NEW APPROACHES TO THE TREATMENT OF STRESS URINARY INCONTINENCE

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ABSTRACT

Micturition is governed by 35 different reflexes; however, only 3 major factors are associated with maintaining continence: urethral closure pressure, which sustains closure and provides resistance to urine flow; intra-abdominal pressure, which increases during physical exertion and generates pressure within the abdominal cavity; and pressure transmission, wherein abdominal pressure is transmitted to the proximal urethra. Stress urinary incontinence (SUI) is caused by diminished urethral function, either through intrinsic sphincter deficiency or urethral hypermobility. The causes of these malfunctions are numerous and are best understood in terms of the neurophysiology of the lower urinary tract. There are numerous treatment approaches to SUI: behavioral changes and exercise, surgery (in severe cases), and pharmacotherapy (no drugs are approved by the US Food and Drug Administration [FDA]). Each approach has shown benefit in some women. Surgery is the most effective approach with respect to cure rate but is only used in those with severe SUI that is adversely affecting the patient’s quality of life.

Recent advances in our understanding of the neurologic mechanisms of SUI have led to the development of duloxetine, a balanced serotonin and norepinephrine reuptake inhibitor. Clinical studies to date have shown that it is a safe and effective treatment for SUI. If approved by the FDA, it will be the first drug to be indicated specifically for SUI. (Adv Stud Med. 2004;4(2A):S88-S94)

PATHOPHYSIOLOGY OF STRESS URINARY INCONTINENCE

Urine storage and release involve numerous reflexes that coordinate activities of the bladder, urethra, and pelvic floor. The bladder is the only involuntary organ in the body under voluntary control. Micturition is governed by 35 different reflexes; however, only 3 major factors are associated with maintenance of continence: urethral closure pressure, which sustains closure and provides resistance to urine flow; intra-abdominal pressure, which increases during physical exertion and generates pressure within the abdominal cavity; and pressure transmission, wherein abdominal pressure is transmitted to the proximal urethra, increasing urethral closure pressure. Intra-abdominal pressure is maintained as long as the proximal urethra is inside the abdominal cavity. In cases of urethral hypermobility (ie, the proximal urethra exits the abdominal cavity), the urethra is displaced during sudden increases in abdominal pressure (eg, during a cough), as shown in Figure 1. Pressure transmission from the abdomen to the urethra is therefore decreased, causing a relative increase in bladder pressure that overrides urethral resistance; stress urinary incontinence (SUI) results.
SUI may also result from intrinsic sphincter deficiency, in which the urethra is unable to generate enough outlet resistance to keep the urethra closed at rest or with minimal physical activity. Intrinsic sphincter deficiency results in a severe form of SUI and may be detected in women during a routine pelvic examination—the patient will eliminate urine during a cough with an almost empty bladder. Overall, SUI is caused by diminished urethral function. Intrinsic sphincter deficiency can occur separately or with urethral hypermobility.

**Neurophysiology of SUI**

Innervation of the lower urinary tract is complex but is generally controlled by the parasympathetic nervous system via the pelvic nerve to the bladder; the sympathetic nervous system via the hypogastric nerve to the bladder, the bladder base, and entire urethra; and the somatic nervous system via the pudendal nerve to the urethral sphincter. For bladder control to be maintained, all components must integrate in such a way that emptying can be delayed until a socially acceptable time and place. This control generally is taught in early childhood, but the capability, which relies on this complex set of functions, can decrease with age.

At least 6 neurotransmitters are involved in both bladder and sphincter control: acetylcholine, norepinephrine, serotonin, gamma amino butyric acid (GABA), dopamine, and glutamate. Glutamate is essential to learning early bladder control because its modulation is responsible for sphincter relaxation or contraction. Acetylcholine and norepinephrine are the primary neurotransmitters involved in direct innervation of the lower urinary tract. Serotonin and norepinephrine, however, play a central role in lower urinary tract function, although they are typically associated with depression and pain perception. In SUI, both serotonin and norepinephrine stimulate the pudendal nerve, which causes the pelvic floor and the urethral sphincter to contract. Norepinephrine and serotonin modulate pain sensitivity through their presence in the descending pain pathways, so they may also account for the discomfort that can occur with excessive pressure on the bladder or from inflammatory conditions. More specifically, they stimulate the pudendal nerve at its origin in the posterior sacral horn, at Onuf's nucleus. Dysregulation of either or both of these neurotransmitters will affect sphincter closure and pelvic floor strength.

**Treatment**

There are 3 types of approaches to correcting SUI: increasing urethral resistance, creating urethral obstruction, or decreasing the magnitude of stress on the bladder. The treatment techniques for each of these approaches are discussed below.

**Behavioral Approaches and Exercises**

Behavioral changes and specific exercises can be sufficient in some women with SUI and in those with urge or mixed incontinence. Important behavioral modifications include limiting fluid intake, decreasing diuretic liquids (eg, caffeinated), and voiding at certain times as part of a bladder retraining program. Bladder retraining is strongly recommended for the treatment of urge and mixed incontinence. In this approach, the voiding response is reconditioned when patients empty only at predetermined intervals. These intervals are gradually increased in half-hour increments on a biweekly schedule until intervals of 3 to 4 hours are attained.

Perhaps more well known are the pelvic floor, or Kegel, exercises, which can be successful in women with SUI. Success absolutely depends on the patient performing the exercises correctly. Correct execution...
can be assessed during a pelvic examination by placing 2 fingers in the vagina and requesting the patient to contract and hold the contraction for a few seconds. If the vagina squeezes around the 2 fingers, this is a correct performance of a Kegel exercise; the pelvic floor muscle is being contracted. Patients should not be bearing down in a Valsalva maneuver or squeezing their buttocks. They should also not perform this exercise when urinating because it can create a conditioned reflex. Biofeedback can be used to help patients identify the correct way to perform Kegel exercises. Of note, for patients with severe intrinsic sphincter deficiency, the benefits of pelvic floor exercises have been found to be minimal. Kegel exercises can be augmented by the use of artificial obstructions during the day, such as wearing tampons during jogging (or other activities associated with SUI) or using vaginal weights, which can be kept inside the vagina only through contraction of the pelvic floor. Finally, electrical stimulation of the vagina has shown some success as a safe alternative in limited clinical studies.

**SURGICAL APPROACHES**

Surgical approaches are determined based on whether the patient has intrinsic sphincter deficiency. The surgical treatment of SUI can be divided into 3 main approaches (Table 1): colposuspension, suburethral sling, or urethral bulking (implants). Colposuspension elevates and stabilizes the urethra by suspending the anterior vaginal wall to the iliopectineal line (Cooper's ligaments) or the pubic bone and typically utilizes either the Burch procedure or the Marshall-Marchetti-Krantz operation, respectively. The suburethral sling stabilizes and provides mechanical obstruction of the urethra during increased intra-abdominal pressure. This is accomplished by surrounding the urethra within a sling and suspending it from the rectus fascia or pubic bone. The sling is usually made from fascial or synthetic materials. Urethral bulking involves injecting or implanting material around the urethra to increase outlet resistance and traditionally uses either bovine collagen or carbon-coated beads.

As shown in Table 2, implants have the lowest rate of postoperative complications, ranging from 0% to 6%, but the cure rate generally is about one third of all patients who undergo the procedure; however, improvement has been reported to be as high as 69%. The Burch procedure is the favored colposuspension approach by many urogynecologists and urologists. Cure rates of 77% to 90% have been published. Suburethral sling surgeries have a comparable success rate. Nonetheless, perioperative and postoperative complications are relatively high for both procedures—20% and 31%, respectively. As a result, only about one half of all patients

| Table 1. Surgical Approaches to Urinary Incontinence |
|---------------------------------|-----------------|-----------------------------|
| **Procedure** | **Technique** | **Goal** |
| Colposuspension | Burch, MMK | Elevates and stabilizes urethra by suspending anterior vaginal wall to iliopectineal (Cooper's) ligaments/pubic symphysis |
| Suburethral sling | Fascial, TVT | Stabilizes urethra by placing it within a sling suspending it from rectus fascia or pubic bone |
| Urethral bulking | Collagen, carbon | Injection of bulking materials around urethra to increase outlet resistance |

MMK = Marshall-Marchetti-Krantz; TVT = transvaginal tape.

| Table 2. Expected Outcomes with Commonly Recommended Surgical Procedures for Incontinence |
|---------------------------------|-----------------|---------------|
| | **Burch (%)** | **Sling (%)** | **Implants (%)** |
| Cure | 77<sup>12</sup>; 90<sup>13</sup> | 73<sup>12</sup>; 94<sup>13</sup> | 48<sup>14</sup>; 69<sup>14</sup> |
| Improved | 5<sup>14</sup> | 6<sup>14</sup> | 16<sup>14</sup>; 28<sup>15</sup> |
| Operative complications | 18–20<sup>14</sup> | 31<sup>14</sup> | 0–6<sup>14</sup> |
| Emptying-phase dysfunction | 2–27<sup>15</sup> | 2–37<sup>13</sup> | … |
| Detrusor overactivity | 8–27<sup>15</sup> | 3–23<sup>15</sup> | … |
| Pelvic-organ prolapse | 3–27<sup>15</sup> | … | … |
| Total satisfaction with procedure | 44–52<sup>13</sup> | … | … |

Data from Weber et al<sup>12</sup>; Jarvis et al<sup>13</sup>; AHCPR<sup>14</sup>; Smith et al.<sup>15</sup>
in one study who underwent the Burch procedure considered the outcome completely satisfactory; other procedures have varying rates of success.\textsuperscript{18} Randomized controlled trials comparing these procedures are limited. Several studies comparing colposuspension techniques have confirmed the better safety and efficacy profile with the Burch technique.\textsuperscript{17-19} A recent study comparing colposuspension versus transvaginal tape in 344 women with SUI showed that the cure rates were comparable (66\% vs 57\%), but transvaginal tape was associated with more operative complications. Colposuspension had more postoperative complications and longer recovery time.\textsuperscript{20}

**Pharmacologic Approaches**

No medication has been approved by the US Food and Drug Administration (FDA) for the treatment of SUI. Tolterodine and oxybutynin have been approved for overactive bladder but do not treat SUI. Nonetheless, several types of medications, including estrogen, alpha-adrenergic agonists, and tricyclic antidepressants, have been used for this purpose, with varying degrees of efficacy. Estrogen is known to thicken the urethral mucosa for a better seal at the sphincter. It also increases the alpha-adrenergic response. It directly affects all lower urinary tract tissues and might increase the sensory threshold of the bladder and increase bladder relaxation.\textsuperscript{1} Hormone therapy can be a useful vehicle for postmenopausal women who suffer from incontinence; however, even with hormone therapy, the doses of estrogen may not be adequate. In those cases, intravaginal estrogen is useful to directly apply estrogen to the site of action. The benefits with estrogen therapy for SUI have not been consistent,\textsuperscript{21} but it may be of benefit to specific patients.

Alpha-adrenergic agonists increase urethral tone and closure pressure by direct stimulation of alpha-adrenergic receptors in the smooth muscle.\textsuperscript{22} Examples include ephedrine, midodrine, pseudoephedrine, and phenylpropanolamine. Again, the benefits are not consistent across studies. Alpha-adrenergic agonists have side effects that often do not result in treatment discontinuation; however, serious side effects, such as cardiac arrhythmias and hypertension, have been reported.\textsuperscript{23-27}

Tricyclic antidepressants (TCAs) are direct urethral smooth muscle stimulants due to their alpha-adrenergic effects. They also stimulate the pudendal nerve, leading to pelvic floor contraction. TCAs also inhibit norepinephrine reuptake in the synaptic cleft.\textsuperscript{1} Overall, the results have been positive, but TCAs are notorious for their side-effect profiles, which are considered intolerable by many patients.

Recent advances in the understanding of the neuromuscular aspects of SUI provided the impetus for the development of duloxetine, a dual-reuptake balanced inhibitor of serotonin and norepinephrine. Its effect occurs in Onuf's nucleus of the sacral spinal cord and leads to an increase in the strength of urethral sphincter contractions, thereby preventing accidental urine leakage. One phase 3 and one phase 2 study have been published evaluating the effectiveness of duloxetine in SUI.

The efficacy of duloxetine 80 mg daily was compared with placebo in 683 North American women who had 7 or more weekly episodes of stress incontinence; 64\% had 14 or more incontinence episodes weekly. The study population had normal diurnal and nocturnal frequency and bladder capacity, and urge was not a predominant feature of incontinence. The patients had a positive cough stress test and a stress pad test exceeding 2 g. The trial also incorporated quality-of-life assessments and patient-reported global impression of improvement as well as time intervals between voiding.\textsuperscript{28}

![Figure 2. Change in Incontinence Episode Frequency with Duloxetine vs Placebo at 12 Weeks*](image)

*This figure contains information on use not approved by the US Food and Drug Administration.

\( P < .001 \) for all between-group comparisons.

IEF = incontinence episode frequency.

Data from Dmochowski et al.\textsuperscript{26}
After a 2-week placebo run-in phase, patients were randomized to duloxetine 40 mg twice daily or to placebo and were followed up for 12 weeks. The primary efficacy variables were incontinence episode frequency (IEF) and a quality-of-life assessment. Overall, duloxetine resulted in a 50% decrease in IEF from baseline to 12 weeks compared with a 27% reduction in the placebo group ($P < .001$), as shown in Figure 2. Among patients with severe stress incontinence ($\geq 14$ episodes weekly), duloxetine resulted in a 52% decrease in IEF compared with 25% in the placebo group ($P < .001$; Figure 2). Similarly, the voiding interval increased 10-fold with duloxetine: 20 minutes vs 2 minutes ($P < .001$).

Quality of life was measured by the Incontinence Quality of Life Instrument (I-QOL), a 22-item, validated, condition-specific instrument evaluating the effects of incontinence in 3 domains: avoidance and limiting behavior, social embarrassment, and psychosocial impact. I-QOL values improved by a mean of 11.0 points in the duloxetine patients compared with 6.8 points in the placebo group ($P < .001$) in the intention-to-treat analysis. For those who had severe incontinence, defined by at least 14 incontinence episodes per week, the mean improvement was 12.8 points with duloxetine and 7.4 points with placebo ($P < .001$; Figure 3).

Comparison of Patient Global Impression of Improvement (PGI-I) scores also demonstrated a significant advantage for duloxetine: 62% of patients said they had improved, compared with 39.6% of patients taking placebo ($P < .001$). Moreover, 4 times as many patients taking placebo felt their condition had worsened at the end of the trial (7.5% vs 1.8% of duloxetine patients; $P < .001$; Figure 4).

Overall, 85% of patients taking duloxetine had reduced urine loss, one half of the patients in the duloxetine arm had at least a 50% reduction in urine loss, and 10% were cured of SUI, as reflected in total resolution of incontinence episodes. In general, patients who responded to duloxetine began to improve within 4 weeks.

The most common adverse event in the duloxetine group was nausea, occurring in 23% of patients. In most cases, the nausea was mild and transient, and only 6.4% of patients discontinued treatment because of nausea. The nausea resolved within 1 week in 50% of affected patients and within 1 month in 80%. The 23% incidence of nausea is comparable to what has been observed with commonly used antidepressants that inhibit reuptake of serotonin, norepinephrine, or both.

In an earlier study, duloxetine (20, 40, and 80 mg daily) was compared with placebo in 553 women aged 18 to 65 years with predominantly SUI. Patients were...
followed up for 12 weeks, during which IEF, I-QOL, and PGI-I were assessed. The IEF decreased by 41% in the placebo group compared with 54%, 59%, and 64% for the 20 mg, 40 mg, and 80 mg duloxetine groups, respectively. Those with more severe incontinence (≥ 14 IEF/week) had roughly twice the reduction in IEF with duloxetine versus placebo (49% to 64% vs 30%). Discontinuation rates were low and primarily due to nausea. Thus, duloxetine is a safe and effective treatment for SUI, with efficacy shown in a dose-dependent manner. If approved by the FDA, duloxetine would become the first pharmacologic agent with a specific indication for treatment of stress urinary incontinence.

CONCLUSION

The neurophysiology of SUI is complex but is best understood via the 3 factors required for continence (urethral closure pressure, abdominal pressure, and pressure transmission) as well as the 3 nerves innervating the lower urinary tract (the pelvic nerve, hypogastric nerve, and pudendal nerve) and the 5 neurotransmitters involved in micturition (acetylcholine, norepinephrine, serotonin, GABA, and glutamate).

There are several approaches to treating SUI, including behavioral changes and exercise, surgery (in severe cases), and pharmacotherapy. Until now, pharmacologic approaches (estrogen, TCAs, alpha-adrenergic agonists) have had limited success, either due to poor or inconsistent efficacy or ultimately intolerable side effects. Duloxetine inhibits the reuptake of norepinephrine and serotonin in a balanced manner. Studies to date indicate that it is a safe and highly effective treatment for SUI and may offer significant benefit with minimal side effects. It is currently under review by the FDA for an SUI indication.

REFERENCES


