

Perspectives in Pharmacology:

EMERGING PHARMACOLOGIC APPROACHES FOR THE
TREATMENT OF LOWER URINARY TRACT DISORDERS

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Abbreviations: BPH: benign prostatic hyperplasia, CGRP: calcitonin gene-related peptide, CNS: central nervous system, 8-hydroxy-2-(di-n-propylamino) tetralin: 8-OH-DPAT, 5-HT: 5-hydroxytryptamine, ET: endothelin, FDA: Food and Drug Administration, LUTD: lower urinary tract dysfunction, LUTS: lower urinary tract symptoms, KCO: potassium channel opener, MED: male erectile dysfunction, mAChR: muscarinic acetylcholine receptors, NO: nitric oxide, PACAP: pituitary adenylate cyclase-activating polypeptide, PDE: phosphodiesterase, PGE: prostaglandin E, PMC: pontine micturition center, PPA: phenylpropanolamine, sGC: soluble guanylate cyclase, SUI: stress urinary incontinence, UUI: urge urinary incontinence, vasoactive intestinal peptide: VIP

ABSTRACT

Lower urinary tract disorders include disorders affecting continence (stress urinary incontinence, urge urinary incontinence and benign prostatic hyperplasia) and male erectile dysfunction. While none of these conditions are fatal, they affect overall quality of life. Throughout modern medicine the treatment of these conditions was limited to psychological counseling or surgical intervention. In recent years, research defining the physiological mechanisms of continence and male sexual function has aided in the pharmacologic design of approaches to these conditions. These agents can act both centrally or on the peripheral genitourinary smooth muscle to alleviate disease symptoms. Incontinence is primarily treated with agents that act directly on the bladder smooth muscle such as muscarinic antagonists. However, afferent blockade to attenuate the spinalbulbospinal reflex pathway including mixed norepinephrine/serotonin reuptake inhibitors may provide a key breakthrough. Erectile dysfunction treatment has been revolutionized via the discovery of the nitric oxide pathway and phosphodiesterase 5 inhibitors. New peripheral targets as well as centrally acting agents represent potential emerging therapies. In this review, the pharmacologic basis of treatment of these disorders is discussed with special emphasis on emerging new therapeutics.

The lower urinary tract functions in continence to store and void urine as well as in sexual function in males. Over the last several decades, an understanding of the physiology and pharmacology of these processes has allowed the development of therapeutics to treat lower urinary tract disorders (LUTD). In this review, emerging pharmacologic treatments of incontinence, benign prostatic hyperplasia (BPH), and male erectile dysfunction (MED) will be discussed.

Incontinence

The biochemical and pharmacologic basis of continence as well as a discussion of physiology and pathophysiology have been reviewed in detail and will only be briefly discussed here (deGroat and Yoshimura, 2001; Yoshimura and Chancellor, 2002). The urinary bladder functions as a reservoir for the storage and release of urine via the urethra (6-8 times/ 24h). The storage and periodic elimination of urine also depends on the coordinated activity of the bladder and urethra (outlet). During storage, the outlet is closed and the bladder smooth muscle is quiescent such that intravesicular pressure is low and constant over various bladder volumes. During voiding, the muscles of the outlet relax and the bladder smooth muscle contracts. The expulsion phase consists of an initial relaxation of the urethral sphincter followed in a few seconds by a contraction of the bladder, an increase in bladder pressure, and flow of urine.

Bladder function is coordinated by three sets of nerves arising from the sacral (excitatory cholinergic and purinergic nerves to bladder and inhibitory nitergic nerves to the urethra) and thoracolumbar vertebrae in the spinal cord (sympathetic nerves to urethra and bladder neck). Three sets of afferent neurons arise in the bladder and go to the spinal cord: small myelinated A δ fibers, unmyelinated C fibers and afferents from the urothelium. These urothelial afferents can sense changes in composition of urine

as well as ATP, NO or prostaglandins. CNS control of voiding is via a spinobulbospinal reflex arc and the rostral brain stem (pontine micturition center, PMC) (deGroat and Yoshimura, 2001). Higher centers in the cerebral cortex and diencephalons underlie the voluntary mode of voiding.

Involuntary loss of urine (urinary incontinence) occurs when pressure inside the bladder (intravesical pressure) exceeds the retentive pressure of the internal urethral sphincter and external urethral sphincter (intraurethral pressure). A glossary of terms used in LUTD is provided in Table 1. From a clinical perspective, incontinence denotes a symptom, a sign, and a condition (Abrams et al., 2003). The symptom indicates the patient's (subjective) statement of involuntary urine loss; the sign is the objective demonstration of urine loss (by the physician); and the condition is the underlying pathophysiologic process as demonstrated by clinical or urodynamic techniques. Due to the complex inter-relationships between CNS input, inhibitory regulation and peripheral myogenic components, incontinence can have both myogenic and/or neurogenic etiologies. The prevalence of incontinence (10-13 million in US; 17-20 million ex-US) is comparable to that of cancer, diabetes and BPH.

Urge Urinary Incontinence/Overactive Bladder. Urge urinary incontinence (UUI) is the complaint of involuntary leakage accompanied by or immediately preceded by a strong desire to void (urgency) (Abrams et al., 2003). In contrast, overactive bladder syndrome is a condition with symptoms of urgency with or without incontinence and usually with increased frequency and nocturia. Approximately 25% of all incontinence patients suffer from overactive bladder syndrome. This syndrome is associated with the urodynamic finding of involuntary bladder contractions, referred to as bladder instability. UUI differs in symptoms and etiology from stress urinary incontinence (SUI). Bladder instability can have a myogenic etiology in which smooth muscle function is

impaired as a result of a partial urethral outlet obstruction (as in BPH), or it can be idiopathic. In a recent study, it was found that 50-80% of men with BPH suffer the irritative symptoms of bladder instability (Elliot and Boone, 2000). Instability may also be of neurogenic origin (e.g. Alzheimer's disease, Parkinson's disease or stroke) that is generally referred to as bladder hyperreflexia.

Myogenic Etiology. In some cases, the symptoms of overactive bladder syndrome may be due to disorders of smooth muscle tone. Bladder tissues from these patients show distinct features at the smooth muscle level predisposing them to unstable contractions. The loss of normal excitatory neural input results in increased signaling between smooth muscle cells, leading to a state of overactivity. Acute sensitivity to agonists increases in gap junctions and enhanced electrical coupling between smooth muscle cells enables widespread depolarization signals sufficient to cause spontaneous muscle activity resulting in increased intravesical (bladder) pressure (Yoshimura and Chancellor, 2002).

Neurogenic Etiology. The symptoms of overactive bladder syndrome may also be triggered by neurologic defects or trauma (e.g. Alzheimer's disease, Parkinson's disease, multiple sclerosis, spinal cord injury, and stroke). In this case, a loss of inhibition of the sacral reflex through the pelvic nerve alters reflex regulation of bladder and urethral function leading to bladder hyperreflexia.

As noted above, another mechanism involves afferent signaling activity where the major component of the afferent input from the bladder to the CNS is mediated by C-fibers originating in the bladder urothelium (Yoshimura and Chancellor, 2002). These afferents control voiding reflexes in infancy, and a body of evidence suggests the re-emergence of C-fiber reflexes may underlie some facets of bladder overactivity.

Pharmacological Approaches to the Treatment of UUI.

Muscarinic Antagonists. Both M_2 and M_3 muscarinic acetylcholine receptors (mAChR) play a role in voiding mechanisms (Chapple et al., 2002). Although M_2 mAChR are more abundant than M_3 mAChR in the lower bladder dome and in the base, M_3 gene knockout mice showed urinary retention while M_2 gene knockout mice do not (Matsui et al., 2000; Stengle et al., 2000). In organ bath experiments, bladder strips from M_2 gene knockout mice had impaired contractility to carbachol compared to wild type, indicating that the M_2 mAChR does play some role in bladder contractility and the voiding mechanism (Stengle et al., 2000). This may especially apply during pathophysiologic changes such as outflow obstruction where M_2 receptors play the key role in bladder contraction in a rat model (Braverman and Ruggieri, 2003).

Muscarinic antagonists take advantage of the role of M_2 and M_3 mAChR receptors in bladder contraction and inhibit these receptors decreasing the response to acetylcholine. These agents reduce pressure during bladder filling and treat unstable bladder contractions. While nonselective agents such as atropine are effective in treating overactive bladder, they have the unwanted side effect of xerostomia (dry mouth) presumably from inhibition of M_3 mAChR in the salivary glands.

Oxybutynin is a potent, competitive muscarinic antagonist that has been a mainstay of therapy for more than 20 years (Table 2) (Yoshimura and Chancellor, 2002; Rovner and Wein, 2000). Studies using binding assays to characterize oxybutynin report 6-fold selectivity of M_3 over M_2 and 4-fold M_3 over M_5 but little selectivity between M_1 , M_3 and M_4 (Eglen et al., 2001). The N-desethyl metabolite of oxybutynin in humans may be responsible for inducing dry mouth. Clinical trial data measuring the decrease in the number of voids and extent of leakage show statistically significant but minimal improvement between placebo and oxybutynin treatment (comparing extended release

to three times daily dosing; both treatments had similar efficacy reducing number of visits 24% compared to 9% in the placebo control group, Nilsson et al., 1997).

Tolteridine is also a competitive, muscarinic antagonist that has similar potency on bladder muscarinic receptors as oxybutynin but eight fold less potency for parotid gland receptors (greater uroselectivity). There is little selectivity for the five muscarinic receptors by binding assays except 2 fold M_3 over M_4 (Eglen et al., 2001). In clinical trials and in head to head comparisons of immediate release oxybutynin, tolteridine shows similar efficacy but tolteridine is better tolerated (Nilvebrant, 2001).

Darifenacin is an M_3 selective antagonist with 60-fold more potency for M_3 over M_2 mAChR and 9-fold selectivity for bladder versus salivary gland receptors (Chapple et al., 2002; Yoshimura and Chancellor, 2002). The Food and Drug Administration (FDA) approved this agent for treatment of overactive bladder in October 2003.

Purinergic Antagonists. Pathological conditions such as denervation or inflammation can cause ATP release that in turn promotes nonadrenergic, noncholinergic bladder contractions. Intravesical ATP, as well as α,β -methylene ATP, stimulate the micturition reflex in freely moving, awake rats, a process that could be blocked with neurokinin-2 antagonist SR48968, potassium channel opener ZD6169 or ganglionic blocker hexamethonium (Pandita and Andersson, 2002). Nitric oxide (NO) is involved in this process as L-NAME, a nonspecific inhibitor of NO synthase, blocked this process. ATP can act on two families of receptors: G-protein coupled receptor P2Y family and ion channel P2X family (Burnstock, 2002). Immunolocalization experiments as well as *in situ* hybridization experiments in rats and humans have identified P2X₁ and P2X₄ receptors in the detrusor and P2X₃ in small diameter afferent neurons in the dorsal root ganglia (Yoshimura and Chancellor, 2002). P2X₃ knockout mice suffer from bladder hypoactivity, decreased afferent activity and a loss of augmented bladder

distension to intravesical P2X agonists (Vlaskovska et al., 2001), suggesting a role for ATP released from the urothelium and P2X₃ in bladder function. It has been hypothesized that by attenuating afferent mechanisms, incontinence could be successfully treated (Yoshimura and Chancellor, 2002). The recent discovery of small molecule non-nucleotide P2X₃ antagonists (Jarvis et al., 2002) could offer proof of principle of this class of therapeutics.

Vanilloid and Tachykinin Receptors. Vanilloids such as capsaicin and resiniferatoxin can activate nociceptive sensory nerve fibers via the VR1 receptor. The observation that intravesicular capsaicin as well as resiniferatoxin activate and desensitize VR1 receptors and decrease bladder hyperactivity suggests that a VR1 agonist might have a therapeutic role (Yoshimura and Chancellor, 2002). This therapy may be particularly valuable in denervated, hyperactive bladders where the VR1 and purinergic pathways exert a key role in bladder hyperactivity via afferent pathways in the spinalbulbospinal reflex pathway (deGroat and Yoshimura, 2001; Yoshimura and Chancellor, 2002). Homozygous mice with a VR1 gene knock-out have a higher frequency of low amplitude, non-voiding bladder contractions and under anesthesia show reductions in the afferent bladder signaling during filling (Birder et al., 2002). Small molecule agonists of the VR1 receptor are eagerly awaited in order to better understand the therapeutic potential of blockade of this receptor. Immunocytochemical studies of bladder afferent neurons reveal co-localization of neuropeptides including calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), pituitary adenylate cyclase-activating polypeptide (PACAP), enkephalins, neurokinin A and substance P on capsaicin-sensitive C-fiber bladder afferents. Bladder hyperactivity induced by capsaicin was reduced by intrathecal administration of neurokinin-1 antagonists. As mentioned above, neurokinin-2 antagonist SR48968 blocked the effects of intravesicular ATP on

voiding in rats, suggesting NK-2 inhibition of P2X receptors (Pandita and Andersson, 2002). A highly selective neurokinin-1 antagonist TAK637 has been reported to be effective in suppressing guinea pig bladder activity and is in Phase II clinical trials in humans for UUI (Furness, 2001).

Potassium Channel Openers (KCOs). Hyperpolarization of bladder smooth muscle cell membrane potential is regulated in part by potassium concentration. The bladder expresses K-ATP potassium channels that have been shown to play a role in bladder contraction and hyperactivity due to their ability to modulate the membrane potential of bladder smooth muscle (Yoshimura and Chancellor, 2002). Openers of K-ATP channels can suppress myogenic bladder contractions by relaxing bladder smooth muscle cells via membrane hyperpolarization. A key challenge in the development of this class of therapeutics is the ability to separate lower urinary tract effects from cardiovascular effects where these channels are also expressed. In a limited clinical trial for overactive bladder, for example, cromakalin reduced patient symptoms 35% but had unacceptable hypotension at the effective doses (Nurse et al., 1991). A number of agents with enhanced uroselectivity versus cromakalin have been described in recent years including ZD6169, WAY133537 and A-278637 (Brune et al., 2002; Fabiyi et al., 2003). However, whether or not this favorable preclinical profile can be translated into a desirable clinical profile in humans with acceptable cardiovascular liabilities remains to be determined.

Stress Urinary Incontinence (SUI). SUI is the complaint of involuntary leakage of urine on effort or exertion or on sneezing or coughing coincident with an increase in intra-abdominal pressure, in the absence of a bladder contraction or an overdistended bladder (Abrams et al., 2003). This is the most common form incontinence affecting approximately 35% of all UI patients.

The most common causes of SUI in women are urethral hypermobility and intrinsic urethral sphincter deficiency. Urethral hypermobility is characterized by a weakness of the pelvic floor support. This may have congenital origins, or may be acquired after surgery, trauma, or a sacral cord lesion. In females, intrinsic urethral sphincter deficiency is commonly associated with multiple incontinence surgical procedures, as well as hypoestrogenism, aging or both. In this condition, the urethral smooth muscle and sphincter is unable to generate enough resistance to retain urine in the bladder.

Pharmacological Approaches to the Treatment of SUI.

Alpha Adrenoceptor Agonists. Noradrenergic input to smooth muscle of the urethra is abundant in marked contrast to the bladder (de Groat and Yoshimura, 1999). Studies in rat, cats and dogs indicate that sympathetic input to the urethra is tonically active during bladder filling. Substantial preclinical physiological, pharmacological and molecular biological evidence suggests that α_{1A} adrenoceptors are responsible for mediating the effects of norepinephrine on urethral tone and intraurethral pressure (Testa et al., 1993). Clinical studies with the non-selective α -adrenoceptor agonists, phenylpropanolamine (PPA) and midodrine have demonstrated limited clinical efficacy (Sullivan and Abrams, 1999). The limited efficacy of these non-selective agents has been attributed to effects on blood pressure and heart rate that occur at doses comparable to those eliciting an effect on urethral function.

A number of highly selective agonists for the α_{1A} subtype relative to the α_{1B} subtype have been generated in an effort to generate the necessary selectivity for urethra versus vasculature. Unfortunately, only modest improvements in urethral selectivity have noted with these agents in preclinical models (Buckner et al., 2002). Although compounds such as ABT-866 are highly selective α_{1A} agonists, only very

modest uroselective effects are observed (Buckner et al., 2002). Increases in blood pressure are observed at doses 3-10 fold higher than those where effects on urethral pressure are observed. Even small increases (e.g. 2-5mm Hg) in blood pressure are unlikely to be acceptable clinically in humans.

Serotonin, Norepinephrine-Reuptake Inhibitors. Serotonin (5-hydroxytryptamine, 5-HT) plays an important central role in the inhibition of the micturition reflex, probably through 5-HT_{1A} receptors in the raphe. Both 5-HT and the serotonergic agonist 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) increased bladder capacity when injected intracerebroventricularly (icv) to conscious rats stimulated micturition, a process that could be blocked by icv administration of the selective 5-HT_{1A} antagonists WAY100635 or NAD-299 (Pehrson et al., 2002). Neither antagonist had any effect on bladder muscle strips in organ baths either electrically stimulated or precontracted with carbachol. It has further been demonstrated in the urethane-anesthetized rat that WAY100635 injected intracerebroventricularly blocked micturition reflex contractions (Yoshiyama et al., 2003). Mesulergine (5-HT_{2C} antagonist) abolished the effects of WAY100635, possibly via spinal receptors. Taken together, these results suggest that the frequency of micturition reflexes via the afferent pathway to the pons micturition center are regulated in part by 5-HT_{1A} receptors while the regulation of bladder contraction is regulated via output from the pons and parasympathetic pathways.

The importance of serotonin in the CNS regulation of both parasympathetic and somatic neural projections to the bladder has prompted the investigation of the serotonin and norepinephrine specific re-uptake inhibitor duloxetine on bladder function in felines (Khaled and Elhilali, 2003). The investigators concluded that duloxetine suppressed bladder activity increasing bladder capacity through serotonergic mechanisms while enhancing bladder sphincter contraction via 5-HT₂ receptors

(consistent with the study above) and α -adrenergic mechanisms. This agent may work through a dual mechanism of norepinephrine action on the urethra as well serotonergic mechanism (Khaled and Elhilali, 2003; Viktrup and Bump, 2003). A 12-week double-blind, placebo controlled phase III clinical trial of duloxetine in 683 women 22-84 years of age with SUI showed a significant decrease incontinence episode frequency with duloxetine (51%) compared to the placebo control (31%) (Dmochowski et al., 2003). Discontinuation rate for duloxetine was 24% with the most common side effect being nausea. The FDA issued an approvable letter for duloxetine for the treatment of stress incontinence in September 2003. Approval is contingent on successful completion of additional acute preclinical and clinical pharmacology studies and is anticipated in late 2004 or first half of 2005.

Benign Prostatic Hyperplasia

BPH is a term reserved for the typical histological pattern that defines the disease (Abrams et al., 2003). As hyperplasia occurs, the prostate can enlarge without urethral obstruction (no LUTS). Benign prostatic obstruction is a form of bladder outlet obstruction and may be diagnosed as BPH with LUTS when the cause is due to histologic BPH (Abrams et al., 2003; Thorpe and Neal, 2003). By age 40, BPH is present in 8% of men increasing to 60% by age 70 and 90% over 80 years of age. BPH with LUTS include complaints of nocturia (nighttime voiding) as well as difficulty voiding and increases in urgency and frequency. One third of men over 50 years old will develop some form of lower urinary tract symptoms with 25% of these requiring surgery (for ex, transurethral resection of the prostate).

Current pharmacologic treatment of BPH utilizes α_1 -adrenoceptor antagonists and 5- α -reductase inhibitors that block testosterone production (Thorpe and Neal,

2003). The mode of action of α_1 -adrenoceptor antagonists has been thought to be prostate smooth muscle and stromal relaxation and relaxation of the urethra with a subsequent increase in urinary flow (Andersson, 2002). One hypothesis is that these agents increase apoptosis in both prostate glandular epithelial and stromal smooth muscle cells after about 6 months of treatment and the resulting decrease in prostate size increases urinary flow rate upon voiding. However, this has only been demonstrated *in vitro* and has yet to be confirmed in a clinical setting. Tamsulosin, doxazosin and terazosin nonselectively antagonize α_1 -adrenoceptors (Andersson, 2002; O'Leary, 2001). As in the case with muscarinic antagonists in the treatment of UUI, α_1 -adrenoceptors fail to fully relieve the symptoms associated with BPH. An example of treatment efficacy is seen in the tamsulosin trials where after 53 weeks of treatment the percentage of respondents with $\geq 25\%$ improvement in LUTS was 51% with placebo, 70% and 74% with 0.4 and 0.8 mg/day tamsulosin, respectively. The same study showed that the percentage of respondents with a $\geq 30\%$ improvement in maximum urinary flow rate were 21% for placebo and 31 and 36% with 0.4 and 0.8 mg/day tamsulosin, respectively (O'Leary, 2001). The uroselective α_1 -adrenoceptor antagonist alfuzosin is in late stage clinical trials and may provide another agent in this armamentarium (Hofner and Jonas, 2002).

The prostate contains both type I and II 5- α -reductase activities which convert testosterone to the more active dihydrotestosterone. Finasteride an azosteroid is a type II 5- α -reductase inhibitor that when taken results in atrophy of the prostatic glandular epithelium due to a decreased synthesis of dihydrotestosterone. While onset is slow, treatment results in a long lasting 20-30% reduction in prostate volume and a decrease in LUTS. Side effects include ejaculatory dysfunction (up to 8%), loss of libido (up to 10%) and erectile dysfunction (up to 16%). Dutasteride (a type I and II 5- α -

reductase inhibitor) reduces risk of urinary retention 48-57% compared to placebo (Thorpe and Neal, 2003). Most recently, a double blind, multicenter trial in over 1000 patients comparing placebo, doxazosin, finasteride and combination therapy found that combination therapy was no more effective over one year in increasing urinary flow rate and reducing LUTS scores than either treatment alone (Kirby et al., 2003).

Male Erectile Dysfunction

MED is defined as the persistent and consistent inability to achieve penile erection during sexual stimulation (Moreland et al., 2001b). This condition occurs in varying degrees of impairment increasing in incidence with aging and associated with cardiovascular disease, hypertension, diabetes as well as neurological conditions and depression (Kubin et al., 2002). The worldwide prevalence of MED has been estimated at over 152 million men and the projections for 2025 with a prevalence of approximately 322 million with MED. Reports of quality of life data suggest that the importance of MED in contributing to other chronic health conditions such as depression has been largely underestimated. Over the past thirty years, the biochemical and pharmacologic basis for penile erection has revealed that this event involves a complex integration of CNS input, hemodynamics and vascular smooth muscle relaxation within the corpora cavernosa of the penis. These processes as well as discussion of pathophysiology, epidemiology and physiology have been reviewed in detail and will only be briefly discussed here (Andersson, 2001; Moreland et al., 2001b).

Penile erection is a spinal reflex under CNS (supraspinal) inhibitory control. Visual, tactile, olfactory and imaginative stimuli from the higher cortical areas of the brain are integrated in the medial preoptical area of the hypothalamus with processes that involve dopaminergic and oxytocinergic neurons. The nonselective D₂-like agonist

apomorphine increased blood flow to the anterior cingulum and the right prefrontal cortex during sexual stimulation as measured by positron emission tomography (Hagemann et al., 2003). Mapping of these neurons as well as understanding which of the D₂-like receptors mediates this process has yet to be reported. These neurons send an impulse that results in the release of NO from nitrergic neurons in the corpus cavernosum penis allowing vasodilation due to activation of smooth muscle soluble guanylate cyclase by NO. NO is also released as a result of action of shear stress and acetylcholine on the corpus cavernosum endothelium. Vasodilation ensues and upon filling veno-occlusion occurs. Pharmacologic targets for the treatment of MED can be divided into central and peripheral. Central nervous system targets are the least explored and take advantage of the known pathways including dopamine and melanocortin. Peripheral targets primarily rely on enhancing smooth muscle vasodilation or blocking the adrenergic or endothelin-mediated vasoconstriction associated with penile flaccidity. As vasodilators, these agents have the challenge of penile specific effects with limited cardiovascular liabilities.

Advances in the Treatment of MED.

Four agents are currently approved by the FDA for treatment of erectile dysfunction (prostaglandin E₁ (PGE₁), and three phosphodiesterase (PDE) 5 inhibitors) while apomorphine is approved for use in Europe and Japan (Table 2). The discovery of NO as one of the major substances in vasodilation of the corpus cavernosum and the onset of penile erection led to the discovery of PDE5 inhibitors as therapeutic agents for the treatment of MED (Corbin et al., 2002). PDE5 inhibitors block the hydrolysis of cGMP that is synthesized by soluble guanylate cyclase in response to NO release. Thus, PDE5 inhibitors enhance the existing NO effects by prolonging cGMP levels in the smooth muscle. Sildenafil was the first oral therapeutic for MED and was FDA

approved in 1998. Sildenafil is a potent inhibitor of PDE5, the predominant isoform in the corpus cavernosum smooth muscle ($IC_{50} = 5.3$ nM). In dose escalation studies of sildenafil, 69% of men achieved erections sufficient for intercourse versus 22% in the placebo control group. The inhibition of PDE1 and PDE6 are also of interest as inhibition of these isoforms that are expressed in vascular and retinal cells may be responsible for the side effects of sildenafil (hemodynamic effects and blue vision). Sildenafil exhibits a 40-fold PDE5/PDE1 ratio and a 5-fold PDE5/PDE6 ratio; however, the plasma levels reached by the 100 mg pill are 450 ng/ml (950 nM) so at these plasma levels PDE5, PDE6 and PDE1 are all inhibited. As PDE5 inhibitors potentiate the effects of NO, co-administration with nitrates (angina) and patients with moderate to severe cardiovascular disease are contraindicated (Moreland et al., 2001b).

Tadalafil is a potent inhibitor of PDE5 with an $IC_{50} = 3.6$ nM and exhibits better PDE5/PDE1 and PDE5/PDE6 ratios than sildenafil (Corbin and Francis, 2002). In human cavernosal cells, tadalafil potentiates the accumulation of cGMP induced by sodium nitroprusside and it enhances the relaxation induced by electrical stimulation in human cavernosal strips at 30 nM. Tadalafil relaxes rabbit cavernosal cells pre-contracted with phenylephrine with $IC_{50} = 138$ nM (similar to the potency of sildenafil, $IC_{50} = 135$ nM).

Two types of clinical trials have been conducted with tadalafil: on demand (5, 10 and 25 mg) as well as 3-week treatment to provide 24 h coverage (20 mg dose) to capitalize on the long half-life of tadalafil (17.5 h; Brock et al., 2002; Porst et al., 2003). In a recent trial to demonstrate efficacy up to 36h after dosing, 59% of men taking 20mg tadalafil had successful intercourse attempts versus 28% in the placebo control group (Porst et al., 2003). In an analysis of five of the clinical trials with tadalafil, 75% of men taking the 20 mg dose had successful intercourse attempts versus 32% in the

placebo controlled group (Brock et al, 2003). The FDA approved tadalafil for treatment of MED in November 2003.

Vardenafil is a potent PDE5 inhibitor ($IC_{50} = 0.4$ nM) that exhibits a similar PDE5/PDE1 or PDE5/PDE6 ratio to sildenafil. Vardenafil can relax rabbit cavernosal strips pre-contracted with phenylephrine with $IC_{50} = 164$ nM. It has a half-life of 3.9 h in humans. In a 26-week phase III trial, 79.7% of men taking 20 mg vardenafil were able to have erections sufficient for intercourse versus 50% in the placebo control group (Hellstrom et al., 2003). The FDA approved vardenafil for treatment of MED in August 2003.

Soluble guanylate cyclase (sGC) activators synergistically enhance the effects of NO by stimulating cGMP synthesis without altering the breakdown of cGMP (Brioni et al., 2002). Both A-350619 and BAY41-2272 allosterically activate sGC *in vitro* while inducing penile erection in animal models *in vivo* (Bischoff et al., 2003, Miller et al., 2003). However, all of these agents have yet to advance beyond the preclinical research stage.

The blockade of endogenous vasoconstrictor induced-corpus cavernosum smooth muscle tone has been proposed as a means of inducing penile erection. However, the nonselective α -adrenoceptor antagonist phentolamine has been recently withdrawn from clinical development after a modest demonstration of efficacy in men with mild to moderate MED (Padma-Nathan et al., 2002). Similarly, endothelin antagonists were thought to be a treatment of MED given the presence and potent contractile activity of endothelins (ET) *in vitro* in this tissue (Andersson, 2001). However, efficacy *in vitro* studies with ET_A selective receptor selective antagonist BMS-193884 on rabbit and human corpus cavernosa fail to confirm these hypotheses in a limited human clinical trial where no improvement of erectile function could be

demonstrated (Kim et al., 2002). The recent discovery that the Rho kinase inhibitor Y-27632 potentiates penile erection has generated a renewed interest in understanding the contractile pathways involved in penile flaccidity and potentiation of erection (Chiatley et al., 2003). The ubiquitousness of the pathway raises some concerns regarding cardiovascular side effects (e.g. hypotension). Rho kinase inhibitors have yet to advance beyond the preclinical research stage.

While NO-cGMP actions are important in penile erection, cAMP mediated pathways via VIP, CGRP or endogenous prostaglandin E₂ (PGE₂) may also play a role in penile erection (Andersson, 2001; Moreland et al., 2001a,b). PGE is synthesized by the corpus cavernosum endothelial and smooth muscle cells and binds to specific PGE (EP₂ and EP₄) receptors on the smooth muscle in turn increasing intracellular cAMP synthesis and potentiating smooth muscle relaxation (Moreland et al., 2001a). PGE₁ continues to be an efficacious agent despite injection and intraurethral delivery.

One of the pharmacologic goals in the treatment of male erectile dysfunction has been to delineate the CNS pathways and develop an orally dosed, CNS-acting agent that can treat MED. Both dopaminergic agonists and melatonin agonists have been explored. Dopamine plays a key role as a CNS neurotransmitter in sexual function and penile erection (Moreland et al., 2001b). Injections into the medial preoptic area of the hypothalamus of rats of apomorphine or quinelorane, both nonselective D₂ agonists, induced penile erections in rats. Apomorphine is the first CNS-acting agent approved for treatment of MED (in Europe; 2001). In a Phase III trial to compare dosing between 3 mg and 4 mg sublingual apomorphine with placebo, it was found that 46.9% of men taking 3 mg and 49.4% of men taking 4 mg had erections sufficient for intercourse versus 34% in the placebo control (Dula et al., 2001). Since apomorphine is an agonist at all three D₂-like receptors, it is possible that a selective dopaminergic agonist with

penile erectile effects but lacking the side effects of nausea and cardiovascular effects could be more efficacious. The effect of apomorphine on penile erection is not mediated by D₂-selective agonists (Hsieh et al., 2004). The recent report of a selective D₄ agonist that facilitates penile erection in rats indicates the dopamine D₄ receptor may play a physiological role in erection (Brioni et al., 2003).

Two other agents that induce penile erection by CNS mechanisms are α -melanocyte stimulating hormone (α -MSH) and oxytocin. In conscious rats, both α -MSH and oxytocin administered icv induced intracavernosal pressure increases and penile erections while only oxytocin had an effect intrathecally (Mizusawa et al., 2002). This suggests that supraspinal α -MSH and supraspinal and spinal oxytocin receptors are involved in this process. The α -MSH peptide agonist Melanotan II has been shown to effectively induce penile erection in humans in a limited clinical trial (Moreland et al., 2001b). A slightly different peptide has been prepared and has also been found to induce penile erection via central and spinal melanocortin receptors (Wessells et al., 2003). This concept has further been developed to the α -MSH agonist PT-141 that will be dosed intranasally and is entering early stage clinical trials (Molinoff et al., 2003). Melanotan-II is a nonselective agonist reacting with four of the five melanocortin receptors. Small molecule, nonpeptide agonists of the melanocortin MC-4 receptor such as THIQ also induce penile erection and may provide a novel means of selective therapy via this pathway but remain in the preclinical stage (Van de Ploeg et al., 2002).

Future Prospects

Incontinence remains a condition with few pharmacologic treatment options. While having limited efficacy, muscarinic antagonists remain the mainstay of UUI therapy. The recent FDA approval of darifenacin allow testing of the hypothesis that

M₃-selective antagonists will be more effective than nonselective agents such as oxybutynin and tolteridine. Preclinically, a critical examination of afferent blockade with new purinergic and tachykinin antagonists may be possible. While K-ATP channel blockers directly relax bladder smooth muscle to relieve UUI, the challenge of achieving uroselectivity over cardiovascular effects in a clinical situation remains to be achieved.

With the recent FDA approval letter for duloxetine for SUI, this serotonin, norepinephrine-selective reuptake inhibitor has the potential to be the one of the first pharmacologic options for the treatment of SUI other than collagen injections, surgery and α -adrenergic agonists. This particular area is ripe for exploration of other drug targets and therapeutic agents as well as a better understanding of serotonergic neurotransmission and SUI mechanisms.

In the treatment of MED, PDE5 inhibitors are the current pharmacological gold standard. Guanylate cyclase activators are an exciting means of taking advantage of the NO-cGMP mechanism but remain in preclinical development (Bischoff et al., 2003; Miller et al., 2003). These agents amplify the effects of endogenous NO while lacking some of the potential cardiovascular risks of PDE5 blockade (Brioni et al., 2002). Prostaglandin E vasodilation remains one of the more effective peripherally induced means of potentiating erection in a wide range of patients but is complicated by a more invasive means of delivery and pain in some patients (e.g., intracorporal injection or intraurethral administration). While the recent characterization of EP receptor subtypes suggests that EP2 may play a major role in regulation of PGE-mediated, cAMP-based relaxation may open the way for orally bioavailable, selective agonists (Moreland et al., 2001a,b), localization of EP2 in the peripheral vasculature and in the gastrointestinal tract may preclude systemic dosing. One of the more exciting findings in the last several years has been the regulation of penile vasoconstrictive pathways via Rho

kinase and the proof of principle that the Rho kinase inhibitor Y-28967 can mediate erection but these agents also remain in preclinical development (Chiatley et al., 2003).

CNS activators are an exciting prospect, but may be complicated by potential side effect issues such as mild nausea with apomorphine and increased libido with Melanotan-II (Moreland et al., 2001b). The availability of a safe and efficacious oral CNS activating agent would provide not only novel therapy but may provide a means of combination therapies with PDE5 inhibitors in patients who have up to now been difficult to treat.

While there have been a number advances in the treatment of LUTD in the last decade, much progress remains to be made. The future is bright with a number of potential drug targets now having small molecules to provide proof of principle and other targets at later stages with drugs to be tested in early phase clinical trials.

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TABLE LEGENDS

Table 1. Glossary of terms relating to Lower Urinary Tract Disorders (LUTD)

Partial list of terms relating to LUTD that are used in this review. Short list of symptoms include conditions discussed in the text. Benign prostatic hyperplasia (BPH) and terms involved in male erectile dysfunction (MED) are defined in the text (Taken from Abrams et al., 2003).

Table 2. Agents currently used in the clinic to treat LUTD.

Midodrine and phenylpropanolamine are only approved in Portugal and Finland, respectively to treat SUI. Imipramine is used off-label for SUI and as a norepinephrine reuptake inhibitor and probably works via increase in norepinephrine that in turn, increases urethral smooth muscle tone (Viktrup and Bump, 2003). Abbreviations: BPH: benign prostatic hyperplasia, MED: male erectile dysfunction, NE: norepinephrine, PPA: phenylpropanolamine, 5-HT: serotonin, SUI: stress urinary incontinence, UUI: urge urinary incontinence.

Table 1

Lower Urinary Tract Symptoms (LUTS) Divided into storage, voiding, and post-micturition symptoms.

Symptoms: subjective indicator of a disease or change in condition as perceived by the patient, caregiver or partner

Increased daytime frequency: complaint by the patient who considers that he/she voids too often by day.

Nocturia: complaint that the individual has to wake at night one or more times to void.

Urgency: complaint of a sudden compelling desire to pass urine which is difficult to defer.

Voiding symptoms: during the voiding phase include hesitancy, difficulty to void or inability to stop the void

Signs: Observed by the physician including simple means, to verify symptoms and quantify them.

Observations: Observed by the physician during urodynamic and clinical studies

Urinary incontinence (UI): Complaint of any involuntary leakage of urine.

Stress urinary incontinence (SUI): Complaint of involuntary leakage on effort or exertion, or on sneezing or coughing

Urge urinary incontinence (UUI): Complaint of involuntary leakage accompanied by or immediately preceded by urgency

Overactive bladder syndrome: Complaint of urgency with or without urge incontinence, usually with frequency and nocturia.

Table 2

Agent	Indication	Target/Class of Agent	Effect
Alfuzosin Doxazosin Tamsulosin Terazosin	BPH	α_1 -adrenoceptor antagonists	Relax urethra (prostate?), increase urine flow during void
Dutasteride Finasteride	BPH	5- α -reductase inhibitors.	Decrease prostate size, increase urine flow during void
Apomorphine PGE ₁ Sildenafil Tadalafil Vardenafil	MED	D ₂ -like Receptor Agonist EP Receptor Agonist PDE5 Inhibitor	Activate CNS pathways, peripheral NO release Increase cAMP, Smooth muscle Relaxation Increase cGMP, Smooth muscle Relaxation
Darifenacin Oxybutynin Tolteridine	UUI	Muscarinic Antagonist	Block spontaneous bladder contractions
Duloxetine	SUI	5-HT, NE Reuptake Inhibitor	Increase NE in urethral SM, Increase urethral pressure, Activate CNS 5-HT _{1A} inhibitory micturition pathways
Imipramine Midodrine PPA		Tricyclic antidepressant α -adrenoceptor agonist	Increase NE in urethral SM, increase urethral pressure Increase urethral pressure