Phosphodiesterase (PDE) inhibitors in the treatment of lower urinary tract dysfunction

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Several disorders of the human upper and lower urinary tract, such as urinary stone disease, lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) and detrusor overactivity, can be therapeutically addressed by influencing the function of the smooth musculature of the ureter, prostate or urinary bladder, respectively. In order to ensure a drug effect without significant adverse events, a certain degree of tissue selectivity is mandatory. The treatment of said conditions aims to focus on orally available drugs acting via intracellular signalling pathways. Specifically, the cyclic nucleotide monophosphate cyclic GMP represents an important mediator in the control of the outflow region (bladder, urethra). The use of phosphodiesterase (PDE) inhibitors, such as sildenafil, tadalafil, vardenafil, avanafil or udenafil, known to restrain the degradation of the second messenger cyclic GMP, offers great opportunities in the treatment of lower urinary tract dysfunction. PDE inhibitors are regarded as efficacious, have a rapid onset of action and favourable effect-to-side-effect ratio. The role of PDE5 inhibitors in the treatment of BPH/LUTS and the overactive bladder has already been addressed in randomized, double-blind, placebo-controlled trials, as well as preliminary open-label studies enrolling either several hundreds or only 20 patients. The purpose of this review is to focus on the potential use and clinical significance of PDE inhibitors in the treatment of storage and voiding dysfunctions of the lower urinary tract. The strategy of modulating the activity of PDE isoenzymes might represent a novel approach in patients with lower urinary tract dysfunction (LUTD).

Introduction

Cyclic nucleotide monophosphates cyclic AMP (cAMP) and cyclic GMP (cGMP) are important endogenous mediators of several processes, including smooth muscle motility [1, 2]. Cyclic nucleotides are synthesized from the corresponding nucleoside triphosphates by the activity of adenyl and guanylyl cyclases. The increase in cAMP or cGMP triggers a signal transduction cascade encompassing the activation of cyclic nucleotide-dependent protein kinases (cAK, cGK), subsequent phosphorylation of the actin-myosin system, as well as Ca^{2+} channels and ATP-driven Ca^{2+} pumps located in the outer cell membrane or the membrane of the sarcoplasmic reticulum. This cascade leads to a reduction in cytosolic Ca^{2+} and, finally, to smooth muscle relaxation. Cyclic nucleotides are degraded by phosphodiesterase (PDE) isoenzymes, a heterogeneous group of hydrolytic enzymes. Phosphodiesterases are classified according to their preferences for cAMP or/and cGMP, kinetic parameters of cyclic nucleotide hydrolysis, sensitivity to the inhibition by various compounds, allos-

teric regulation by other molecules and chromatographic behaviour on anion exchange columns. Eleven families of PDE isoenzymes have been distinguished: Ca^{2+} /calmodulin-stimulated PDE (PDE1), cGMP-stimulated PDE (PDE2), cGMP-inhibited PDE (PDE3), cAMP-specific PDE (PDE4), cGMP-specific PDE (PDE5) and the cGMP-binding, cGMP-specific PDE of mammalian rods and cones (PDE6). While PDE7 (cAMP-high affinity) and PDE8 (IBMX-insensitive) have preferred selectivity for cAMP, PDE9 exclusively degrades cGMP. PDE isoenzymes 10 and 11 can inactivate both cAMP and cGMP. Some of these isoenzyme families consist of more than one gene and some genes are alternatively spliced so that more than 50 isoenzymes or variants have been identified. Some PDE genes are also variably expressed in different tissues [3, 4]. Since the distribution and functional significance of PDE isoenzymes can vary in different tissues, isoenzyme-selective inhibitors have the potential to exert specific effects on the target tissue. To date, six out of the 11 PDE isoenzymes have been proven to be of pharmacological importance: PDE1, PDE2, PDE3, PDE4, PDE5 and PDE11 (Table 1) [5].

Table 1

Overview on the phosphodiesterase (PDE) families currently known, their (preferred) substrate(s) (cyclic AMP and/or cyclic GMP), selective inhibitors and allosteric activators, as well as (potential) clinical indications for the use of isoenzyme-specific PDE inhibitors

PDE	Substrate	Selective inhibitor(s)	Activator(s)	(Potential) clinical indication(s)
PDE1	cAMP/cGMP	Vinpocetine, calmodulin-antagonists	Ca ²⁺ /calmodulin	Hypertension, cerebral arterial insufficiency, overactive bladder (OAB)
PDE2	cAMP (>>cGMP)	EHNA (MEP1)	cGMP	Diseases of the cardiovascular system
PDE3	cAMP (>>cGMP)	Enoximone, milrinone, amrinone, quazinone, cilostamide, cGMP, SK&F 94120, siguazodan		Cardiac insufficiency, <i>Asthma bronchiale</i> , <i>Claudicatio intermittens</i> , colon cancer
PDE4	cAMP (>>cGMP)	Rolipram, Ro 20-1724, roflumilast (RP 73401), zardaverine, etazolate, denbutylline (BRL 30982), SB 207499, TVX 2706, ZK 803616		Dementia in the elderly, Depression, <i>Asthma bronchiale</i> , colon cancer, chronic colitis, gut hypermotility disorders, COPD, BPH/LUTS, OAB, Urolithiasis, FSD/FSAD, premature ejaculation (PE)
PDE5	cGMP (>>cAMP)	Sildenafil(citrate), NCX 911 (=sildenafil nitrate), vardenafil, tadalafil, zaprinast, dipyrindamole, TA 1790 (avanafil), udenafil, lodenafil, MY 5445, E 4021		Erectile dysfunction (ED), Peyronie disease, vascular arterial thrombosis, pulmonary hypertension, Raynaud disease, BPH/LUTS, OAB, PE, FSD/FSAD
PDE6	cGMP (>>cAMP)			
PDE7	cAMP (>>cGMP)			
PDE8	cAMP (>>cGMP)			
PDE9	cGMP (>>cAMP)	BAY 73-6691, SCH 51866		Anti-diuretic effect, Alzheimer disease
PDE10	cAMP/cGMP			
PDE11	cAMP/cGMP	exisulind, tadalafil		Prostate carcinoma

BPH, benign prostatic hyperplasia; cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; COPD, chronic obstructive pulmonary disease; ED, male erectile dysfunction; FSD, female sexual dysfunction; FSAD, female sexual arousal disorder; LUTS, lower urinary tract symptoms (adapted, with permission, from [61]).

PDE inhibitors and lower urinary tract symptoms (LUTS) suggestive of benign prostatic hyperplasia (BPH) (BPH/LUTS)

Findings from basic research studies

Clinical data on the safety and efficacy of the orally active PDE5 inhibitors sildenafil (Viagra™), vardenafil (Levitra™) and tadalafil (Cialis™) for the treatment of male erectile dysfunction (ED) have boosted research activities on intracellular signal transduction pathways controlling the function of the lower urinary tract, including the prostate, urinary bladder (detrusor) and urethra [6, 7].

The expression of the cAMP and cGMP phosphodiesterase isoenzymes PDE1, PDE2, PDE4, PDE5, PDE7, PDE8,

PDE9 and PDE10 in the human prostate was shown by means of molecular biology methods (reverse transcriptase polymerase chain reaction). The activities of PDE4 and PDE5 were isolated using anion exchange chromatography from cytosolic supernatants prepared from tissue specimens taken from the transition zone of the prostate. PDE4 was also detected in the microsomal fraction of prostate tissue [8]. Later, immunohistochemistry revealed the distribution of PDE4 and PDE5 in stromal and glandular areas of the transition zone [9].

In organ bath studies, the tension of prostate strip preparations mediated via the activation of α_1 -adrenergic receptors was dose-dependently reversed by the PDE4 inhibitors rolipram, Ro 20-1724 and RP 73401, as well as the PDE5 inhibitors sildenafil, tadalafil and vardenafil. The

Table 2

Randomized, placebo-controlled clinical trials that investigated the efficacy of the phosphodiesterase type 5 (PDE5) inhibitors sildenafil, tadalafil or vardenafil in patients with lower urinary tract symptoms (LUTS)/benign prostatic hyperplasia (BPH)

Author(s)	Drug evaluated	Treatment period	Number of patients enrolled	Improvement in IPSS	Changes in $Q_{\max}$ or Q_{ave}	Change in PVR
McVary <i>et al.</i> (2007)*,†[20]	Sildenafil	3 months	369	‡	ns	ns
McVary <i>et al.</i> (2007)*[21]	Tadalafil	3 months	281	‡	ns	ns
Stief <i>et al.</i> (2008)*[24]	Vardenafil	2 months	222	‡	ns	ns
Roehrborn <i>et al.</i> (2008)*[22]	Tadalafil	3 months	1058	‡	ns	ns
Porst <i>et al.</i> (2009)*,†[23]	Tadalafil	3 months	581	‡	ns	+8.6 ml‡
Guyen <i>et al.</i> (2009)†[33]	Sildenafil	> 2 h (acute study)	68	NA	‡	na

*double-blind study protocol;

†study included patients with both BPH/LUTS and erectile dysfunction (ED);

‡significant when compared with placebo and/or baseline values ($P \leq 0.05$). ns, not significantly different from placebo and/or baseline values; IPSS, International Prostatic Symptom Score; na, not applicable (parameter was not evaluated); PVR, postvoid residual urine; Q_{ave} , average urine flow; $Q_{\max}$, flow at maximum detrusor pressure. All studies listed, except the one conducted by Guven *et al.* (2009) [33], represent evidence based medicine (EBM) level 1b

reversion of tension was accompanied by an enhancement in tissue cAMP or cGMP [8–10]. Interestingly, the contraction of isolated prostate tissue brought about by the vasoconstrictor peptide endothelin 1 (ET-1) was also counteracted by rolipram, tadalafil, sildenafil and vardenafil, with rolipram and tadalafil being most effective [11]. In experiments using a model of cultured human prostate smooth muscle cells, the number of cells showing constriction in response to ET-1 was significantly reduced by the non-specific PDE inhibitor theophylline, PDE5 inhibitor sildenafil and the adenylyl cyclase activator forskolin [12]. These results provided evidence for a significance of both the cGMP and cAMP signalling in controlling the function of prostate smooth muscle and are considered important for the identification of new drug options to treat BPH/LUTS. Another hypothesis postulates that the abnormal growth pattern of smooth muscle, connective and glandular tissue in prostatic stromal and glandular compartments, respectively, seen in conjunction with BPH might be induced by hypoxia resulting from an age-related impairment in local blood flow. Consequently, a key role of urogenital ageing and subsequent alterations in the blood supply to the prostate has been suggested in the development of BPH. This issue is addressed in more detail at the end of the following section.

PDE5 inhibitors in the treatment of BPH/LUTS

The basic research efforts outlined above have provided the basis for the development and introduction of new therapeutic modalities into the management of lower urinary tract dysfunction (LUTD), some of which might soon be offered to patients. BPH represents a major health care problem in westernized countries. Symptoms and signs of BPH comprise storage and voiding dysfunction, as well as benign prostatic enlargement (BPE) with variable degrees of benign prostatic obstruction (BPO) [13]. Major symptoms include urinary frequency, nocturia and slow

stream. It is estimated that approximately 50% of men older than 50 years have moderate to severe LUTS, as measured by means of the International Prostate Symptom Score (IPSS, 8–19 = moderate symptoms, 20–35 = severe symptoms) [14]. The current pharmacological management of LUTS and BPE involves α_1 -adrenoceptor antagonists, such as alfuzosin, doxazosin, silodosin, tamsulosin and terazosin, or intervention into the hormonal control of prostate growth by using the enzyme 5 α -reductase inhibitors (5-ARI) finasteride or dutasteride [15–17].

The role of PDE5 inhibitors sildenafil, vardenafil and tadalafil in the treatment of BPH/LUTS was initially addressed by preliminary open-label studies [18, 19]. Later, larger randomized, double-blind trials, of which some were placebo-controlled, were conducted enrolling patients presenting with LUTS with or without erectile dysfunction (ED) (Table 2). Main study endpoints were changes in the IPSS, BPH Impact Index (BPH II), Quality of Life Questionnaire (QoL), LUTS Global Assessment Questionnaire (GAQ) and parameters from uroflowmetry measurements, such as peak urinary flow ($Q_{\max}$), average urinary flow (Q_{ave}) and postvoid residual urine (PVR). The duration of the trials was 8–12 weeks. Administration of the PDE5 inhibitors significantly reduced IPSS and led to an improvement in the BPH II and QoL. In some protocols, patients presenting with severe LUTS experienced greater improvement in IPSS than those with moderate symptoms. A significant reduction of bladder storage and voiding symptoms during treatment was also noted while PVR and $Q_{\max}$ did not change significantly. From this finding, it was concluded that extraprostatic pathophysiological mechanisms related to an impairment in the activity of the nitric oxide (NO) system might also be involved in the onset of LUTS. Although some studies showed an increase in $Q_{\max}$ with an increased dose of a PDE5 inhibitor, this observation was not significantly different from the placebo group [20–24]. This might be due to the fact that baseline values

measured were already close to normal at the time patients were enrolled into the studies [24].

The combination of the PDE5 inhibitors sildenafil (25 mg once daily) or tadalafil (10 mg once daily) and the α_1 -adrenoceptor antagonist alfuzosin (10 mg once daily) for the treatment of LUTS has also been evaluated. Men with untreated LUTS (and concomitant ED) were randomized to either alfuzosin, sildenafil or tadalafil, or the combination of the α -adrenoceptor blocker and a PDE5 inhibitor. Study endpoints were changes from baseline in IPSS, $Q_{\max}$, Q_{ave} and PVR volume. Improvement in IPSS was significant in all treatment arms but most pronounced with the drug combinations. PVR, $Q_{\max}$, frequency and nocturia were significantly improved with alfuzosin only and the combination regimen [25, 26]. The efficacy of tadalafil (20 mg day⁻¹) and tamsulosin (0.4 mg day⁻¹) (administered for 45 days) vs. tamsulosin only (0.4 mg day⁻¹) was also assessed in a randomized, double-blind, crossover study design. Improvements in the IPSS and IPSS-QoL were greater with the drug combination. Both drug regimens improved $Q_{\max}$ and decreased PVR. However, no significant differences between tamsulosin only vs. tamsulosin in combination with tadalafil were noted [27]. Similar findings emerged from a protocol evaluating the efficacy of administering the PDE5 inhibitor udenafil in patients with BPH and concomitant ED. One hundred and twenty patients who had been treated with α -adrenoceptor blockers for BPH were given udenafil (100 mg day⁻¹) for 8 weeks. At study end point, IPSS scores had improved significantly when compared with baseline values [28]. It was concluded that combined therapy was more effective than monotherapy with either agents to improve voiding dysfunction in men with BPH/LUTS. A very recent study conducted by Tuncel *et al.* [29] evaluated the efficacy of sildenafil citrate (25 mg, four times per week for 8 weeks), tamsulosin (0.4 mg, once daily for 8 weeks) and the combination of both regimens in 60 men presenting with BPH/LUTS. The authors found that the improvements in IPSS, $Q_{\max}$ and PRV were significantly more pronounced in those patients who had received the combination therapy than in those who were on sildenafil citrate only. However, treatment with the drug combination did not enhance the improvements in IPSS and voiding symptoms seen in the tamsulosin group [29]. Additional large-scale, randomized, placebo-controlled studies are needed in order to assess further the clinical effectiveness of combining PDE5 inhibitors and α -adrenoceptor blockers to treat BPH/LUTS.

Some studies focused in particular on the urodynamic effects of PDE5 inhibitors on voiding function, including $Q_{\max}$ and detrusor pressure at maximum urinary flow, in men with BPO. Dose-dependent changes in $Q_{\max}$ or detrusor pressure at maximum urinary flow rate were registered in comparison with placebo in men with BPH/LUTS who had been given tadalafil on a once daily basis. However, these improvements were not significant [30, 31]. In contrast, it was shown that the acute administration of sildena-

fil can improve $Q_{\max}$ and Q_{ave} in men with BPH/LUTS. A single dose of the PDE5 inhibitor (50 mg or 100 mg) resulted in an improvement in $Q_{\max}$ in the patients. Q_{ave} and the mean voided volumes of the patients also increased while no significant differences were registered in $Q_{\max}$, Q_{ave} and voided volumes of the control group before and after placebo administration [32, 33]. It should be taken into consideration that the study design, and especially the small number of patients, made it rather difficult to draw firm conclusions from these observations.

A few clinical studies have provided evidence that an impairment in the blood supply of the prostate might account for the development of BPH/LUTS. It was shown by means of transrectal contrast-enhanced colour Doppler ultrasonography that perfusion of the transition zone of the prostate was significantly lower and mean flow resistance index significantly higher in men with BPH than in healthy controls. Similar observations were made in men with diabetes mellitus and/or peripheral arterial occlusive disease but not coronary arterial disease. These findings are in support of the hypothesis that an age-related limitation in blood supply to the lower urinary tract might be an important aspect of the pathophysiology underlying BPH/LUTS. Thus, it seems likely that the regular administration of a PDE5 inhibitor may, to a certain degree, overcome ischaemia due to vascular damage and normalize local blood flow patterns [34–36].

PDE inhibitors and the overactive bladder (OAB)

Findings from basic research studies

Anticholinergic drugs (m-cholinoceptor antagonists) are currently the therapy of choice to treat urgency and urgency incontinence, lately known as the overactive bladder syndrome (OAB) [37]. Nevertheless, up until now, anticholinergic drugs acting exclusively on detrusor smooth muscle are not available. Moreover, the unstable detrusor seems to be regulated in part by non-cholinergic mechanisms. This might explain the side effects and limited clinical efficacy of anticholinergic drugs [38]. Important central or peripheral non-cholinergic mechanisms known to be involved in the control of micturition involve purinergic, gamma aminobutyric acid (GABA), glutamatergic, opioid and serotonergic receptors. Positive signals for drugs acting at other sites, such as the vitamin D analogue elocalcitol and the neurokinin-1 receptor antagonist aprepitant, have also been found. Although positive proof-of-principle studies are available for some of these therapeutic approaches, there is not sufficient information for proper clinical assessment and none of the strategies has so far been approved for treatment of OAB [39, 40]. However, the specific modulation of intracellular second messenger pathways may offer a promising possibility to achieve selective modulation of function of

the urinary bladder, especially with regard to the contraction and relaxation of detrusor smooth muscle.

Using chromatographic methods, the presence of the PDE1 (cAMP/cGMP-PDE, Ca^{2+} /calmodulin-dependent), PDE2 (cAMP-PDE, cGMP-dependent), PDE3 (cAMP-PDE, inhibited by cGMP), PDE4 (cAMP-PDE) and PDE5 (cGMP-PDE) was shown in the human detrusor [41]. It was also described that the tension of human isolated detrusor strip preparations contracted by the muscarinic agonist carbachol was reversed by the non-specific PDE inhibitor papaverine and the PDE1 inhibitor vinpocetine. The relaxing effects of the drugs were paralleled by an increase in the production of cAMP and cGMP [42]. The predominant expression of PDE1 in the human detrusor was later confirmed by Real Time-PCR analysis [43]. It was concluded from these findings that the cAMP pathway and PDE1 might be of significance in the control of detrusor smooth muscle. This hypothesis is supported by the observation that the PDE4 inhibitor rolipram effectively inhibited the phasic myogenic contractile activity of human isolated detrusor smooth muscle. It was proposed that PDE4 is involved in the control of the phasic myogenic activity of the human bladder and that inhibitors of PDE4 might represent an alternative strategy for the treatment of the OAB [44]. The *in vitro* relaxant action of sildenafil on human isolated bladder neck smooth muscle pre-contracted with the α -adrenoceptor agonist phenylephrine was also shown. Both the NO-synthase inhibitor L-NAME and guanylyl cyclase inhibitor ODQ abolished the relaxation induced by the PDE5 inhibitor, thereby demonstrating an involvement of the NO/cGMP pathway [45]. The reversal by sildenafil of the tonic contraction induced by the muscarinic agonist carbachol of human isolated detrusor strip preparations remained unaltered in the presence of the NO donor sodium nitroprusside but was significantly attenuated by the guanylyl cyclase inhibitor ODQ and adenylyl cyclase inhibitor MDI-12.330, as well as glibenclamide, known as an inhibitor of ATP-sensitive potassium channels, or iberiotoxin and apamin, both known to block Ca^{2+} -activated potassium channels. Therefore, it was suggested that the relaxation of human detrusor smooth muscle induced by sildenafil is mediated by cGMP- and cAMP-dependent pathways and K^+ channels, with only a minor contribution of NO [46].

Studies on the expression and activity of PDE5 in the human bladder demonstrated that the enzyme is expressed in muscle fibres and the vascular endothelium [47, 48]. The PDE5 inhibitors sildenafil, tadalafil and vardenafil blocked 70% of the total cGMP-degrading PDE5 activity isolated from human detrusor tissue. In an *in vivo* rat model of bladder outlet obstruction, chronic treatment with vardenafil ($10 \text{ mg kg}^{-1} \text{ day}^{-1}$) significantly reduced the non-voiding bladder contractions. *In vitro*, vardenafil enhanced significantly the anti-proliferative effects of Sp-8-Br-PET-cGMPs (a cGMP analogue resistant to PDE5 activity) and the NO donor sodium nitroprusside on

bladder smooth muscle cells [49]. These results have been interpreted in terms that PDE5 is involved in mediating bladder smooth muscle relaxation and controlling tissue proliferation. Hence, blocking PDE5 might represent an option for the treatment of the OAB.

Aside from a direct effect on the smooth muscle of the detrusor, there are also hints that PDE5 inhibitors may act in a way to help prevent deleterious alterations of the histological structure of the urinary bladder that may lead to disturbances in urine storage and voiding. It has been shown in a mouse model of bladder overactivity due to BOO that daily treatment of the animals with sildenafil citrate (10 mg kg^{-1} bodyweight) might prevent the development of detrusor muscle hypertrophy and subsequent increase in bladder weight, as well as the deposition of collagen in the lamina propria and smooth muscle [50]. Another *in vivo* study demonstrated that sildenafil (10 mg kg^{-1} bodyweight for 5 days x 12 weeks), either given immediately or after 12 weeks of the induction of bladder outlet obstruction (BOO), ameliorated detrusor overactivity caused by bladder outlet obstruction without affecting bladder contractility or improving detrusor hypertrophy [51]. A link between structural and functional changes and the activity of mitochondrial key enzymes, such as the citrate synthase, malate dehydrogenase, succinate cytochrome c reductase, NADH cytochrome c reductase and cytochrome c oxidase, has been demonstrated [52, 53]. However, so far, no evidence has been presented that sildenafil or other PDE5 inhibitors can modify the activity of the mitochondrial energy supply, namely the citric acid cycle and electron transport chain.

PDE inhibitors in the treatment of the OAB

Results from a randomized, double-blind, placebo-controlled trial to assess the effects of the PDE1 inhibitor vinpocetine in 19 patients with urgency incontinence, who had failed standard pharmacological treatment with anti-muscarinic drugs, demonstrated that vinpocetine was superior to placebo in the majority of patients (58%) with regard to the outcome parameters voiding frequency, bladder volume at first sensation, bladder volume at voiding desire, maximum detrusor pressure and voided volume [54]. Recently, the acute effects of the PDE5 inhibitor vardenafil were investigated in a single centre, randomized, double-blind, placebo-controlled trial in a group of 25 spinal cord injured males with micturition disorders who were on oxybutynin treatment. Following a baseline urodynamic evaluation, another urodynamic test was performed 1–3 h after the administration of 20 mg vardenafil or placebo. Primary endpoints were changes in maximum detrusor pressure during voiding, maximum cystometric capacity and bladder volume at first (overactivity) sensation. Vardenafil administration significantly decreased maximum detrusor pressure, considerably improved cystometric capacity and increased volume at first sensation [55].

In an attempt to assess the role of PDE5 inhibitors in the recovery of urinary continence after bilateral nerve sparing radical prostatectomy, 39 patients were assigned after surgery to three treatment arms in a double-blind fashion: vardenafil on demand, vardenafil daily at bed-time (nightly) or placebo. Urinary function (UF) and urinary bother symptoms (UB) according to the University of California Los Angeles (UCLA) Prostate Cancer Index questionnaire were assessed immediately after surgery and at 1, 3, 6, 9, 10 and 12 months. Bother scores measure the distress associated with post-prostatectomy urinary dysfunctions while the UF domain reflects dryness rather than general voiding function in the patients. The improvement in UF and UB at month 1 and month 12 was significant in the vardenafil treatment groups. Administration of the drug once daily at bed-time resulted in greater UF after 3, 6 and 9 months and less UB after 6 months. The improvements in maximal recovery were also more pronounced. Patients who had received vardenafil daily at bed-time experienced less bother after 3 months and 6 months than those who were subjected to on-demand use [56]. The exact mechanism by which PDE inhibitors modulate/affect urinary voiding and storage function in humans remains to be elucidated in detail.

Conclusions

Based on the knowledge of the mechanisms controlling the male and female urinary tract, the use of selective PDE inhibitors has been suggested as a logical approach for the treatment of various urological diseases. Due to the unending challenge to conceive first-line treatments demonstrating advanced efficacy over the previous options, the strategy of modulating the activity of PDE isoenzymes might represent a novel approach in patients with lower urinary tract dysfunctions. Future studies will delineate as to whether PDE inhibitors may gain significance in the treatment of BPH/LUTS, OAB and urge incontinence. While some approaches should involve the NO/cGMP system, others should also take into account the modulation of the cAMP pathway [57–60], as well as the combination of active agents, e.g. combining a PDE inhibitor with a NO donor, an α -adrenoceptor antagonist or antimuscarinic drug, in order to affect multiple peripheral targets.

Competing interests

There are no competing interests to declare.

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