Pharmacotherapy for Stress Urinary Incontinence

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The purpose of this review article is to highlight new pharmacotherapies on the horizon for the treatment of stress urinary incontinence. Although behavioral and surgical therapies are currently the mainstay of treatment for this condition, we are hopeful that pharmacotherapy will one day take center stage of the various treatment options. Currently, there are no medications approved by the US Food and Drug Administration for the treatment of stress urinary incontinence. However, exciting clinical data are becoming available about an oral medication for the treatment of stress urinary incontinence that appears to be clinically safe and efficacious. In addition to discussing medications currently under development, this article also discusses pharmacologic targets that could be suitable future targets to treat stress urinary incontinence.
[Rev Urol. *2003;5(3):135–141*]

Key words: Duloxetine • Stress urinary incontinence • Urethra • Serotonin

Stress urinary incontinence (SUI) is a major urologic health care problem worldwide. In the United States, it is estimated to affect approximately 25 million women.[1] In addition, the number of patients with SUI is expected to rise dramatically as women in the baby-boomer generation age. The primary etiologic factor of SUI is vaginal parity,[2-6] usually due to a combined muscular, nerve, and connective tissue injury.[7-11] Urinary incontinence causes unnecessary social isolation and expense. The annual direct cost of caring for women with urinary incontinence in the United States was estimated to be $12.4 billion in 1995 dollars.[12] The predominant cost can be attributed to management measures, such as pads and diapers, and not to treatment measures.

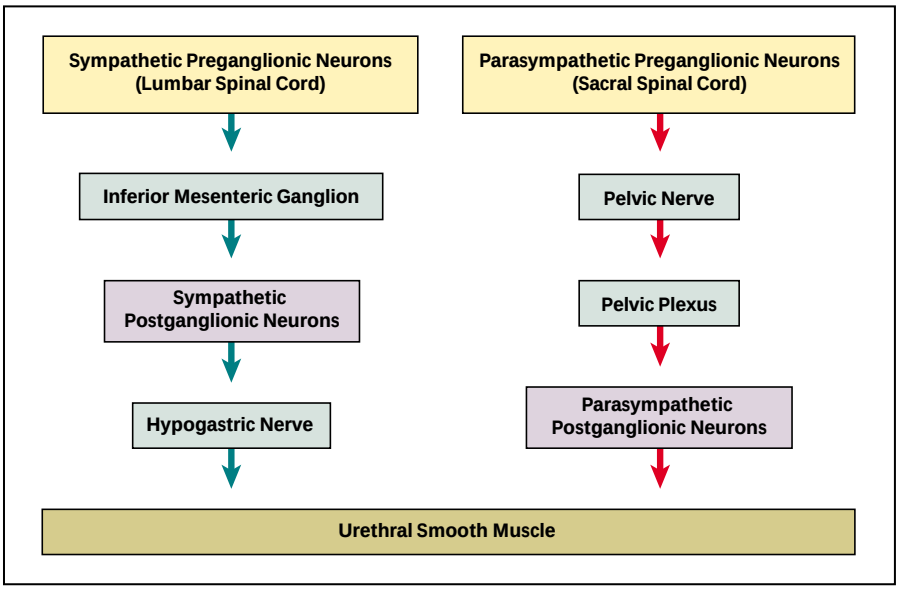


Figure 1. *Sympathetic and parasympathetic control of urethral smooth muscle. Red and green arrows indicate inhibition and excitation, respectively.*

Current Therapies for Stress Urinary Incontinence

There are a variety of therapies for SUI, including conservative measures involving physical therapy (such as pelvic floor muscle training, biofeedback, and electrical stimulation), bladder retraining, anti-incontinence devices (such as intravaginal urethral compression devices, occlusive devices, and intraurethral devices), and a combination of these strategies. These conservative therapies often fail or are unsatisfactory options for patients with more severe SUI. Periurethral bulking agents, retropubic suspension procedures, and various transvaginal anti-incontinence procedures are more invasive options.

The one type of treatment of SUI that has been sufficiently devoid of novel strategies is pharmacologic therapies that increase urethral resistance. Although several medications have been used to treat SUI, none is FDA-approved and none is very successful. Once patients have completed a full evaluation, initial treatment often consists of behavioral modification, followed by surgical therapies. The concept of pharmacologic therapy as a first-line therapy for SUI is presented in this paper, along with the possibility of synergy between pharmacologic therapy and current conservative measures to help improve our current treatment strategies for SUI.

The sympathetic, parasympathetic, and somatic nervous systems all contribute to urethral innervation coordinated by the central nervous system.

Review of Urethral Continence Mechanisms

The sympathetic, parasympathetic, and somatic nervous systems all contribute to urethral innervation coordinated by the central nervous system. These neural pathways control the function of the bladder and urethra to maintain continence. A simple diagram of the involved neuropathways is shown in Figure 1.

Sympathetic

Preganglionic sympathetic nerves emanate from the lumbar spinal cord and synapse in the inferior mesenteric ganglion. Postganglionic sympathetic nerves travel through the hypogastric nerve and provide noradrenergic input to the urethral smooth muscle.

Parasympathetic

Arising from the sacral spinal cord, pelvic parasympathetic nerves also innervate urethral smooth muscle. The sacral spinal cord has a region identified as the sacral parasympathetic nucleus (SPN), from which parasympathetic preganglionic neurons send axons through the pelvic nerve and synapse in the pelvic plexus. The postganglionic parasympathetic neurons are predominately cholinergic and innervate the urethral smooth muscle.

Somatic

The external urethral sphincter (EUS)

Figure 2. *Somatic control of the external urethral sphincter.*

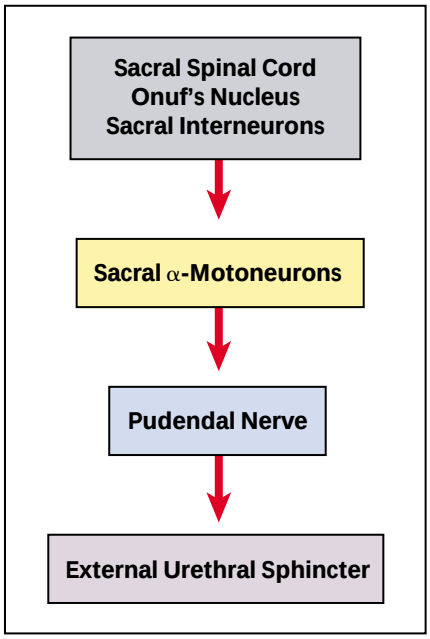


Table 1
Pharmacotherapy to Increase Outlet Resistance

- α-Adrenergic agonists
- Tricyclic antidepressants
- β-Adrenergic antagonists
- Estrogens
- β2-Adrenergic agonists

is under voluntary control through the somatic system. Onuf's nucleus, which is the location of the EUS motoneurons, is situated in the lateral border of the ventral horn of the sacral spinal cord. The axons of the EUS motoneurons traverse the pudendal nerve and innervate urethral striated muscle (Figure 2).

Pharmacotherapy to Increase Outlet Resistance

A basic understanding of the neurourology of the lower urinary tract has provided researchers with many different avenues to approach the goal of increased outlet resistance (Table 1).

α-Adrenergic Agonists

The bladder neck and proximal urethra contain α-adrenergic receptors that produce smooth muscle contraction when stimulated.[13] Many oral pharmacologic agents that produce α-adrenergic receptor stimulation are available; however, the potential side effects of these drugs at doses that can promote continence can be severe and life-threatening. Some of the side effects include hemorrhagic stroke, hypertension, anxiety, insomnia, headache, tremor, weakness, palpitations, and cardiac arrhythmias.[13] α-Adrenergic agonists that have been tested as potential pharmacologic therapies for SUI include ephedrine, norfenefrine, phenylpropanolamine hydrochloride, and midodrine.[14-19] It appears that α-adrenergic agonists and agents that have an α-adrenergic effect in the urethral sphincter can produce satisfactory or partial improvement in mild cases of SUI but rarely bring about total dryness in patients with severe or moderate SUI.

Tricyclic Antidepressants

Tricyclic antidepressants, imipramine hydrochloride and doxepin in particular, can decrease bladder contractility and increase urethral resistance.[20] Although these agents have many pharmacologic actions, the mechanism by which they produce the observed effects on the lower urinary tract is not known. It is hypothesized that tricyclic antidepressants produce an enhanced α-adrenergic effect in the smooth muscle of the bladder base and proximal urethra, where α-receptors outnumber β-receptors, thereby increasing outlet resistance.[13] The primary reason that tricyclic antidepressants have not been widely used to treat SUI is their side effect profile. Some common side effects of tricyclic antidepressants are listed in Table 2.[13]

Table 2
Side Effects of Tricyclic Antidepressants

- Rash
- Hepatic dysfunction
- Jaundice
- Agranulocytosis
- Weakness
- Fatigue
- Tremors
- Sedation
- Postural hypotension
- Sexual side effects
- Arrhythmia

ß-Adrenergic Antagonists

Theoretically, β-adrenergic blocking agents should unmask or potentiate an α-adrenergic effect, resulting in increased urethral resistance.[13] A few initial studies have reported success in treating SUI with propranolol.[21,22] However, subsequent reports do not support the efficacy of propranolol in the treatment of SUI. In addition, propranolol has some major potential side effects, including heart failure and increased airway resistance.

Estrogens

Although estrogens do not appear to affect the pharmacology of urethral continence directly, they can indirectly affect pharmacologic interactions in the lower urinary tract, such as receptor sensitivity, density, and neurotransmitter metabolism.[23-25] Estrogens also affect the vascular and connective tissue elements of the urethral wall, which are important features of female continence.

ß2-Adrenergic Agonists

There have been a few reports examining β2-adrenergic agonists for treatment of SUI. These agents have been reported to increase the contractility of fast-contracting striated muscle fibers and suppress the slow-contracting fibers in guinea pigs.[26] Clenbuterol is one such selective β2-adrenergic agonist.[13]

The Future

In-depth neurourology research has enhanced our understanding of urethral continence mechanisms and EUS function. Studies have demonstrated that serotonergic agonists generally suppress parasympathetic activity and enhance sympathetic and somatic activity in the lower urinary tract, promoting urine storage. Serotonergic antagonists have opposing effects.[27-29] Noradrenergic agonists and antagonists also produce effects on sympa-

Table 3
Selective Serotonin and/or Norepinephrine Reuptake Inhibitors

	Selective Serotonin Reuptake Inhibitor	Norepinephrine Reuptake Inhibitor
Venlafaxine	✔	✔
Duloxetine	✔	✔
S-norfluoxetine	✔	
Thionisoxetine		✔

Data from Katofiasc et al.[37]

thetic and somatic activity in the lower urinary tract, which are dependent on the adrenergic receptor subtype with which the agonists and antagonists interact.[28,30-34] Based on these potentially continence-promoting properties of serotonin and norepinephrine, animal studies have been conducted with various serotonin-selective, norepinephrine-selective, or dual serotonin and norepinephrine reuptake inhibitors (Table 3).

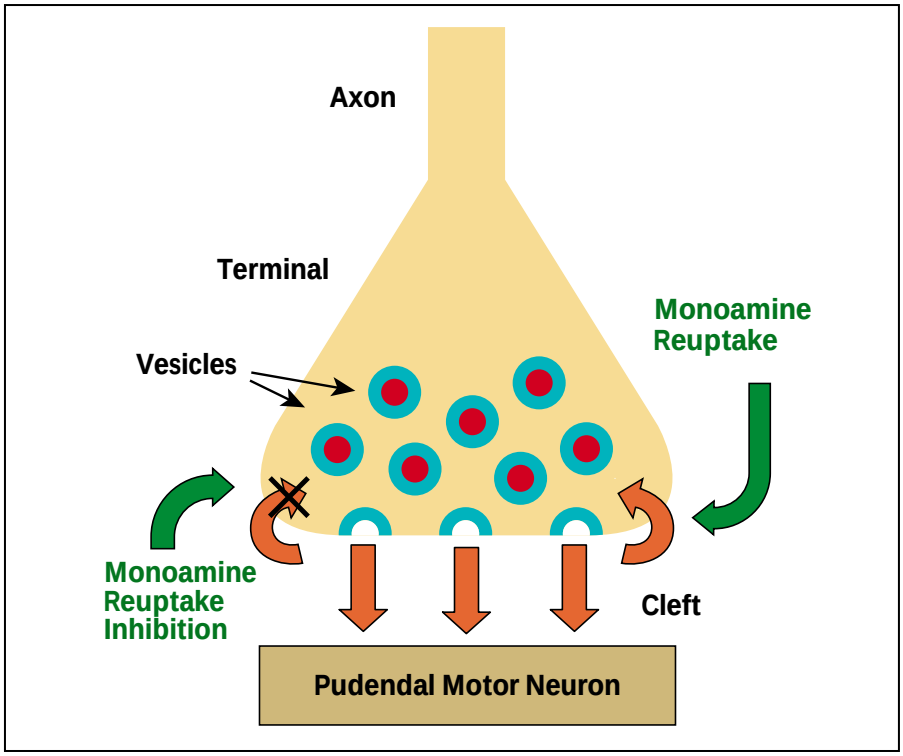
Serotonin and the Lower Urinary Tract
In cat studies by Danuser and Thor,[29] administration of a 5-HT2 agonist (2,5-dimethoxy-4-iodophenylliso-propylamine) produced a marked increase in the amplitude of the sphincter reflex. These effects could be reversed by administration of a 5-HT2 antagonist (LY53857). This suggests that stimulation of 5-HT2 receptors enhances guarding reflexes and may improve continence.[35]

Noradrenergic Neurotransmitters and the Lower Urinary Tract
Selective α1-adrenergic receptor antagonists have long been used to decrease urethral obstruction in men with benign prostatic hyperplasia. Given this fundamental knowledge and animal studies demonstrating that α1-antagonists (such as prazosin) can decrease the amplitude of sphincteric reflexes, a logical pharmaceutical target would be a selective norepinephrine agonist to facilitate urethral continence.[36] Thionisoxetine is a norepinephrine-selective reuptake inhibitor; however, in recent cat studies this drug has shown no effect on bladder capacity or sphincter electromyography (EMG) activity.[37]

Targeting Both the α1 Receptors and the 5-HT2 Receptors
There are several possible methods of increasing the effects of serotonin and norepinephrine on the storage mechanisms of the lower urinary tract. One method is to block the reuptake of these neurotransmitters at the nerve terminals, thereby increasing receptor stimulation (Figure 3). Duloxetine and venlafaxine are two such drugs that block both serotonin and norepinephrine reuptake.

Animal Studies
Duloxetine has been used to study neural control of the lower urinary tract in cats. In studies by Katofiasc, Thor, and colleagues, duloxetine significantly increased bladder capacity and EUS EMG activity in a cat model of irritated bladder function.[35,37] The effects of duloxetine on bladder capacity could be antagonized by methiothepin, a nonselective 5-HT receptor antagonist.[35] The effects of

Figure 3. *Monoaminergic synapse, illustrating monoamine reuptake from the synaptic cleft and monamine reuptake inhibition.*



duloxetine on the EUS EMG activity could be antagonized not only by methiothepin but also by LY53857 (a 5-HT2 serotonergic receptor antagonist) and prazosin (an α1-adrenergic receptor antagonist).[35]

These studies and others propose that the effect of dual serotonergic and noradrenergic reuptake inhibitors is to prolong serotonin and norepinephrine neurotransmitters in the synaptic cleft, thereby increasing the amount of receptor stimulation (see Figure 3). The ability of duloxetine to increase the activity of the EUS makes it an attractive compound for the treatment of SUI.

Duloxetine is not the only dual serotonin and norepinephrine reuptake inhibitor that has potential in the treatment of SUI. Another compound, venlafaxine, has been demonstrated to produce dramatic increases in bladder capacity and EUS EMG activity in cats. However, venlafaxine does not appear to be as potent as duloxetine.[37]

There are many unanswered questions concerning the mechanism of action of these dual serotonergic and noradrenergic reuptake inhibitors. In a recent study, Katofiasc and colleagues[37] attempted to determine the relative importance of serotonin versus norepinephrine reuptake inhibitors. S-norfluoxetine, a serotonin-selective reuptake inhibitor, was administered to cats and produced small but significant increases in bladder capacity and EUS EMG activity. Thionisoxetine, a norepinephrine-selective reuptake inhibitor, produced no effects on bladder capacity or EUS EMG activity. The coadministration of S-norfluoxetine and thionisoxetine did not produce any effects on bladder capacity or EUS EMG activity. Thus, the dramatic effects of dual 5-HT and norepinephrine reuptake inhibitors on bladder capacity and EUS EMG activity cannot be reproduced with the combined administration of selective 5-HT and norepinephrine reuptake inhibitors. The pharmacologic difference between the effects of single compounds that have dual reuptake inhibition and the combination of 2 compounds with selective inhibition has yet to be explained.

The ability of duloxetine to increase the activity of the EUS makes it an attractive compound for the treatment of SUI.

Duloxetine Studies in Humans

Duloxetine is currently being evaluated for the treatment of SUI in phase III clinical trials.[38,39] It is the first drug to be tested for the treatment of SUI in a large, randomized trial. A recent report by Zinner and colleagues[39] assessed the efficacy and safety of duloxetine for the treatment of SUI in a double-blind, randomized, placebo-controlled study. To qualify for the study, women had to have a predominant symptom of SUI, a weekly incontinence episode frequency (IEF) of 7 or more, and multiple other qualifiers, which are listed in Table 4. A total of 683 women aged 22 to 84 years were randomized to placebo (n = 339) or duloxetine, 80 mg/d (n = 344), for 12 weeks. Outcome variables assessed after 12 weeks of treatment included IEF, voiding diaries, and the Incontinence Quality of Life (I-QOL) and Patient Global Impression of Improvement (PGI-I) scales.

Duloxetine was associated with a significant decrease in IEF and improvements in the PGI-I and I-QOL scales. The PGI-I results demonstrated that 62% of duloxetine subjects considered their bladder condition to improve with treatment compared with 39.6% of placebo subjects ($P < .001$). In addition, duloxetine subjects demonstrated statistically significant improvements compared with placebo in the 3 I-QOL domains of avoidance and limiting behavior, social embarrassment, and psychosocial impact. These improvements with duloxetine were associated with significant increases in voiding intervals compared with placebo.[39]

Table 4
Phase III Duloxetine Study Qualifiers

- Predominant symptoms of stress urinary incontinence
- Weekly incontinence episode frequency ≥ 7
- Absence of predominant urge symptoms
- Normal diurnal and nocturnal frequencies
- Bladder capacity ≥ 400 mL
- Positive cough stress test
- Positive stress pad test

Data from Zinner et al.[39]

The rate of discontinuation because of side effects among patients who received duloxetine, 80 mg, was 24%, compared with 4% for those who received placebo.[39] The discontinuation rate for adverse events recognized as attributable to duloxetine was 16.6%. Nausea was the most common reason for discontinuation (6.4%) and tended to be mild and transient. In the phase II duloxetine studies, other reasons for discontinuation included somnolence, dizziness, and menorrhagia.[38] None of the reported adverse events was considered to be clinically severe.

Summary

The monoamines serotonin and norepinephrine are clearly implicated and appear to be intimately involved in

the continence mechanisms of the smooth and striated urethral musculature. Not surprisingly, these neurotransmitters are being investigated as potential pharmaceutical targets in the treatment of SUI. The monoamine reuptake inhibitors, a new generation of antidepressant drugs with fewer side effects than tricyclic antidepressants, have been investigated as potential therapeutic agents for the treatment of SUI. Duloxetine, a compound with dual activity as a selective serotonin and norepinephrine reuptake inhibitor, is one such drug. Duloxetine is believed to increase efferent output from Onuf's nucleus via stimulation of the pudendal motor neuron α1-adrenergic and 5-HT2 receptors, resulting in enhanced contractility of the rhabdosphincter.[35] In phase II and III trials, duloxetine demonstrated efficacy and safety as a pharmacologic therapy for SUI, independent of the baseline of incontinence severity.[38,39] ■

The authors acknowledge the support of the following NIH grants: PO1 HD39768, RO1 AR049398, K12 DK02656; as well as a clinical trial consultancy grant from Eli Lilly and Company.

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Main Points

- Stress urinary incontinence (SUI) is estimated to affect approximately 25 million women in the United States, and this number is expected to rise dramatically as baby boomers age.
- Invasive treatments include periurethral bulking agents, retropubic suspension procedures, and various transvaginal anti-incontinence procedures.
- α-Adrenergic agonists and agents that have an α-adrenergic effect in the urethral sphincter can produce satisfactory or partial improvement in mild cases of SUI but rarely bring about total dryness in patients with severe or moderate SUI.
- Tricyclic antidepressants, imipramine hydrochloride and doxepin in particular, can decrease bladder contractility and increase urethral resistance, but their side effects have prevented widespread use for treatment of SUI.
- Initial studies reported success in treating SUI with propranolol, but subsequent reports did not support the efficacy of this treatment. In addition, propranolol has some major potential side effects, including heart failure and increased airway resistance.
- Duloxetine and venlafaxine block both serotonin and norepinephrine reuptake and, hence, may increase the effects of serotonin and norepinephrine on the storage mechanisms of the lower urinary tract.
- In a study of women with SUI and a weekly incontinence episode frequency (IEF) of 7 or more, duloxetine was associated with a significant decrease in IEF and improvements in quality-of-life scales.

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