of tadalafil (2.5, 5, 10, and 20 mg per day) have been evaluated in many high-quality RCTs, 5 mg and higher doses can relieve LUTS symptoms significantly. However, only tadalafil 5 mg once daily has been licensed for the treatment of LUTS with or without ED which was probably due to unnecessary higher dose will increase economic burden and potential drug-related side effects.73–78 The majority of the studies demonstrated that PDE5-Is alone were efficacious on decreasing IPSS total score, storage subscore, and voiding subscore except on maximum urinary flow rate ($Q_{\text{max}}$). One RCT even showed that LUTS/BPH patients with daily tadalafil (5 mg) treatment had greater treatment satisfaction compared with daily tamsulosin (0.4 mg) therapy or placebo.79 We recently performed a systematic review and network meta-analysis including 64 RCTs with 28,196 participants comparing the effectiveness of different oral drug therapies for LUTS/BPH.80 As shown in Figure 2, our novel data showed that among all the drug treatments, PDE5-Is combined with ABs ranked highest in efficacy for decreasing the IPSS total score, storage subscore, and voiding subscore. ABs combined with 5ARIs ranked highest in efficacy for increasing of $Q_{\text{max}}$. ABs plus MRAs showed great effectiveness on improving storage symptoms. PDE5-Is alone also showed promising effect except on $Q_{\text{max}}$. The results suggest combination therapies, especially ABs plus PDE5-Is, have the greatest efficacy for treatment of LUTS/BPH, which is the optimal approach for difficult-to-treat cases, especially for those who are reluctant to surgical procedures. In 2012, Gacci et al. conducted an extensive pair-wise meta-analysis on the use of PDE5-Is alone or in combination with ABs for the treatment of LUTS/BPH. They indicated that PDE5-Is could significantly improve LUTS and be a promising treatment for this disorder, although they were ineffective on $Q_{\text{max}}$ either.81 Gacci et al. explained that PDE5-Is concomitant relaxation of the detrusor muscle may counteract the relaxation of the prostate and bladder neck. However, for detrusor SM, the role of PDE5-Is may not just be limited to relaxation and the mechanism remains to be fully clarified.82–84 Also, the combination of tadalafil and 5ARIs is an attractive approach for the management of LUTS/BPH, especially for patients have large volume prostate. Casabe et al. conducted a large-scale, randomized, double-blind study to evaluate this approach and reported that coadministration of tadalafil and finasteride achieved early amelioration of LUTS as well as an improvement EF.85

**Preclinical studies**

The potential mechanisms of PDE5-Is in treating LUTS/BPH are multifactorial and not as ABs, which reducing urethral resistance

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**Figure 1:** Phosphodiesterase type 5 (PDE5) expression and immunolocalization in rat and human tissues. Left: The rat prostatic gland section shows the main PDE5 immunostaining in fibromuscular stroma (black arrows) as well as in the endothelial and smooth muscle cells of blood vessels (black triangle). Right: Cy3-immunofluorescence (red) indicating the presence of PDE5 was abundantly observed in the fibromuscular stroma in human prostate. DAPI (blue) indicates nuclear staining.

**Figure 2:** Cumulative probabilities of different kinds of oral drug therapies as measured by the included outcomes. The Bayesian approach could apply the rank probabilities of each drug therapy and the cumulative probability sum the rank probabilities to give an overall probability. Larger cumulative probability represents the better effect on the improvement of IPSS total score, $Q_{\text{max}}$, IPSS storage subscore, IPSS voiding score and QoL, which also represent the rank of the drug therapies. ABs: α-blockers; 5ARIs: 5α-reductase inhibitors; MRAs: muscarinic receptor antagonists; PDE5-Is: phosphodiesterase 5 inhibitors (Credited to Wang et al.80).
PDE5 inhibitors in urology
WH Zhang and XH Zhang

The plausible mechanisms of PDE5-Is in treating LUTS/BPH. This schematic depicts the possible mechanisms that PDE5-Is treat LUTS/BPH. PDE5-Is: phosphodiesterase 5 inhibitors; LUTS: lower urinary tract symptoms; BPH: benign prostatic hyperplasia.

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by attenuating the tension of SM fibers. Besides the expression and functional activity of PDE5 in bladder, urethra, and prostate. Morelli et al. revealed that human vesicular-deferential artery (provides blood flow to prostate and bladder) and rat iliac artery (provides blood supply to the prostate) expressed high levels of active PDE5 and found that tadalafil increased prostate tissue oxygenation in spontaneously hypertensive rat through detecting the immunosignal of hypoxia markers. However, the increase of prostate blood flow was not confirmed by an RCT that daily tadalafil (5 mg) was used 8 weeks for LUTS/BPH patients. This ineffectiveness may ascribe to low baseline blood flow in prostate and insufficient sensitivity of techniques. In addition, they also found that in vitro treatment with tadalafil or vardenafil on human myofibroblast prostatic cells reduced interleukin 8 (IL-8) secretion induced by either tumor necrosis factor α (TNF-α) or metabolic factors, which indicated that PDE5-Is could blunt intraprostatic inflammation. Also, Fibbi et al. showed that vardenafil enhanced dose-dependent antiproliferation induced by SNP (NO donor) and BAY 41-8543 (sGC stimulator) in prostatic SM cell. Finally, Minagawa et al. showed that systemic administration of tadalafil reduced mechanosensitive afferent activities of both A-δ- and C-fibres elicited by bladder distension in the rat. Recently, men with LUTS/BPH were involved in an RCT assessing IPSS and Qmax, who were randomized to either placebo (n = 172) or tadalafil (5 mg; n = 171) or tamsulosin (0.4 mg n = 168). Subjects who took tadalafil and tamsulosin showed significant improvement in IPSS and Qmax versus placebo after 12 weeks of treatment. This international study showed that tadalafil 5 mg once daily for 12 weeks had the same effect with tamsulosin 0.4 mg once daily in treating men with LUTS/BPH. Similar result was found in another RCT accessing the efficacy and safety of daily tadalafil (10 mg), daily tamsulosin (0.4 mg) and combination in treating LUTS/BPH. The significant improvement in Qmax with tadalafil in these studies contrast with the majority of previous studies on PDE5-Is for LUTS/BPH. The authors attributed this increase of Qmax, possibly due to lower baseline Qmax in the treatment group compared with previous tadalafil studies, which could allow more room for improvement. Another multicenter, well-designed clinical trial assessing the effect of UK-369,003 (a PDE5-1) on LUTS/BPH patients found the same change of Qmax, and high selectivity of this drug compared with other PDE5-Is could be a possible explanation for the significant increase of Qmax. Indeed, the effect of PDE5-Is on Qmax remains controversial.

In summary, as shown in Figure 3, the plausible mechanisms of PDE5-Is in treating LUTS/BPH may be: (1) slight-to-moderate relaxation of muscle tone in prostate and bladder; (2) significant dilation of local blood vessels which provide adequate blood; (3) significant augmentation of oxygen perfusion to local organs; (4) inhibition of afferent nerve activity of bladder; (5) bluntness of intraprostatic inflammation; and (6) antiproliferation in prostate.

PRIAPISM
Among men with sickle cell disease, the prevalence of priapism is more than 40%. This disorder is poorly understood from a pathophysio metric standpoint, and thus effective treatments are still lacking. Recently, we established a novel, rat priapism model induced by intracavernous injection of myosin specific inhibitor blebbistatin. At various time point of 2 h, 4 h, 4-day, and 7-day prolonged erection, the major contractile and relaxant molecules were determined in CC. Importantly, this model showed CC contractile molecules including PDE5 upregulated, and relaxation molecules downregulated with ICP reversible in the early compensated stage while these pathways were opposite (contraction decrease and relaxation increase, ICP irreversible) in the later decompensated stage with eventual severe fibrosis and atrophy. Champion et al. also demonstrated that the disturbance of NO/cGMP pathway mediating penile erection plays an important role in priapism. This dysregulation specifically involves the decreased expression of PDE5 in CC. The excessive amount of cGMP accounts for the prolonged erectile tissue relaxation that manifests as priapism. This discovery makes PDE5 a novel molecular target for treatment. Burnett et al. reported serial clinical trials that long-term, low-dose sildenafil or tadalafil treatment reduced the frequency and duration of disordered erection in men with recurrent priapism. In these trials, the initial dose of sildenafil was 25 mg daily with escalation up to 50 mg daily, and doses of tadalafil at 5–10 mg 3 times a week. Only one patient with severe recurrent episodes did not respond to treatment. The findings are encouraging and support the useful role of PDE5-Is against mild or moderate priapism. They hypothesized that continuous, long-term, low-dose PDE5-Is treatment may achieve an upregulation of PDE5 gene (although reversible) and reset the PDE5 expression in penile tissue, which would control the excessive cGMP signaling associated with priapism. Recently, Burnett et al. conducted the first double-blind, placebo-controlled RCT including 13 patients to assess the efficacy and safety of sildenafil in prevention of recurrent ischemic priapism associated with sickle cell disease. Although no significant difference was found between sildenafil and placebo at the end of phase 1 study, a reduction in priapism episodes was observed in the majority of patients participating in the open-label phase. Also, an overall 4-fold fewer priapism-related hospital visits occurred among patients adherent to therapy than those who were nonadherent or receiving placebo. These results suggested a beneficial role of PDE5-Is in the management of priapism. It should be noted that PDE5-Is therapy should be started when the penis is in its flaccid state and not during an acute episode. Current use of PDE5-Is for treatment of recurrent priapism is contraindicated by the labeled indications and multicenter, and placebo-controlled RCTs are underway to further evaluate the potential of PDE5-Is for this disorder.
PREMATURE EJACULATION

PE is another very common sexual disorder among males with a prevalence of 20%–30%. It is a multicomponent dysfunction, including anxiety, penile hypersensitivity, and serotonin receptor dysfunction. The treatment of PE has been primarily focused on behavioral therapy, topical anesthetics, and selective serotonin reuptake inhibitors (SSRIs). However, none of them is reliable. The importance of the NO/cGMP pathway in the control of the ejaculatory apparatus such as seminal vesicle (SV) and vas deferens (VD) has been previously reported. It was also reported that the adrenergic tension of isolated human SV strip was dose-dependently attenuated by the NO-donating compounds, PDE1-I, PDE4-I, and PDE5-I. Recently, several clinical trials have demonstrated PDE5-Is is effective in treating PE subjects. Seventeen clinical studies assessed PDE5-Is treatment as monotherapy or combination therapy with SSRI for PE were reviewed, among them, seven found that PDE5-Is was helpful for PE, whereas two did not. Five other studies demonstrated that the combined use of PDE5-Is and SSRI led to significantly improved results regarding intravaginal ejaculation latency time (IELT) and overall sexual satisfaction when compared with SSRI monotherapy. Sildenafil was the main PDE5 agent that was used at a usual dosage of 50 mg. Based on these studies, it seems that PDE5-Is are promising options against PE by mechanism of relaxing the SM of VD, SV, prostate, and prolonging the duration of erection and increasing confidence, finally overall sexual satisfaction. A meta-analysis conducted by Asimakopoulos et al. showed an overall positive effect for the use of PDE5-Is as monotherapy or as components of a combination regimen in the treatment of PE, however, considering the lack of a unique PE definition as well as the lack of appropriate endpoints for outcome evaluation of a placebo control arm, these results should be considered with caution. Overall, on-demand dapoxetine remains the first line therapy for PE populations as PDE5-Is are not approved medications. If coexisting PE and ED, combined therapy is preferred.

PEYRONIE'S DISEASE

One of the most efficient treatments for PD is the prevention of fibrosis. No satisfactory medical treatments for PD are currently available. However, recent studies have been demonstrated that the NO/cGMP system plays an important role in antifibrotic mechanism. Especially, the use of PDE5-Is as an antifibrotic modality has provided new insights into the management of PD. Ferrini et al. found long-term vardenafil treatment significantly decreased collagen I and III deposition and reduced the numbers of myofibroblasts in PD plaques in a rat model of PD. A RCT conducted by Ozturk et al. found that 50 mg sildenafil daily for 12 weeks could significantly reduce penile plaques. However, this first clinical study has a lot of limitations, such as small patient population, non-double-blind design, and short study duration. Despite the promising role of PDE5-Is in PD therapy, its utility may be restricted to the early stage since the progression of PD plaque to fibrosis and calcification cannot be hampered by PDE5-Is alone. More preclinical studies and clinical trials are needed.

OTHER DISEASES

Many basic investigations also support the use of PDE5-Is in treating other urogenital disorders, such as urinary tract calculi, OAB, and FSD although clinical data are still lacking. Stief et al. showed that ureteral tissue contained NO-containing nerves within the smooth musculature and suggested that ureteral relaxation may involve the NO/cGMP pathway. Regarding OAB, inhibition of PDE5 may also become an intriguing approach since both LUTS and urge urinary incontinence symptoms originate within the bladder and are characterized by detrusor overactivity. The occurrence and hydrolytic activity of PDE5 in human clitoral CC and vagina have been discovered, and it is expected that PDE5-Is may improve vaginal and clitoral blood flow and facilitate arousal and orgasm in women as the same mechanism of treating ED. However, the results pooled from clinical trials in which PDE5-Is were used against FSD were not encouraging, which probably due to the psychological influence in female sexual behavior. We believe PDE5-Is may have a promising potential in the management of this disease and more preclinical and clinical studies should be carried out.

CONCLUSION

On-demand PDE5-Is are efficacious for most cases of ED while daily dosing and combination with T are recommended for refractory cases. SGC stimulators also have promising role in the management of severe ED conditions. PDE5-Is are also the first rehabilitation strategy for postoperation or postradiotherapy ED for PCa patients. PDE5-Is, especially combined with ABs, are very effective for LUTS/BPH except on Qmax with tadalafil recently proved for BPH with/without ED in the USA and European Union. Furthermore, PDE5-Is are currently under various phases of clinical or preclinical researches with promising potential for other urinary and genital illnesses, such as priapism, PE, PD, urinary tract calculi, OAB, and FSD. The potential uses of PDE5-Is for indications outside the scope of sexual medicine are intriguing. However, further clinical studies and basic researches investigating mechanisms of PDE5-Is in disorders of UGTs are required.

COMPETING INTERESTS

All authors declared that they have no competing interests.

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