ABSTRACT

As many as one-third of women are affected by urinary incontinence, the most common of which being stress urinary incontinence (SUI). Incontinence exacts heavy economic and emotional tolls, affecting nearly every aspect of a woman's life. Fewer than half of women affected by incontinence report the problem to a physician, probably because of embarrassment, low expectations for treatment, and the availability of absorbent products. When a patient does report incontinence to a physician or other healthcare provider, the complaint should be evaluated thoroughly, and include medical and urinary histories, urinary diary, pelvic examination, stress testing, and other basic investigations as indicated. Treatment strategies for SUI include behavior modification, pelvic muscle exercises, and surgery. Success rates for incontinence surgery range between 50% and 85%, but surgery does not meet all patients' needs. Currently no approved medication exists for treatment of SUI, although off-label use includes alpha-adrenergic agonists, estrogen, and tricyclic antidepressants. Recent findings relative to neurologic regulation of urinary continence have led to development of a new pharmacologic approach to treatment of SUI, based on modulation of neurotransmitters. The first such agent of this type, duloxetine, has demonstrated efficacy with respect to improving incontinence and quality of life in initial clinical trials.

(Advanced Studies in Medicine 2002;2(15):541-545)

*Professor of Obstetrics and Gynecology, Medical College of Virginia, Richmond, Virginia.
Address correspondence to: W. Glenn Hurt, MD, Medical College of Virginia, Department of Obstetrics and Gynecology RCUHS, Box 980034, Richmond, VA 23298.
women in different studies have UI compared with 2% to 5% of men. Prevalence and severity increase with age, and more than 50% of nursing home patients are affected by UI.1

Incontinence has wide-ranging effects on quality of life. Adverse effects include social isolation; limitations on activities; avoidance of sexual activity; psychological effects, including depression and loss of self-esteem; decreased productivity; and a detrimental impact on personal hygiene.

Estimated direct costs related to the management of incontinence in the US range between $16 billion and $26 billion annually. Stress incontinence accounts for more than 80% of total treatment costs.2,3

The number of people affected by incontinence has likely increased since the International Continence Society (ICS) revised its terminology to redefine the condition. In 1988, the ICS defined incontinence as involuntary loss of urine that is objectively demonstrable and that constitutes a social or hygienic problem. In 2001, the ICS redefined incontinence simply as a complaint of any involuntary leakage of urine.

The 3 broad symptom-based categories of urinary incontinence are stress, urge, and mixed incontinence (Table 1). Other types of incontinence include overflow incontinence, caused by conditions such as a fistula, urethral diverticulum, or ectopic ureter; and functional incontinence, which encompasses a variety of patient-specific, environmental, disease-related, and medication-related factors.

**LOWER URINARY TRACT FUNCTION**

Urine storage and micturition are under central nervous system control via reflexes that coordinate the activity of the bladder, urethra, and pelvic floor muscles. The autonomic nervous system has control over involuntary aspects of lower urinary tract function, including sympathetic regulation of the storage function and parasympathetic regulation of micturition. The somatic nervous system assists with bladder control by contracting the periurethral skeletal muscle, which is known as the rhabdosphincter. The central nervous system coordinates overall bladder and urethral activity by means of afferent and efferent communication with the peripheral nervous system.

At each level of control, different nerves and neurotransmitters affect lower urinary tract function. Parasympathetic activity involves the pelvic nerve and the neurotransmitter acetylcholine. Sympathetic control over urinary tract activities involves the hypogastric nerve and norepinephrine. Somatic control centers on the pudendal nerve and acetylcholine. Each of these control mechanisms offers potential targets for therapy to treat SUI.

Separate neurologic reflex systems regulate urine storage and micturition. As the bladder fills with urine, stretch receptors in the fundus of the bladder communicate with the sympathetic nervous system via the pelvic nerve. The sympathetic system responds through the hypogastric nerve, inducing norepinephrine-mediated stimulation of inhibitory beta-3 receptors that relax the bladder and excitatory alpha-1 receptors that tighten the smooth muscle of the urethra. Simultaneously, impulses travel through Onuf’s nucleus in the sacral cord, activating the somatic system and the pelvic nerve. Impulses transmitted through the pelvic nerve stimulate nicotinic receptors to contract the urethra’s rhabdosphincter.

When the bladder fills to capacity and voiding is inevitable, the micturition reflex is activated. Impulses traverse the pudendal nerve to the periaqueductal gray and to the pontine micturition center. This initial neurocommunication generates additional impulses to the parasympathetic system, through the pudendal nerve, and stimulates muscarinic-2 and muscarinic-3 receptors to induce voiding.

As voiding is initiated, inhibitory reflexes travel from the pontine micturition center to reverse storage-related sympathetic activity and terminate the pudendal nerve’s tightening of the rhabdosphincter. The

<table>
<thead>
<tr>
<th>Table 1. Urinary Incontinence: Classification According to Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptom</strong></td>
</tr>
<tr>
<td>Stress</td>
</tr>
<tr>
<td>Urge</td>
</tr>
<tr>
<td>Mixed</td>
</tr>
</tbody>
</table>
sphincter relaxation and bladder contraction last for a sufficient amount of time to allow the bladder to empty itself.

**Evaluation and Diagnosis**

The initial workup should be tailored to the individual patient's complaints. The assessment should cover medical, surgical, and medication history. An incontinence questionnaire can help separate and categorize different factors that might be contributing to the patient's symptoms, such as physical factors, neurologic factors, and local factors, which would include infection. A urinary diary can help provide clarity to issues such as fluid intake, urine output, leakage, and pad usage.

A physical examination, pelvic examination, and focused neurologic examination should be incorporated into every incontinence workup. Stress testing is useful for demonstrating the timing and characteristics of urine leakage. A pelvic exam can be performed while the patient has a full bladder. If the patient leaks when asked to cough, the initial pelvic exam and stress test can be combined into a single examination.

The patient should be asked to void in order to determine the postvoid residual urine. A specimen should also be evaluated by standard urinalysis to identify a possible infectious cause of the symptoms, and culture tests should be performed as indicated. The pelvic examination may be repeated when the patient has an empty bladder.

Further evaluation should be dictated by the findings of the initial workup. Additional evaluation is indicated when the diagnosis or treatment plan is uncertain or the patient has not responded to treatment. Other reasons for further assessment include the need for surgical consultation, presence of hematuria, a history of recurrent urinary tract infections, and incontinence complicated by comorbid conditions.

**Treatment Strategies for SUI**

Normal lower urinary tract anatomy allows for a very narrow margin of stress continence, or the ability to hold urine. Three different forces impinge on this margin: pressure transmission, intra-abdominal pressure, and urethral closure pressure. Therapeutic strategies for SUI aim to correct deficiencies related to 1 or more of these forces.

**Surgical Therapy**

Surgery remains the gold standard for treatment of SUI; between 80,000 and 85,000 continence procedures are performed in the US each year. The majority of operations involve patients aged 40 to 59 years, and the fixed costs of these procedures exceed $220 million. In 1999, retropubic urethral suspensions accounted for almost three fourths of SUI operations, followed by suburethral slings (approximately 20%), complications of the urethrovesical junction, and periurethral suspensions.

Worldwide, retropubic suspensions are the treatment against which all other SUI therapies are compared. The most popular operations are the original Marshall-Marchetti-Krantz procedure, developed more than 50 years ago, and the Burch modification, which emerged in the early 1960s. Both procedures are relatively simple and easy to learn.

Suburethral slings originally were obstructive procedures. Patients often did not void for weeks after surgery and often required prolonged self-catheterization, sometimes for life. Development of minimally obstructive operations has resulted in much lower rates of long-term voiding difficulty and need for prolonged self-catheterization. Moreover, surgeons now have a choice of natural and synthetic materials for slings.

Traditionally, the goals of SUI surgery have been to achieve high retropubic positioning of the urethrovesical junction to provide a compensatory continence mechanism. There was the hope of preserving posterior or rotational descent of the trigone and bladder base. The end result was a "kinking" effect that would take place at the bladder neck and prevent the patient from leaking urine when coughing.

In recent years, the basic goals of continence surgery have changed. Today, the primary objective is to stabilize the urethrovesical junction, trigone, and bladder base and provide a support "hammock" or platform. Additionally, some support may be given to the urethrovesical junction and to the midurethra.

Recently, alternatives to conventional surgical procedures have begun to emerge. One intervention that has attracted considerable attention is the tension-free vaginal tape (TVT). The Burch procedure and TVT were compared in a randomized clinical trial reported late in 2001 at the International Urogynecological Association meeting. The trial involved 316 SUI patients, and the data showed comparable cure rates, depending upon the defini-
tion of cure. When cure was defined as a negative cystoureterogram and pad test, the cure rate was 66.4% with the Burch procedure and 68.8% with TVT. Cure rate varied markedly among participating physicians and institutions.

The Burch procedure was associated with increased hospital resource utilization, blood loss, and time away from normal activities. TVT was associated with a higher rate of bladder injury (9% vs 2%). However, neither procedure showed a difference in postoperative SUI, detrusor instability, or voiding dysfunction.

Though often considered definitive treatment, surgery does not cure incontinence in all cases. Estimated rates of effectiveness range from 50% to 60% for anterior colporrhaphies, to 80% to 85% for retropubic urethropexies and suburethral slings. Moreover, initially successful surgery does not guarantee lifelong freedom from incontinence; durability of surgical procedures appear to be approximately 10 to 12 years. For example, a woman who has successful surgery at age 50 years is highly unlikely to remain totally continent for the remainder of her life. If she develops postoperative incontinence, it may or may not be due to SUI.

Many patients are not good candidates for surgery, either because of advanced age or infirmities. Some patients will not agree to surgery under any conditions. In some instances involving minimal urine leakage, surgery might be inappropriately invasive. Additionally, surgery will not address problems related to frequency and urgency in patients who have mixed incontinence. Finally, the healthcare system simply cannot handle the large volume of SUI patients who might qualify for surgery.

**Medical Therapy**

No FDA-approved medication is available for the treatment of SUI. Several medications are used off label to treat SUI, including alpha agonist, estrogen, and tricyclic antidepressants (TCAs). Among these pharmacologic agents, the use of TCAs has provided a possible glimpse of the future in medical treatment of SUI. Tricyclic antidepressants inhibit norepinephrine and serotonin (5-HT) and exert neuromodulatory effects through the somatic nervous system.

Recent investigations in neurourology have shown that inhibiting norepinephrine and 5-HT reuptake inhibition increases activation of alpha-1 adrenergic receptors and 5-HT2 receptors, which in turn increases pudendal nerve activation. Activation of the pudendal nerve strengthens rhabdosphincter function. Contraction of the urethral sphincter helps prevent urine leakage in response to increased pressure on the bladder. Much of this activity occurs within Onuf's nucleus, a neuron-rich site located in the sacral region of the spinal cord.6,7

Advances in the understanding of the neurourology connection have led to the development of a class of pharmacologic agents for SUI, the first of which being duloxetine, a dual balance norepinephrine-serotonin reuptake inhibitor. In a phase 2 randomized clinical trial involving 553 patients with SUI, patients treated with duloxetine showed significant improvement in incontinence episode frequency and quality of life.8

The trial involved women who had more than 4 stress incontinence episodes in 1 week. All patients had normal frequency, and urge was not a predominant symptom. The patients had normal bladder capacity and positive cough stress test. The patients had no history of surgery.

The patients were randomized to placebo or to 1 of 3 doses of duloxetine (20 mg/day, 40 mg/day, or 80 mg/day), and were followed up for 12 weeks. The primary efficacy variable was incontinence episode frequency (IEF). Secondary endpoints were voiding frequency, changes in global quality-of-life (global QoL) score, and change in score on the incontinence-specific quality-of-life (I-QoL) questionnaire.

| Table 2. Duloxetine Effects on Incontinence Frequency and Quality-of-Lifea |
|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | 20 mg (P)       | 40 mg (P)       | 80 mg (P)       | Placebo         |
| Median IEF pooled| -54 % (.06)     | -59% (.002)     | -64% (<.001)    | -41%            |
| QoL Mean Change  | +5.3 (.6)       | +7.8 (.2)       | +9.3 (.03)      | +5.8            |
| PGHI ≥ Much Better| 31% (.5)       | 37% (.09)       | 44% (.005)      | 27%             |

IEF = incontinence episode frequency; QoL = quality-of-life; PGHI = patient global impression-improvement.
The results showed statistically significant improvement in the median IEF for the 2 higher doses of duloxetine compared with placebo, and patients who received the lowest dose of duloxetine exhibited a strong trend toward improvement (Table 2). I-QoL and global QoL scores revealed significant improvement with the highest dose of duloxetine and a trend toward improvement with the 40-mg dose.

Duloxetine had a favorable safety profile. The most common reason for discontinuation in the duloxetine groups was nausea, which accounted for fewer than 5% of patients in each group. The nausea in those who remained on the medication was noted to be of short duration, and it did not worsen. The results of the trial provided impetus for large, multinational phase 3 trials, which have already begun.

SUMMARY

Stress urinary incontinence is the most common type of incontinence in women and adversely affects quality of life, leading to social isolation and reduced productivity. SUI may be cured by surgery in as many as 85% of cases. However, surgery is not appropriate for many patients, and the effectiveness of surgery wanes over time. Currently, no FDA-approved medical therapy exists for SUI. Modulators of the central nervous system might have a role in the treatment of stress incontinence. Evolving concepts emphasize that UI should not be viewed as inevitable or shameful and should be viewed as treatable.

REFERENCES

5. Ward KL, Hilton P. A randomised trial of colposuspension and tension-free vaginal tape (TVT) for primary genuine stress incontinence - 2 year follow up. Paper presented at International Urogynecological Association Scientific Meeting; December 5, 2001; Melbourne, Australia.