The Forefront for Novel Therapeutic Agents Based on the Pathophysiology of Lower Urinary Tract Dysfunction: Pathophysiology of Voiding Dysfunction and Pharmacological Therapy

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Abstract. Normal lower urinary tract function consists of voiding and storage. During voiding, the pontine micturition reflex center orders the sacral parasympathetic nucleus to increase parasympathetic activity, resulting in urinary bladder detrusor contraction via activation of post-synaptic muscarinic receptors (M2/3) and in the relaxation of both urethral and prostatic smooth muscle by nitric oxide (NO). In addition, the rhabdosphincter relaxes by inhibition of the pudendal nucleus at the sacral portion. During the storage phase, increase in sympathetic activity relaxes the urinary bladder via activation of post-synaptic β3-receptors and in the contraction of both urethral and prostatic smooth muscles via α1-adrenoceptor. Many factors influence voiding function, including lower urinary tract disorders (benign prostatic hyperplasia in males, urethral stricture) and neurological disorders (central and peripheral). Theories of pharmacotherapy for voiding dysfunction are 1) increase detrusor contractility and 2) decrease urethral resistance. The former includes agonists for muscarinic receptors and cholinesterase inhibitor; and the latter includes α1-adrenoceptor antagonists, NO donors, benzodiazepines, baclofen, dantrolene, and botulinum toxin.

Keywords: lower urinary tract symptoms (LUTS), voiding dysfunction, pharmacotherapy

1. Normal lower urinary tract function

Normal lower urinary tract function consists of two-phases: filling/storage and emptying/voiding (1 – 3).

Bladder filling and urine storage require 1) accommodation of increasing volumes of urine at a low intravesical pressure (normal compliance), with appropriate sensation; 2) a bladder outlet that is closed at rest and remains so during increases in intra-abdominal pressure; and 3) absence of involuntary bladder contractions (detrusor overactivity).

Bladder emptying/voiding requires the following conditions: 1) a coordinated contraction of the bladder smooth musculature of adequate magnitude and duration, 2) a concomitant lowering of resistance at the level of the smooth and striated sphincter, and 3) absence of anatomic (as opposed to functional) obstruction.

The bladder and urethra constitutes a functional unit, which is controlled by a complex interplay between the central and peripheral nervous system and local regulatory factors (Fig. 1).

1.1. Mechanisms underlying bladder emptying/voiding phase (2, 4 – 7)

1.1.1. Voiding with a normal bladder contraction

Voiding can be voluntary or involuntary and involves an inhibition of the spinal somatic and sympathetic reflexes and activation of the vesical parasympathetic pathways, the organizational center for which is in the rostral brain stem.

Initially, there is a relaxation of the outlet musculature, mediated not only by the cessation of the somatic and...
sympathetic spinal reflexes but probably also by a relaxing factor, very possibly nitric oxide (NO), released by parasympathetic stimulation or by some effect of bladder smooth muscle contraction itself.

A highly coordinated parasympathetically induced contraction of the bulk of the bladder smooth musculature occurs, with shaping or funneling of the relaxed outlet, owing at least in part to smooth muscle continuity between the bladder base and the proximal urethra (Fig. 2).

1.1.2. Active decrease in outlet resistance

A decrease in outlet resistance occurs, with adaptive shaping or funneling of the relaxed bladder outlet. Besides the inhibition of any continence-promoting reflexes that have occurred during bladder filling, the change in outlet resistance may also involve an active relaxation of the smooth sphincter area through a nonadrenergic noncholinergic (NANC) mechanism, probably mediated by NO (7, 8).

The adaptive changes that occur in the outlet are probably also due at least in part to the anatomic interrelationships of the smooth muscle of the bladder base and proximal urethra (Fig. 2).

Hence, lower urinary tract dysfunction can be classified into 2 categories, and each category contains typical diseases.

2. Abnormalities and pathophysiology of emptying/voiding

The pathophysiology of failure of the lower urinary tract to empty adequately must logically be secondary to reasons related to the bladder, the outlet, or both (Table 1) (9). Absolute or relative failure to empty the bladder results from decreased bladder contractility (a decrease in magnitude or duration), increased outlet resistance, or both (3, 10).

2.1. Bladder underactivity

Bladder hypocontractility/acontractility may result from temporary or permanent alteration in one of the neuromuscular mechanisms necessary for initiating and

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**Table 1. Pathophysiology of voiding dysfunction (9)**

1. Decreased contractility of bladder detrusor smooth muscle (detrusor hypocontractility)
   1) Denervation to detrusor muscle: DM, pelvic organ surgery (uterus, rectum, and colon)
   2) Drug side-effects: mainly anti-cholinergic effect
   3) Degeneration and destruction of detrusor muscle: aging, prolonged bladder outlet obstruction
   4) Decreased blood flow to detrusor muscle: atherosclerosis, bladder outlet obstruction
      
      #1 – 3) may be the results of prolonged obstruction and/or peripheral nerve injury.

2. Increased urethral resistance (obstruction)
   1) Mechanical: BPH, urethral stricture (post-traumatic, iatrogenic)
   2) Dynamic: BPH, detrusor sphincter dyssnergia due to several causes (spinal cord injury and other)

BPH: benign prostatic hyperplasia.
maintaining a normal detrusor contraction. Inhibition of the voiding reflex in a neurologically normal individual may also occur; it may be by a reflex mechanism secondary to increased afferent input, especially from the pelvic and perineal areas, or may be psychogenic. Non-neurogenic causes also include impairment of bladder smooth muscle function, which may result from overdistention (hypoxia), various centrally or peripherally acting drugs, severe infection, or fibrosis (11).

2.2. Outlet overactivity or obstruction

Pathologically increased outlet resistance is much more common in men (BPH: benign prostatic hyperplasia) than in women. Although it is most often secondary to anatomic obstruction, it may be secondary to a failure of relaxation or active contraction of the striated or smooth sphincter during bladder contraction. Striated sphincter dyssynergia is a common cause of functional or nonanatomic (as opposed to fixed anatomic) obstruction in patients with neurologic disease or injury. A common cause of outlet obstruction in the female is compression or fibrosis following surgery for sphincteric incontinence.

3. Possible therapies to facilitate bladder emptying mechanisms

The treatment of emptying failure generally consists of maneuvers to increase intravesical/detrusor pressure, facilitate the micturition reflex, decrease outlet resistance, or a combination. If other means fail or are impractical, intermittent catheterization is an effective way to circumvent emptying failure.

4. Possible pharmacotherapies to correct bladder emptying mechanisms (Table 2)

4.1. Increasing intravesical pressure and bladder contractility

4.1.1. Parasympathomimetic agents

In general, either muscarinic receptor agonist or acetylcholinesterase inhibitor is widely used in combination with \( \beta_1 \)-adrenoceptor antagonists for the treatment of voiding difficulty in Japan, but there is little evidence to support their success in facilitating bladder emptying.

Bethanechol: By stimulation of muscarinic receptor and release of acetylcholine in parasympathetic postganglion, physiologic bladder contraction is mediated. Acetylcholine is rapidly hydrolyzed by acetylcholinesterase and by butryrylcholinesterase (12). Many acetylcholine-like drugs exist, but only bethanecol chloride exhibits a relatively selective in vitro action on the urinary bladder and gut with little or no nicotinic action (12, 13).

Distigmine: According to a systematic literature review about the use of parasympathomimetics in the treatment of an underactive bladder, the use of acetylcholinesterase inhibitor therapy is not of proven benefit in treating underactive urinary bladder (14).

Metoclopramide: This drug is a dopamine receptor antagonist with cholinergic properties; hence, this agent might increase detrusor contractility, but there are no controlled studies documenting a useful clinical effect in the treatment of detrusor underactivity (15).

4.1.2. Prostaglandins

Prostaglandins may contribute to the maintenance of bladder tone and bladder contractile activity. However, there is no consensus regarding the effect of prostaglandin to facilitate voiding (7, 16 – 18). However, the EP1 receptor seems to have a role in the development of detrusor overactivity caused by PGE\(_2\) and outlet obstruction (19). EP1 receptor was present in the bladder urothelium and could be activated by PGE\(_2\) to release ATP. EP1 receptor in the urothelium might be important for reflex voiding in pathological conditions (20). Now, an EP1 receptor antagonist (ONO-8539) is under clinical development for bladder hyperactivity.

4.1.3. Opioid receptor antagonists

Opioid receptor antagonists therefore may offer possibilities for stimulating reflex bladder activity, because endogenous opioids have been hypothesized to have a tonic inhibitory effect on the micturition reflex at various levels. However, no opioid antagonist is under clinical investigation at present (21).

Table 2. Pharmacotherapy to facilitate bladder emptying mechanisms

<table>
<thead>
<tr>
<th>1. Increasing intravesical pressure and bladder contractility</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Parasympathomimetic agents: bethanechol, distigmine</td>
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<td>2) Prostaglandins</td>
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<td>3) Opioid receptor antagonists</td>
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<tr>
<th>2. Decreasing outlet resistance</th>
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<tbody>
<tr>
<td>1) ( \alpha_1 )-Adrenoceptor antagonists</td>
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<tr>
<td>2) Anti-androgens (5-( \alpha )-reductase inhibitor) for BPH (mechanical obstruction)</td>
</tr>
<tr>
<td>3) Nitric oxide donors / PDE5 inhibitors</td>
</tr>
<tr>
<td>4) Benzodiazepines, baclofen, and dantrolene</td>
</tr>
<tr>
<td>5) Botulinum toxin</td>
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<tr>
<td>6) Other agents</td>
</tr>
</tbody>
</table>

PDE: phosphodiesterase.
4.2. Decreasing outlet resistance

4.2.1. \( \alpha \)-Adrenoceptor antagonists

The human lower urinary tract contains more \( \alpha_2 \)- than \( \alpha_1 \)-adrenoceptors, but prostatic smooth muscle contraction and human lower urinary tract smooth muscle contraction are mediated largely by \( \alpha_1 \)-adrenoceptors. There are at least three subtypes of \( \alpha_1 \)-adrenoceptors, designated \( \alpha_{1A} \), \( \alpha_{1B} \), and \( \alpha_{1D} \). Smooth muscle contraction in the human lower urinary tract is mediated largely by the \( \alpha_{1A} \)-subtype (and in the detrusor, the \( \alpha_{1D} \)-subtype). In addition to the three cloned \( \alpha_1 \)-adrenoceptors, there is a possible fourth, \( \alpha_{1L} \), although the \( \alpha_{1L} \)-adrenoceptor is probably a variant of the \( \alpha_{1A} \)-adrenoceptor (22 – 25).

So far, many researchers have confirmed the usefulness of \( \alpha \)-adrenoceptor blockade in the treatment of voiding dysfunction (especially neurogenic bladder dysfunction other than BPH), but the efficacy of \( \alpha \)-adrenoceptor antagonists for voiding difficulty not related to BPH have been somewhat less clear.

4.2.2. Anti-androgens

Testosterone 5-\( \alpha \)-reductase is a key enzyme for the activity of androgen in the prostate, and this enzyme catalyzes the conversion of testosterone to dihydrotestosterone (DHT). DHT, but not testosterone, can bind testosterone receptor, and elicits transcription of several growth factors, resulting in prostate growth (Fig. 3).

There are 2 isoforms of 5-\( \alpha \)-reductase, and there are also 2 types of 5-\( \alpha \)-reductase inhibitors for the treatment of BPH. Now, 5-\( \alpha \)-reductase inhibitors are first-line treatment options for symptomatic BPH with a considerable volume (bigger than 30 ml) (26 – 29).

4.2.3. NO donors

In the future, there may be studies to elucidate other pharmacologic mechanisms producing relaxation in the smooth muscle of the bladder neck, urethra, or prostatic stroma. NO is a neurotransmitter capable of producing smooth muscle relaxation, at least in the female rabbit urethra, pig urethra, dog urethra, and human bladder neck (25, 30, 31).

A selective nitrergic action on bladder neck and urethral smooth muscle is an interesting theoretical possibility. On the basis of many findings, NO donors could offer a potential pharmacologic option to treat detrusor-sphincter dyssynergia in spinal cord-injured patients (32, 33).

4.2.4. Phosphodiesterase (PDE) 5 inhibitors

The vas deferens, prostate, seminal vesicle, and corpus cavernosum were found to have high levels of Ca\(^{2+}\)-dependent NO synthase (NOS) activity. Ca\(^{2+}\)-independent NOS activity was not found in the urogenital tract. Functional, biochemical, and immunohistochemical evidences of Ca\(^{2+}\)-dependent NOS in the human prostate have been

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Fig. 3. Anti-androgen therapy for BPH/LUTS: testosterone 5-\( \alpha \)-reductase inhibitors. Both finasteride and dutasteride can reduce prostate volume, resulting in relief of bladder outlet obstruction.

Fig. 4. Inhibitory mechanism for acetylcholine release at the efferent nerve terminal by botulinum toxin. Acetylcholine is released from the efferent nerve terminal by exocytosis, and several proteins (syntaxin, synaptobrevin, and SNAP25) are necessary for this process. Botulinum toxin type A, which is composed of heavy chain and light chain, is absorbed into cytoplasm by endocytosis. Then, light chains of botulinum toxin type A are released and excreted into cytoplasm. SNAP25 is destructed by light chain, and exocytosis of acetylcholine is inhibited.
The effect of NO is mediated by soluble guanylyl cyclase, which converts guanylyl triphosphate (GTP) to cyclic guanosine monophosphate (cGMP), resulting in relaxation of smooth muscle. PDE degrades cGMP, thereby inhibiting smooth muscle relaxation. There are more than 11 subtypes of PDEs, and most of them have been found in human prostate tissue (37). Investigations have demonstrated that drugs interfering with the cyclic nucleotide–mediated pathways can reverse the tension induced by norepinephrine in isolated prostatic tissue and elevate cyclic adenosine monophosphate (cAMP) and cGMP. Several findings serve to explain how PDE inhibitors can affect male lower urinary tract symptoms (LUTS) and BPH (38, 39) (Tables 3 and 4).

Several preliminary studies of PDE5 inhibitors, sildenafil and tadalafil, have recently been conducted in men with concomitant erectile dysfunction and LUTS, and they have demonstrated efficacy, both alone and in combination with an α-blocker, in treating LUTS along with sexual dysfunction (40 – 42).

Any significant change in objective outcomes in these trials could not be obtained despite symptomatic improvement. A new larger scale randomized controlled trial (RCT) using tadalafil has been conducted, and once daily tadalafil demonstrated clinically meaningful and statistically significant efficacy; it was well tolerated in men with BPH/LUTS. Of the doses studied 5 mg tadalafil appeared to provide a positive risk-benefit profile (43).

### Table 3. Profiles of 3 PDE5 inhibitors available in Japan

<table>
<thead>
<tr>
<th>Name of products (Commercial name)</th>
<th>Sildenafil (Viagra®)</th>
<th>Valdenafil (Revitora®)</th>
<th>Tadalafil (Sialis®)</th>
</tr>
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<tbody>
<tr>
<td>Company</td>
<td>Pfizer</td>
<td>Bayer</td>
<td>Lilly</td>
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<tr>
<td>Duration</td>
<td>4 h</td>
<td>4 – 5 h</td>
<td>36 h</td>
</tr>
<tr>
<td>Dose</td>
<td>25, 50 (100 mg)</td>
<td>10, 20 mg</td>
<td>10, 20 mg</td>
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<tr>
<td>Reduction of efficacy by diet</td>
<td>Yes</td>
<td>High fat diet has some effect</td>
<td>No</td>
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<tr>
<td>Launch in Japan</td>
<td>1999</td>
<td>2004</td>
<td>2007</td>
</tr>
<tr>
<td>Reimburse for erectile dysfunction (ED) in Japan</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>New indication with reimbursement in Japan</td>
<td>2008: 20 mg tablet for pulmonary hypertension</td>
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### Table 4. Distribution of PDE isozymes in human tissues

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<th>4A</th>
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<th>7A</th>
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<td>Lung</td>
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PDE: phosphodiesterase. Modified from Tables 1 – 3 of Ref. 36.

4.2.5. Benzodiazepines, baclofen, and dantrolene

There is no class of pharmacologic agents that will selectively relax the striated musculature of the pelvic floor. Three different types of drugs have been used to treat voiding dysfunction secondary to outlet obstruction at the level of the striated sphincter: the benzodiazepines, dantrolene, and baclofen. γ-Aminobutyric acid (GABA) and glycine have been identified as major inhibitory transmitters in the central nervous system (CNS) (5, 7, 44). GABA is the most widely distributed inhibitory neurotransmitter in the mammalian CNS. GABA receptors have been divided into three types.

**Benzodiazepines:** Benzodiazepines potentiate the action of GABA by facilitating neuronal hyperpolarization through the GABA<sub>A</sub> receptor (45). Few references are available that provide valuable data on the use of any of the benzodiazepines in the treatment of functional obstruction at the level of the striated sphincter.
Baclofen: Baclofen depresses monosynaptic and polysynaptic excitation of motoneurons and interneurons in the spinal cord by activating GABA_B receptors. Baclofen’s primary site of action is in the spinal cord. For the adequate effect, bypassing the blood-brain barrier by intrathecal infusion, not by oral administration, is required.

Dantrolene: Dantrolene (Dantrium) exerts its effects by a direct peripheral action on skeletal muscle. The drug has been reported to improve voiding function in some patients with classic detrusor-striated sphincter dysynergia with a high risk of hepatotoxicity (46, 47).

4.2.6 Botulinum toxin

Botulinum A toxin (Botox®) is an inhibitor of the release of acetylcholine and other transmitters at the neuromuscular junction of somatic nerves in striated muscle and of autonomic nerves in smooth muscle (48) (Fig. 4).

Its urologic use for the treatment of detrusor-striated sphincter dysynergia in spinal cord injury patients was first reported by Dykstra and colleagues (49).

Botox® was injected transurethrally or transperineally into striated sphincter with a considerable efficacy. A potential side effect is the spread to nearby muscles, particularly when high volumes of Botox® are injected. Botulinum toxin should be used only under close supervision in patients with already disturbed neuromuscular transmission or during treatment with aminoglycosides (50 – 53).

References
27 Tsuchamoto T, Endo Y, Narita M. [Assessment of recommended dose of dutasteride on Japanese men with benign prostatic hyper-


40 Kaplan SA, Gonzalez RR, Te AE. Combination of alfuzosin and sildenafil is superior to monotherapy in treating lower urinary tract symptoms and erectile dysfunction. Eur Urol. 2007;51:1717–1723.


