CONSERVATIVE MANAGEMENT OF STRESS URINARY INCONTINENCE IN WOMEN

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ABSTRACT

Although behavioral and surgical therapies are currently the mainstay of treating stress urinary incontinence (SUI), medications to treat SUI may possibly become first-line therapy. Currently, there are no medications approved by the US Food and Drug Administration that are indicated for SUI. However, results are becoming available on duloxetine, an oral medication that appears to be clinically safe and efficacious for the treatment of SUI. In addition to discussing medications currently under development, we will also discuss exciting pharmacologic targets that may be suitable for the treatment of SUI. Biofeedback also has demonstrated promise as an aid to the management of SUI, and many clinicians who treat SUI routinely incorporate this intervention into their therapeutic strategies. Pelvic floor muscle training remains a useful therapy for virtually all patients with SUI. Bladder retraining has demonstrated some promise, and its role in therapy continues to evolve.


Millions of women suffer from urinary incontinence, often in silence. In the United States, urinary incontinence affects an estimated 25 million women.1 The number of patients with stress urinary incontinence (SUI) is expected to rise dramatically as women in the “baby boom” generation age. SUI can cause unnecessary social isolation, and disposable products to manage urinary incontinence can be quite costly over the long term. The annual direct cost of care for women with urinary incontinence in the United States was estimated to be $12.4 billion in 1995.2 The predominant costs involve management measures, such as pads and diapers, not treatment measures. The primary etiologic factor of SUI is vaginal parity,3-7 usually due to a combination of muscular, nerve, and connective-tissue injuries.8-12 Many clinicians have considered SUI to be a purely anatomical deficit and therefore have not been enthusiastic about the potential of pharmacologic therapy. However, due to innovative basic and clinical research, new pharmacologic options are being studied.

CURRENT MANAGEMENT OF SUI

A variety of conservative treatments exist for SUI, including pelvic floor muscle training, biofeedback, electrical stimulation, bladder retraining, and anti-incontinence devices (intravaginal urethral compression devices, occlusive devices, and intraurethral devices). However, traditional conservative therapies often fail or are unsatisfactory for patients with more severe SUI. Periurethral bulking agents, retropubic suspension procedures, and various transvaginal anti-incontinence procedures are more invasive options.
SUI therapy has been relatively devoid of novel pharmacologic strategies to increase urethral resistance. Although several medications have been used to treat SUI, none are approved by the US Food and Drug Administration (FDA), and none have been very successful. Emerging pharmacologic options may offer the possibility of a new approach to first-line therapy for SUI, including potentially synergistic therapeutic action with the combination drug treatment and existing conservative measurements, which could lead to improved treatment of SUI.

**Urethral Continence Mechanisms**

The emerging pharmacologic strategies for SUI have evolved from improved understanding of the neurologic control of bladder and urethral function. The sympathetic, parasympathetic, and somatic nervous systems all contribute to urethral innervation, coordinated by the central nervous system (Figure 1). These neural pathways control the function of the bladder and urethra to maintain continence.

**Sympathetic Control**

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 (Figure 1). Activation of sympathetic nerves innervating the urethra induces urethral contraction and urine storage.

**Parasympathetic Control**

Arising from the sacral spinal cord, pelvic parasympathetic nerves also innervate urethral smooth muscles. The sacral spinal cord includes the region known as the sacral parasympathetic nucleus, from which parasympathetic preganglionic neurons send axons through the pelvic nerve and synapse in the pelvic plexus. Postganglionic parasympathetic neurons that innervate urethral smooth muscle are mediated predominantly by nitric oxide to induce urethral relaxation during voiding (Figure 1).

**Somatic Control**

The external urethral sphincter (EUS) consists of striated muscles that are controlled by the somatic nervous system, which can be activated voluntarily or by reflex mechanisms elicited by bladder distension. EUS motor neurons are located in Onuf’s nucleus, which is located at the lateral border of the ventral horn of the sacral spinal cord. Axons of these motor neurons traverse the pudendal nerve and innervate urethral striated muscles (Figure 1).

**Pharmacotherapy to Increase Outlet Resistance**

Improved understanding of the neurourology of the lower urinary tract has provided researchers with many different avenues to approach the goal of pharmacologic therapy to increase outlet resistance.

**Alpha-adrenergic Agonists**

The bladder neck and proximal urethra contain alpha-adrenergic receptors, which, when stimulated, produce smooth muscle contraction. Many oral pharmacologic agents that produce alpha-adrenergic receptor stimulation are available. However, potential side effects of these drugs at doses that can promote continence can be severe or life threatening and include hypertension, anxiety, hemorrhagic stroke, insomnia, headache, tremor, weakness, palpitations, and cardiac arrhythmias. The alpha-adrenergic agonists that have been tested as a potential pharmacologic treatment for SUI include norfenefrine, ephedrine, phenylpropanolamine hydrochloride, and midodrine. It appears that alpha-adrenergic agonists,
which induce urethral smooth muscle contractions by activation of alpha-adrenoceptors, can achieve satisfactory improvement in some patients with mild cases of SUI, but rarely total dryness in patients with moderate or severe SUI.

**Tricyclic Antidepressants**

Tricyclic antidepressants, particularly doxepin and imipramine hydrochloride, can decrease bladder contractility and increase urethral resistance. These agents have many pharmacologic actions, and the mechanisms by which they affect the lower urinary tract are not known. One hypothesis is that tricyclic antidepressants enhance alpha-adrenergic activity in the smooth muscle of the proximal urethra and bladder base, where alpha-receptors outnumber beta-receptors, thereby increasing outlet resistance. The primary reason that tricyclic antidepressants have not been widely used to treat SUI is their side-effect profile (Table 1).

**Beta-adrenergic Antagonists and Agonists**

Theoretically, beta-adrenergic blocking agents should unmask or potentiate an alpha-adrenergic effect to increase urethral resistance. Preliminary studies demonstrated success with propranolol in patients with SUI. However, subsequent reports have not corroborated the efficacy of propranolol for the treatment of SUI. Additionally, propranolol has some major potential side effects, including increased airway resistance and heart failure.

**Estrogens**

Estrogens do not directly affect the pharmacology of urethral continence. However, it does appear that estrogens can indirectly affect pharmacologic interactions in the lower urinary tract, such as receptor density, sensitivity, and neurotransmitter metabolism. Also, estrogens affect the vascular and connective tissue elements of the urethral wall, which is also an important feature of female continence.

**Beta2-adrenergic Agonists**

A few reports have examined beta2-adrenergic agonists, which have been reported to increase the contractility of fast-contracting striated muscle fibers and to suppress the slow-contracting fibers in guinea pigs. Clenbuterol is one such selective beta2-adrenergic agonist.

**Future Urethral Targets**

In-depth neurourology research has enhanced 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. Noradrenergic agonists and antagonists have similar effects on sympathetic and somatic activity in the lower urinary tract.

**Table 1. Side-effect Profile of Tricyclic Antidepressants**

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<tr>
<th>Side-effect Profile of Tricyclic Antidepressants</th>
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<td>Tremors</td>
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**Figure 2. Norepinephrine and Serotonin Reuptake Inhibition and Increase in Receptor Activation**

![Diagram of norepinephrine and serotonin reuptake inhibition and increase in receptor activation.](image-url)
tinence-promoting properties of norepinephrine and serotonin, animal studies have been conducted with various norepinephrine-selective, serotonin-selective, or dual serotonin and norepinephrine reuptake inhibitors (Figure 2).

**SEROTONIN**

Danuser et al.²⁹ reported that administration of the 5-HT₂ agonist 2,5-dimethoxy-4-iodophenyllisopropylamine produced a marked increase in the amplitude of the sphincter reflex. Administering a 5-HT₂ antagonist (LY53857) reversed these effects, suggesting that stimulation of 5-HT₂ receptors enhances guarding reflexes and could improve continence.³⁵

**NORADRENERGIC NEUROTRANSMITTERS**

Selective α₁-adrenergic receptor antagonists have long been used to decrease urethral obstruction in men with benign prostatic hyperplasia. This fundamental knowledge, combined with data from animal studies demonstrating that α₁-antagonists (such as prazosin) can decrease the amplitude of sphincteric reflexes,²⁹,³⁶ indicated that a selective norepinephrine agonist would be a logical pharmaceutical target to facilitate urethral continence. However, thionisoxetine, a norepinephrine-selective reuptake inhibitor, had no effect on bladder capacity or sphincter electromyographic (EMG) activity.³⁷

**ALPHA₁ AND 5-HT₂ RECEPTORS**

Several possibilities exist for 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 2). Duloxetine and venlafaxine are 2 such drugs that block both serotonin and norepinephrine reuptake.

Animal Studies: Duloxetine’s effect on neural control of the lower urinary tract has been investigated in cats. Studies demonstrated that duloxetine significantly increased EUS EMG activity and bladder capacity in a 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 duloxetine on EUS EMG activity could be antagonized by methiothepin, by LY53857 (a 5-HT₂ serotoninergic receptor antagonist), and by prazosin (α₁-adrenergic receptor antagonist). These studies and others propose that dual serotoninergic and noradrenergic reuptake inhibitors prolong serotonin and norepinephrine neurotransmitters in the synaptic cleft, thereby increasing receptor stimulation (Figure 2). The ability of duloxetine to increase the activity of the EUS makes this an attractive compound in the treatment of SUI.

Venlafaxine, another dual reuptake inhibitor, produced dramatic increases in EUS EMG activity and increases in bladder capacity in cats.³⁷ However, venlafaxine does not appear to be as potent as duloxetine.

Many questions remain unanswered concerning the mechanism of action of these dual serotonergic and noradrenergic reuptake inhibitors. A recent study by Katofiasc et al.³⁷ attempted to determine the relative importance of serotonin versus norepinephrine reuptake inhibition. S-norfluoxetine, a serotonin-selective reuptake inhibitor, was administered to cats and produced small but significant increases in EUS EMG activity and bladder capacity. Thionisoxetine, a norepinephrine, selective reuptake inhibitor, had no effect on bladder capacity or EUS EMG activity. Coadministration of S-norfluoxetine and thionisoxetine also had no effect on bladder capacity or the 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 norepinephrine and 5-HT reuptake inhibitors.

The beneficial effects of duloxetine are mediated centrally via both motor efferent and sensory afferent modulation. The ability of duloxetine to improve bladder storage appears to be unique to the combination of 5-HT and norepinephrine reuptake inhibition in a single molecule.³⁷ The pharmacologic differences between a single compound that has dual reuptake inhibition and the combination of 2 compounds with selective inhibition have yet to be explained.

**CLINICAL INVESTIGATION OF DULOXETINE FOR SUI**

A phase 2 clinical study compared duloxetine with placebo as treatment for SUI.³⁸ In this 12-week double-blind study, investigators enrolled and randomized 553 women aged 18 to 65 years to receive placebo (n = 138) or one of 3 doses of duloxetine (138 patients at 20 mg daily, 137 at 20 mg twice daily, and 140 at 40 mg twice daily). At 12 weeks, pooled diary analysis showed that incontinence episode frequency (IEF) declined by a median of 41% with placebo compared
with 54% with duloxetine 20 mg daily (P = .06), 59% with duloxetine 40 mg daily (P = .002), and 64% with duloxetine 80 mg daily (P < .001). Half of the patients receiving the 80-mg dose had 64% or greater reduction in IEF (P < .001 vs placebo), and 67% had 50% or greater reduction (P = .001 vs placebo). These improvements occurred despite a significant concurrent dose-dependent increase in average voiding interval in the duloxetine groups compared with the placebo group. Similar statistically significant improvements were demonstrated in a subgroup of 163 patients with more severe SUI (≥14 episodes of incontinence per week): 49% to 64% reduction in IEF in the duloxetine groups compared with 30% in the placebo group.38

A phase 3, randomized, double-blind, placebo-controlled clinical trial of duloxetine for SUI was recently completed in women with stress-predominant incontinence.39 Inclusion criteria included a weekly IEF of 7 or greater and multiple other qualifiers (Table 2). The trial involved 683 women ages 18 to 65 years, who were randomized to treatment with placebo (n = 339) or duloxetine 80 mg daily (n = 344) for 12 weeks. Outcome variables following 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.39 Duloxetine was associated with significant decreases in IEF and improvements in the I-QOL and PGI-I scales. In intention-to-treat analysis, 51.4% of participants taking duloxetine had a 50% to 100% decrease in IEF compared with 33.5% in those taking placebo (P < .001). Superior IEF improvements in patients taking duloxetine were observed at the first visit after randomization to therapy (4 weeks) and persisted throughout the 12-week treatment period. Similarly, significant improvements in I-QOL scores were shown in patients taking duloxetine compared with those taking placebo. These improvements were also apparent at the first visit after randomization to therapy and were maintained throughout the trial. The PGI-I results demonstrated that 62% of duloxetine subjects considered their incontinence improved compared with 39.6% of patients taking placebo (P < .001). Patients taking duloxetine demonstrated statistically significant improvements compared with those taking placebo in the 3 I-QOL domains of social embarrassment, avoidance and limiting behavior, and psychosocial impact. Moreover, duloxetine was associated with significant increases in voiding intervals compared with placebo.39

Discontinuation rates due to side effects among patients taking the 80-mg dose of duloxetine and those taking placebo were 24% and 4%, respectively.39 The discontinuation rate for adverse events attributable to duloxetine was 16.6%. Nausea was the most common reason for discontinuation (6.4%), however this tended to be mild and transient.39 Phase 2 studies identified other causes for duloxetine discontinuation, such as somnolence, dizziness, and menorrhagia.39 No adverse event was reported as severe.

A concurrent phase 3 study was conducted in 494 women in Europe and Canada.40 The results showed a significant decrease in IEF with duloxetine compared with placebo (median decrease of 50% vs 29%; P = .002) with comparable significant improvements in the more severely incontinent subgroup. Of the subjects taking duloxetine, 52% had a 50% to 100% reduction in IEF compared with 34% of subjects taking placebo (P < .001). In the intention-to-treat analysis, changes in I-QOL scores did not differ significantly between treatment groups due to very early discontinuations in the duloxetine group. An analysis of patients who completed the 12-week protocol showed that the duloxetine group had significantly greater improvement in I-QOL scores compared with the placebo group (7.3 vs 4.3; P = .008). The side-effect profiles for the study groups were nearly identical to those seen in the US trial.40

OTHER CONSERVATIVE OPTIONS

BIOFEEDBACK

Biofeedback, either as primary therapy or as an adjunct to other therapies, has been studied extensively. Typically, biofeedback involves use of vaginal or rec-
tal monitoring instruments to detect physiologic events; these events are translated electronically into visual or auditory signals. These visual and auditory representations help patients develop conditioned responses. Overall, studies of biofeedback training for urinary incontinence have yielded mixed results. For example, a meta-analysis of 10 trials involving women with SUI found no significant difference in leakage rates for biofeedback-assisted pelvic floor muscle training (PFMT) versus PFMT alone.41

A large clinical trial of biofeedback-assisted behavioral therapy demonstrated considerable promise and suggested that biofeedback might have a prominent role in management of urinary incontinence.42 The study involved almost 200 women with urodynamic evidence of bladder dysfunction. A majority of the patients (51.3%) had mixed symptoms of stress and urge incontinence.

The patients were randomized to 3 treatment groups: 8 weeks of biofeedback-assisted behavioral treatment; pharmacologic treatment with oxybutynin 2.5 mg to 5.0 mg 3 times daily; or placebo. The primary outcome parameter was incontinence frequency. Bladder diaries and patient self-reported improvement and comfort also were evaluated.

Behavioral training consisted of instruction in techniques and strategies to prevent incontinence, including pelvic floor muscle exercises to practice at home. All patients in the behavioral group completed 1 session of anorectal biofeedback training. The first session helped patients to identify pelvic muscles and learn how to contract and relax the muscles while keeping abdominal muscles relaxed. Patients who had not achieved at least a 50% reduction in the frequency of incontinence episodes by the third clinic visit received 1 session of bladder sphincter biofeedback. The second form of biofeedback training was to help patients learn to contract pelvic muscles in response to increasing urine volume, to increased urgency, and to detrusor contraction. About three fourths of the behavioral therapy group (73.8%) received a single session of anorectal biofeedback training.

At the end of the study, patients in the biofeedback-assisted behavioral therapy group had a mean reduction of incontinence episodes of 80.7%, compared with 68.5% in the drug-treatment patients (P = .04) and 39.4% in the placebo group (P < .01). Drug therapy also was more effective than placebo. Patient-perceived improvement was substantially greater in the behavioral therapy group, as 74.1% said they were “much better,” compared with 50.9% of the drug-treatment group and 26.9% of the placebo group. Moreover, 14% of the behavioral-therapy group wanted to change treatment, compared with 75.5% of each of the other groups.

Positive results such as this have influenced clinical opinion about the role of biofeedback training in the management of urinary incontinence, including SUI. Many physicians who have a large population of patients with incontinence, such as the authors of this publication, have made biofeedback a routine component of conservative therapy.

Pelvic Floor Muscle Training

More than 50 years have passed since Kegel first described successful use of the exercises that bear his name.43 In the 21st century, Kegel exercises remain a useful therapy for all patients with SUI, although numerous variations in the original technique have evolved. The aforementioned meta-analysis by Hay-Smith et al found PFMT significantly better than no treatment for self-reported rates of cure, cure or improvement, and 24-hour incontinence frequency for women with SUI, and the results were consistent across the PFMT techniques employed.41 PMFT can easily be incorporated as an adjunct to other forms of therapy.

Bladder Retraining

Bladder retraining has been used as sole therapy and in combination with other conservative treatments for women with various types of urinary incontinence. Fantl et al reported success with an outpatient program for a population that included women with SUI, detrusor instability, and mixed incontinence.44 After 6 weeks of training and practice, 76% of patients had at least a 50% reduction in the frequency of incontinence, and 12% of patients reported complete restoration of continence. The improvements were maintained during 6 months of follow-up.

Bladder retraining demonstrated equivalence to biofeedback-assisted PFMT in a multicenter randomized clinical trial that compared the 2 forms of conservative therapy for women with SUI, detrusor instability, or both.45 A third randomized group that received the combination of bladder retraining and PFMT had greater improvement immediately after the trial ended, but the advantage had disappeared at 3 months. Quality-of-life data showed that effective treatment had the greatest impact on women with genuine SUI.
**Conclusion**

Most physicians who treat patients with SUI encourage a trial of conservative therapy before pursuing a surgical option. A notable limitation of conservative management has been the lack of US FDA-approved pharmacologic therapies for SUI. This will likely change in the near future, as advances in basic understanding of the neuromuscular function have fueled investigation into new pharmacologic strategies to treat SUI. Duloxetine, a dual serotonin-norepinephrine reuptake inhibitor, has demonstrated ability to reduce incontinence frequency and improve quality of life in phase 1 to phase 3 clinical trials of women with SUI. The dual neurotransmitter reuptake inhibitor will likely become commercially available in the near future.

Another notable development in conservative therapy for SUI has been the emergence of biofeedback training, especially as an adjunct to other noninvasive approaches. PFMT remains a useful therapeutic tool for virtually all patients with SUI. Bladder retraining has shown promise, although the precise role of the modality remains to be determined, particularly in combination with PFMT.

**References**