New Treatments for Incontinence

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Urinary incontinence (UI) is a common, yet underdetected and under-reported, health problem that can significantly affect quality of life. UI may also have serious medical and economic ramifications for untreated or undertreated patients, including perineal dermatitis, worsening of pressure ulcers, urinary tract infections, and falls. To prevent incontinence, the urethral sphincter must maintain adequate closure to resist the flow of urine from the bladder at all times until voluntary voiding is initiated and the bladder must accommodate increasing volumes of urine at a low pressure. UI can be categorized as a result of urethral underactivity (stress UI), bladder overactivity (urge UI), a combination of the 2 (mixed incontinence), or urethral overactivity/bladder underactivity (overflow incontinence). The main goal of therapy for the management of UI is to reduce the number of UI episodes, prevent complications, and, if possible, restore continence. This review highlights the existing treatment of stress, urge, mixed, and overflow UI in adult men and women and discusses many of the novel treatments including potential future or emerging therapies.
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DEFINITION, CLASSIFICATION, AND TYPES OF URINARY INCONTINENCE

Urinary incontinence (UI) is defined as involuntary leakage of urine.[1] During the normal micturition cycle, the bladder and urethra operate in unison during the bladder filling and storage phase. To prevent incontinence, the urethra, or more accurately the urethral sphincter, must maintain adequate closure to resist the flow of urine from the bladder at all times, and the bladder must accommodate increasing volumes of urine at a low pressure until voluntary bladder emptying is initiated.

UI may occur as a result of abnormalities of the urethra (including the bladder outlet and urinary sphincter) or the bladder or as a combination of abnormalities of both. Abnormalities may result in either overfunction or underfunction of the bladder and/or urethra, with resulting development of UI. Although this simple classification scheme excludes extremely rare causes of UI, such as congenital ectopic ureters and urinary fistulas, it is useful for gaining a working understanding of the condition and understanding the basis for therapeutic intervention.

Urethral Underactivity (Stress Urinary Incontinence)

Stress UI is defined as the involuntary leakage of urine on effort or exertion or on sneezing or coughing.[1] The pathophysiology of stress urinary incontinence (SUI) is related to decreased or inadequate urethral closure forces that are not able to resist the transient increases in intra-abdominal pressure that occurs during these episodes of physical exertion.

Risk factors for SUI in the women include pregnancy, childbirth, menopause, cognitive impairment, obesity, and aging.[2,3] In men, SUI is rare and is most commonly the result of previous lower urinary tract surgery and injury to the sphincter mechanism within and external to the urethra. Radical prostatectomy for treatment of adenocarcinoma of the prostate and transurethral resection of the prostate are probably the most common proximate causes of SUI in the men.

Bladder Overactivity (Urge Urinary Incontinence)

Urge urinary incontinence (UUI) is defined as the involuntary leakage of urine accompanied by or immediately preceded by urgency, which is a compelling desire to void.[1] This is most often related to detrusor (bladder) overactivity because of involuntary bladder contractions that occur inappropriately during urinary storage, which in the neurologically normal individual, results in a sense of urinary urgency.

Clearly identifiable risk factors for UUI include normal aging, neurologic disease (including stroke, Parkinson's disease, multiple sclerosis, and spinal cord injury), and bladder outlet obstruction (eg, because of benign prostatic hyperplasia or prostate cancer).

Mixed Incontinence

Mixed incontinence is defined as involuntary leakage associated with urgency and also with exertion, effort, sneezing, or coughing.[1] This is most often related to the combination of bladder overactivity and urethral underactivity. The diagnosis can often be difficult because of the confusing array of presenting symptoms.

Some studies have found that mixed UI (SUI plus UUI) is the most common type of UI. However, the proportions of SUI, UUI, and mixed UI vary considerably with age group and gender of patients studied, study methodology, and a variety of other factors.

Urethral Overactivity and/or Bladder Underactivity (Overflow Incontinence)

Overflow incontinence is urinary leakage resulting from an overfilled and distended bladder that is unable to

empty. Another term related to overflow incontinence is chronic urinary retention.

Overflow incontinence is the result of urethral overactivity, bladder underactivity, or a variable combination of both. Clinically and practically, the most common cause of urethral overactivity in men is anatomic urethral obstruction, including that because of benign prostatic hyperplasia and prostate cancer. Urethral stricture disease in men could be secondary to previous sexually transmitted infections, previous catheterization, trauma, urethral surgery, or radiation therapy. In women, urethral overactivity is rare but may result from cystocele formation (with resultant kinking or obstruction of the urethra) or surgical overcorrection after surgery for the repair of SUI (iatrogenic obstruction). In both men and women, overflow UI may be associated with systemic neurologic dysfunction or diseases, such as spinal cord injury or multiple sclerosis.

Bladder underactivity occurs as a result of the detrusor muscle of the bladder becoming progressively weakened (underactive because of impaired contractility) and eventually losing the ability to voluntarily contract and expel urine during voiding. Both myogenic and neurogenic factors have been implicated in producing the impaired contractility seen in this condition.

Other Types of Urinary Incontinence

"Functional incontinence" is not caused by bladder- or urethra-specific factors. Rather, in patients with conditions such as dementia or cognitive or mobility deficits, the UI is linked to aberrant toileting habits more than any extrinsic or intrinsic deficit of the lower urinary tract. Treatment of this type of UI may involve simple interventions such as placing a urinal or commode at the bedside that allows for uncomplicated access to toileting or directed toileting (timed or prompted voiding).

EPIDEMIOLOGY

UI is a highly prevalent yet under detected and under-reported health problem that can significantly affect quality of life. UI may also have serious medical and economic ramifications for untreated or undertreated patients, including perineal dermatitis, worsening of pressure ulcers, urinary tract infections (UTIs), and falls. Determining the true prevalence of UI is difficult because of problems with definition, reporting bias, and other methodologic issues.[4] The Medical, Epidemiologic, and Social Aspects of Aging survey found that the prevalence of UI in noninstitutionalized women of 60 years and older was approximately 38%. Almost one-third of those surveyed noted urine loss at least once weekly and 16% noted UI daily.[5]

A publication from a National Institutes of Health working group conference estimated the median level of UI prevalence to be approximately 20% to 30% during young adult life, with a broad peak around middle age (30% to 40% prevalence) and an increase in the elderly population (30% to 50% prevalence).[6]

Consistent across all studies of unselected, noninstitutionalized populations is that UI is at least half as common in men as in women.[7] Overall, the prevalence of UI in men has been estimated to be approximately 9%.[8] Unlike in women, the prevalence of UI in men increases steadily with age across most studies, with the highest prevalence recorded in the oldest patient cohorts.[9]

EVALUATION OF URINARY INCONTINENCE

When evaluating a patient with UI, the incontinence should be defined and characterized to guide proper treatment planning. A careful and thorough history should always be obtained from the patient. The elements of the history should include: (1) subjective characterization, (2) quantification when possible, (3) assessment and association with other voiding patterns/habits, (4) characterization of the onset and duration of the symptoms and any known inciting events, and (5) a determination of the impact that the leakage has had on the patient's quality of life. Physical examination should include at minimum a pelvic examination in women with assessment of urethral mobility, associated vaginal prolapse and atrophy, a genital examination in men, a digital rectal examination in both men and women, and a neurologic examination for those patients with a known or suspected neurologic condition. A urinalysis and post-void residual measurement should be obtained in all patients who are undergoing evaluation of UI. Symptom quantification instruments, such as voiding diaries (frequency-volume charts) or pad weight tests, can provide useful data for the evaluation and differentiation between various types of UI. Cystoscopic evaluation of the bladder can be considered for those patients who present with urinary urgency, hematuria, or other irritative symptoms, particularly if they have undergone previous pelvic surgery or pelvic irradiation. Urodynamic testing can also be considered for those patients who present with a more complex history, such as elevated post-void residual, neurologic disease, previous pelvic surgery, or associated obstructive urinary symptoms.

TREATMENT OF URINARY INCONTINENCE

The efficacy goals for the management of UI include restoration of continence, reduction of the number of UI episodes, and prevention of complications (pressure ulcers,

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CLINICAL SUMMARY

- Urinary incontinence (UI) can be categorized as a result of urethral underactivity (stress UI), bladder overactivity (urge UI), a combination of the 2 (mixed incontinence), or urethral overactivity/bladder underactivity (overflow incontinence).

- The main goal of therapy for the management of UI is to reduce the number of UI episodes, prevent complications, and, if possible, restore continence.

- Treatment for UI can include behavioral therapy, pharmacologic therapy, office-based procedures, and surgical therapy.

- New and emerging therapies aim to improve the overall efficacy compared with existing therapies, while minimizing adverse effects/complications, improving tolerability, and reducing invasiveness.

nursing home placement, etc.). Other desired outcomes are minimization of adverse treatment consequences and cost and also improvement in patient's quality of life.

Nonsurgical, nonpharmacologic intervention is the first-line treatment for UI.[10] Drug therapy may be considered in patients with UUI whose incontinence is not adequately controlled by nonpharmacologic therapies and who have no major contraindications to drug treatment (Fig 1). In general, drug therapy for UUI provides better response when combined with nonpharmacologic interventions.[11] Notably, there is no approved pharmacologic therapy for SUI in the United States. Surgery can be considered when the degree of bother or lifestyle compromise is sufficient and other nonsurgical interventions are undesired or ineffective.

Individuals with UI of all types should be counseled that noninvasive measures are generally but not invariably less efficacious than more invasive measures such as surgery, but this must be balanced against the increased cost, risks, and recovery times associated with these interventions.

Bladder Overactivity and UUI

The goal of treatment of UUI is to reduce bladder (detrusor) overactivity and associated urgency by one of a number of treatments.

Behavioral Therapy. Nonpharmacologic treatment of UI is recommended as the first-line therapy.[10] It is the only option for patients in whom pharmacologic or surgical management is inappropriate or undesired, such as those with comorbid conditions that place them at high risk for adverse effects from drug therapy or who are not fit for surgery. Behavioral interventions include lifestyle modifications, fluid management, and toilet scheduling regimens. Lifestyle modifications include caffeine reduction as it is a known nervous system stimulant that promotes bladder overactivity and weight loss for overweight/obese patients. Recent studies suggest that weight loss is effective in reducing or eliminating UUI and SUI. Loss of as little as 10% of BMI in patients who are obese has a substantial favorable effect on UI.[12] For those patients with evidence of polydipsia and excessive fluid intake on their frequency-volume chart, fluid reduction to achieve a goal of approximately 48 fluid ounces of urine output in 24 hours can reduce UI. Toilet scheduling regimens can include timed voiding every 2 to 3 hours for those patients with infrequent voiding and/or diminished bladder sensation. Bladder retraining programs gradually increase the intervals between voids in combination with urge inhibition techniques (Kegel exercises) to treat bladder overactivity. Such interventions reduce or eliminate UUI by limiting the amount of fluid volume in the bladder on a regular basis, thereby preventing or reducing involuntary bladder contractions.

Pelvic floor muscle rehabilitation reduces UI in both men and women by suppressing reflex involuntary bladder contractions and increasing bladder outlet closure forces to prevent the egress of urine from the urethra. Pelvic floor
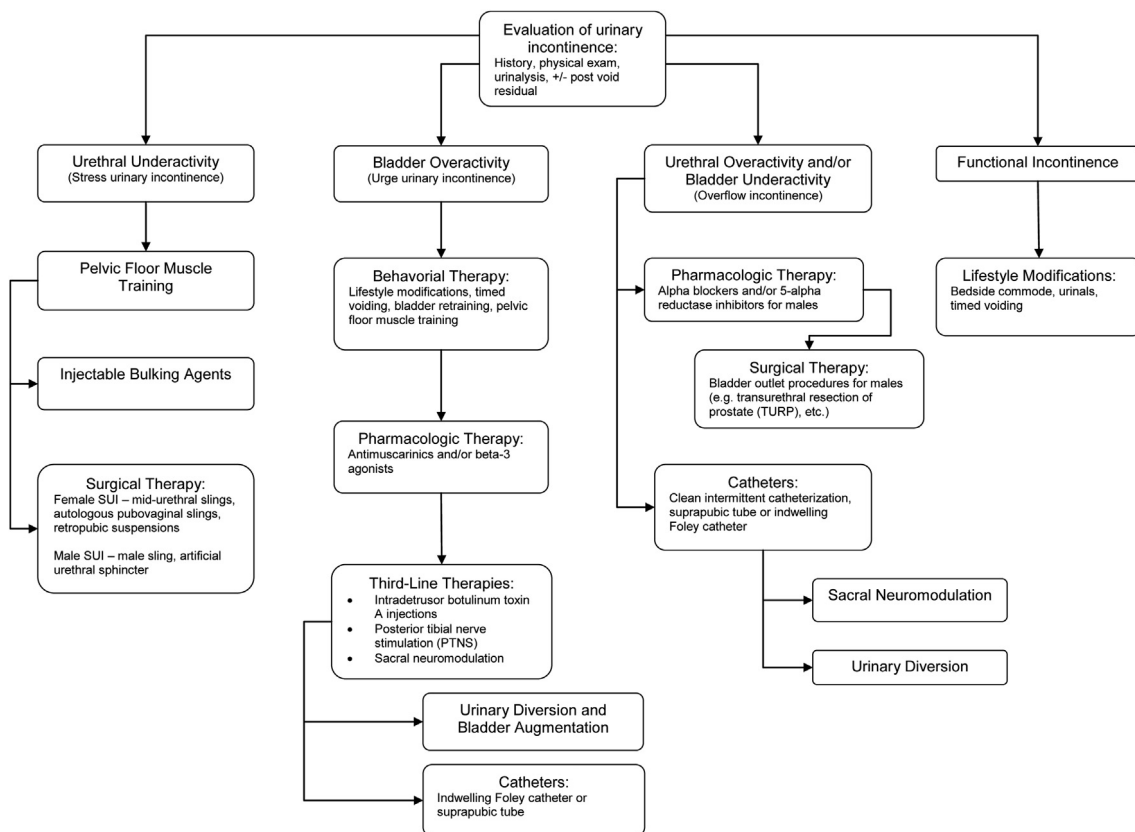

Figure 1. Algorithm for the evaluation and treatment of urinary incontinence.

muscle rehabilitation can be augmented by biofeedback, vaginal weights for women, and electrical stimulation. Supportive interventions, such as physical therapy, may be beneficial for patients with muscle weakness and slow gait to reach the toilet in a timelier manner, and absorbent products will provide greater confidence in dealing with unpredictable urine loss. Regular follow-up is needed to help motivate patients and caregivers, provide reassurance and support, and monitor treatment outcomes.

Antimuscarinics. Antimuscarinic agents are still considered the first-line drug therapy for relieving UUI symptoms. Anticholinergic/antimuscarnic agents are competitive antagonists at the level of the muscarinic receptor and suppress premature detrusor contractions, thereby enhancing bladder storage. Previously available only as immediate release agents, newer extended release formulations of these agents have enhanced patient compliance and acceptability and improved adverse event profiles and tolerability over the predicate drugs. The number of these agents approved for use in the United States has greatly increased over the last 15 years with 6 agents currently in use: oxybuytnin, tolterodine, trospium, solifenacin, darifenacin, and fesoterodine. Each of the agents has been touted to have specific clinical or theoretical benefits, which to a greater or lesser degree may have relevance in certain specific patient populations (cardiac safety, penetration of the blood brain barrier, constipation, etc.), but such differences are likely small and controversial.

In clinical trials, major efficacy outcomes for these agents in the management of UI are reduction of the mean number of UI episodes, decrease in the number of micturitions per day, and increase of urine volume voided per micturition.[13] A Cochrane review of antimuscarinics vs placebo for bladder overactivity demonstrated a statistical significant difference in cure or improvement compared with placebo (RR 1.39, 95% CI 1.28 to 1.51) and an improvement in leakage episodes in 24 hours (weighted mean difference −0.54, 95% CI −0.67 to −0.41).[14]

The most common side effect of antimuscarinics are constipation and dry mouth, which should be managed with bowel regimens, fluid management, dose modification, or alternative antimuscarinics before abandoning effective antimuscarinic therapy.[10] According to the American Urological Association Overactive Bladder Guideline, clinicians should avoid antimuscarinic agents in patients with narrow-angle glaucoma unless approved by the treating ophthalmologist.[10] The antimuscarinic agents are predominantly eliminated by hepatic metabolism through the cytochrome P450 (CYP) 3A4 pathway, and dose reductions are recommended for those patients taking potent CYP3A4 inhibitors (eg, azole antifungals, macrolide antibiotics, fluoxetine, and sertraline). Most antimuscarinic agents are not recommended in patients with severe hepatic impairment. For those patients with renal impairment and a creatinine clearance <30 mL/min, dose reduction by 50% of daily dose is recommended.

Beta-adrenergic Agonists. Beta-adrenergic agonists represent a new class of agents for treating overactive

bladder and UUI with a distinct mechanism of action compared with the antimuscarinics. Activation of β$_3$-adrenergic receptors relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle resulting in an increase in bladder capacity.[15,16] Mirabegron is a β$_3$-adrenergic agonist approved in June 2012 for the treatment of overactive bladder with symptoms of UUI, urgency, and urinary frequency. It may be considered as first-line therapy or in patients who do not adequately respond to or cannot tolerate antimuscarinic drugs.

In 3 international, multicenter, phase III studies comparing mirabegron with placebo in male and female patients 18 years or older, mirabegron was associated with significant improvements in incontinence episodes and micturition frequency and was well tolerated. In a pooled analysis of these 3 randomized, double-blind, placebo-controlled studies, mirabegron demonstrated a statistically significant improvement in mean number of incontinence episodes per 24 hours (mean change −1.49, 95% CI −1.63 to −1.36) and an improvement in mean number of micturitions per 24 hours (mean change −1.75, 95% CI −1.89 to −1.61).[17] The same analysis found significant improvements in key secondary end points, such as an increase in mean volume voided per micturition, decrease in mean level of urgency, and decrease in mean number of nocturia episodes.

Mirabegron circulates in plasma as the unchanged form and as other metabolites that are all inactive. It is highly lipophilic and is metabolized in the liver through multiple pathways, mainly by CYP3A4 and 2D6.[18] The dose should be limited to 25 mg once daily in patients with severe renal impairment or moderate hepatic disease. It should be avoided in patients with ESRD, severe hepatic impairment, or severe uncontrolled hypertension (≥180/110 mm Hg).

Most commonly reported adverse reactions were hypertension (7% to 11%), nasopharyngitis (4%), UTI (3% to 6%), and headache (3% to 4%). Because of the presence of β$_3$-adrenoreceptors in cardiac and vascular tissue, the potential collateral effects of mirabegron on cardiac and vascular function are a relevant concern. In the previously mentioned phase III studies, patients were excluded if they had severe hypertension with sitting average systolic blood pressure of 180 mm Hg or greater and/or an average diastolic blood pressure of 110 mm Hg or greater. These studies have shown that mirabegron was only minimally associated with changes in blood pressure and pulse compared with placebo, and such findings were not related to a higher incidence of cardiovascular adverse events.[17]

Combination Therapy. Antimuscarinics and beta-3 agonists are both individually safe and reasonably efficacious, but neither is universally effective in ameliorating bladder overactivity. Because these agents have different mechanisms of action, there is new interest in investigating the combination of an antimuscarinic agent with a beta-3 agonist to improve efficacy in the treatment of overactive bladder. A combination drug may provide an attractive therapeutic approach to maximize efficacy while increasing patient tolerability and compliance.

A recent multicenter, randomized, double-blind, parallel-group, placebo-controlled phase 2 study evaluated the efficacy of 6 combination groups of an antimuscarinic agent (solifenacin 2.5, 5, or 10 mg) and a beta-3 agonist (mirabegron 25 or 50 mg) compared with solifenacin 5 mg monotherapy. Compared with solifenacin 5 mg monotherapy, all combinations of mirabegron with solifenacin 5 or 10 mg significantly improved mean voided volume, with adjusted differences ranging from 18.0 ml (95% CI 5.4 to 30.0) to 26.3 ml (95% CI 12.0 to 41.0).[19] Three combination groups significantly reduced micturition frequency and 5 of 6 combinations significantly reduced urgency episodes compared with solifenacin 5 mg monotherapy. There were no observed dose-related trends between combination and monotherapy groups in treatment emergent adverse events, blood pressure, pulse rate, post-void residual volume, or laboratory or electrocardiographic parameters. There was a slight increase in the incidence of constipation with combination therapy.

Posterior Tibial Nerve Stimulation. Posterior tibial nerve stimulation (PTNS) is an office-based percutaneous treatment for UUI or overactive bladder that is refractory to behavioral and pharmacologic treatment. Therapy consists of weekly 30-minute treatments over the course of 12 weeks with a needle placed posterior to the medial malleolus of the ankle in the vicinity of the posterior tibial nerve. The specific mechanism of action is unknown, but it is postulated that neuromodulation may have a direct effect on the bladder or a central effect on the micturition centers of the brain.[20] By stimulating the posterior tibial nerve, neuromodulation can be delivered to the pelvic floor through the S2 to S4 junction of the sacral nerve plexus. This anatomical area of S2 to S4 with its projections to the sacral nerve plexus has long been recognized as the bladder center, and retrograde stimulation of the posterior tibial nerve creates a feedback loop that can modulate bladder innervation.[21]

Efficacy of PTNS treatment appears to be similar to or slightly better than oral pharmacotherapy.[22] In a randomized, multicenter, controlled study comparing PTNS to extended-release tolterodine, there was a statistically significant improvement in subjective assessment with 79.5% reporting cure or improvement compared with 54.8% on tolterodine ($P = .01$). When objective measures were compared, both groups were similar in reductions of urinary frequency, UUI episodes, urge severity, and night-time voids.[22]

After an initial treatment of 12 weekly 30-minute treatments, responders to treatment can continue therapy to sustain their symptom improvement with approximately 1 treatment per month. A long-term treatment study was performed to assess the durability of PTNS effectiveness and safety.[23] After the conclusion of an initial 12-week PTNS treatment protocol, patients underwent a 14-week prescribed tapering protocol, and then subsequent PTNS treatments were adjusted based on patient reporting of symptoms. The patients received a median of 1.1 treatments per month after the 14-week treatment tapering protocol, and 77% patients (95% CI 64 to 90) maintained moderate or marked improvement in their overactive bladder symptoms at 3 years.[23]

Botulinum Toxin A. Botulinum toxin injection into the detrusor muscle was approved by the US Food and Drug Administration in January 2013 for the treatment of UI because of idiopathic overactive bladder that is refractory to anticholinergic medications. Botulinum toxin causes flaccid paralysis of skeletal muscle by blocking presynaptic release of acetylcholine from the nerve terminal. Botulinum toxin type A cleaves the SNAP-25 protein located on the plasma membrane of the presynaptic nerve terminal. When this occurs, the SNARE complex cannot form, which prevents vesicals containing acetylcholine to fuse with the neuronal membrane and release their neurotransmitters.[24]

Usually, 100 units of the toxin is administered by endoscopic injection under local anesthesia as an office-based procedure. Botulinum toxin injection is safe and successful in increasing functional bladder capacity, reducing intravesical pressure, and improving continence and quality of life for both the neurogenic patient and the patient with idiopathic overactive bladder.[25-27] In a phase 3, randomized, placebo-controlled trial, botulinum toxin A decreased the daily frequency of UI episodes compared with placebo (-2.65 vs -0.87, $P < .001$) and increased the number of patients who became continent (22.9% vs 6.5%, $P < .001$).[26] Compared with anticholinergic therapy, botulinum toxin A had a higher rate of complete resolution of urgency urinary incontinence (27% vs 13%, $P = .003$).[28] However, the mean reduction in episodes of urgency urinary incontinence per day were similar between botulinum toxin A and anticholinergic therapy.

The duration of therapeutic effect varies, lasting usually from 4 to 9 months, after which time repeat injections are necessary to maintain the beneficial effects.[29,30] Botulinum toxin A injections can be associated with excessive detrusor relaxation, resulting in detrusor underactivity and subsequent transient elevation of postvoid residual volume or urinary retention. Studies have reported urinary retention occurring in approximately 5% of patients and the need for intermittent catheterization in up to 16%.[26] Patients should be counseled regarding this potential outcome, and affected patients may require intermittent catheterizations or indwelling catheters for bladder drainage temporarily. Fortunately, the impaired emptying resolves within days to weeks. Other then urinary retention, the most common adverse effects of botulinum toxin injection when used in the urinary tract include UTIs, dysuria, and hematuria.[31] Systemic spread of botulinum toxin A from the urinary tract resulting in muscle weakness or respiratory depression has not been reported in neurologically normal patients. Botulinum toxin A is not found in the peripheral blood after intramuscular injection, so there is no dosage adjustment required in patients with renal failure.

Sacral Neuromodulation. Patients refractory to medical treatment may benefit from sacral neuromodulation techniques, which use percutaneously placed electrodes in the S3 or S4 foramen to stimulate the afferent nerve fibers involved in sensory processing and micturition reflexes.[32] This therapy was approved for use in the United States in 1997 but has not been widely adopted.

Sacral neuromodulation is a 2-step process with an initial evaluation period using either a temporary

electrode lead or a permanent lead. The placement of temporary leads is an office-based procedure performed under local anesthesia that is referred to as a percutaneous nerve evaluation. The placement of a permanent lead is performed in an ambulatory surgery setting under anesthesia and is referred to as a staged procedure. The patient then undergoes an evaluation period that lasts from 3 days to 14 days to assess if there is an improvement in their symptoms. An improvement of >50% in a patient's symptoms can warrant implantation of the permanent device, which would include the electrode lead and battery. Battery life can range from 3 to 5 years, depending on energy consumption. Patients should be counseled on the potential need to exchange the battery every 3 to 5 years, which is performed as an ambulatory surgery under anesthesia.

The exact mechanism of action is unknown, but it is hypothesized that this device exerts its favorable effects on urination and UUI by rebalancing the afferent and efferent nerve impulses to the lower urinary tract and pelvic floor. Patient selection for this therapy is not well defined. Advanced age, and individuals with certain types of neurogenic disorders, appears to do less optimally.

Successful outcomes at 5 years after implantation can be seen in up to 68% of patients with non-neurogenic refractory urgency, frequency, and urge incontinence.[33] Magnetic resonance imaging is contraindicated for patients who have received sacral neuromodulation implantation. Although, MRI of the head only may be safely performed under certain circumstances.[34,35]

Urinary Diversions and Bladder Augmentations. Patients with intractable detrusor overactivity may be candidates for urinary diversion or physical enlargement of the bladder by augmentation cystoplasty. A vascularized segment of small bowel, colon, or stomach can be used as a urinary conduit or as a patch after bivalving the bladder. Adverse events postoperatively include bowel obstruction, metabolic disturbances, perforation of an augmented bladder, and malignancy. Because of these problems associated with bowel segments, investigators have explored an alternative approach for reconstruction using autologous engineered bladder tissues, created with autologous cells seeded on collagen-polyglycolic acid scaffolds.[36] Such studies in humans are very preliminary, but if they were successful, would potentially reduce or eliminate many of the adverse events associated with urinary tract reconstruction currently encountered when bowel is incorporated into the genitourinary tract.

Urethral Underactivity and SUI

Treatments directed at SUI exert their favorable effects by augmenting urethral closure forces.

Pelvic Floor Muscle Training. Pelvic floor muscle training (PFMT) is the most commonly used nonsurgical treatment for women with SUI. This remains a first-line therapy for the conservative management of SUI.[37] PFMT uses pelvic floor exercises (Kegel exercises) to strengthen the effectiveness of a pelvic floor contraction in an effort to clamp the urethra and increase the urethral pressure to prevent leakage during times of effort or exertion. As with PFMT for UUI, such therapy may be augmented using biofeedback, vaginal weighted cones, and a number of other techniques.

Duloxetine. Duloxetine is a dual inhibitor of serotonin and norepinephrine reuptake that was approved in 2004 for treatment of depression and painful diabetic neuropathy in the United States.[38] It is not approved for the treatment of SUI in the United States but does hold this indication in Europe. It is believed to facilitate the bladder-to-sympathetic reflex pathway, increasing urethral and external urethral sphincter muscle tone during the storage phase. Efficacy in the treatment of SUI is modest and side effects include nausea.

Injectable Bulking Agents. Bulking agents are injected into the urethra at the level of the urinary sphincter or at the bladder neck to increase urethral closure forces. This can be performed as an office-based procedure using endoscopic techniques and is generally considered quite safe. Materials and techniques used in this mode of therapy have evolved over time, with several agents currently available in the United States. Previously, glutaraldehyde cross-linked bovine collagen was the most common agent; however, this is no longer available. Currently, available bulking agents in the United States include carbon-coated zirconium oxide beads (DurasphereR; Boston Scientific, Natick, Massachusetts), calcium hydroxylapatite (CoaptiteR; Boston Scientific), and cross-linked polydimethylsiloxane (MacroplastiqueR; Uroplasty Inc., Minnetonka, Minnesota).

Studies have shown improvement rates of up to 80% using these agents; however, durability of effect remains a limiting factor with most individuals requiring repeat injections every 4 to 12 months to maintain effect.[39-42]

Mid-urethral Slings. If patients with uncomplicated SUI become dissatisfied with the initial management approaches of pelvic floor exercises, medications, and/or behavioral modification, surgical treatment assumes the primary role.[43] Mid-urethral synthetic slings using either a retropubic or transobturator approach came into widespread use in the late 1990s as they provided surgeons with a minimally invasive approach to SUI surgery. It has now become the most common approach to the treatment of SUI in women in the United States.[44] These can be inserted as outpatient procedures, which have shorter convalescence periods and allow faster return to usual activities compared with many of the older SUI surgical procedures. These procedures are generally felt to be highly durable and efficacious with estimated cured/dry rates ranging from 81% to 84%.[45] Risks of mid-urethral sling surgery include urinary retention (2% to 4%), bladder injury (2.7% to 3.8%), de novo urinary urgency (0.2% to 15%), UTI (2.2% to 17%), and voiding dysfunction (approximately 7.6%).[45,46] There have been recent safety concerns expressed regarding the implantation of surgical mesh in some patients, the implications of which are yet to be fully clarified.[47] Although rare, mesh erosion into the urinary tract is a feared complication of this

surgery, and the true incidence is unknown.[45] Vaginal mesh exposure is a known complication occurring approximately in 0% to 7% of patients.[45]

Autologous Pubovaginal Slings. Pubovaginal slings using autologous fascia (rectus fascia or fascia lata) are placed at the bladder neck and proximal one-third of the urethra generally through a combined vaginal and retropubic approach. Estimated cured/dry rates after autologous pubovaginal slings range between 90% at 12 to 23 months and 82% at 48 months or longer.[45] These procedures are associated with longer operating room time, longer postoperative convalescence, and greater postoperative discomfort compared with MUS. The risks for these procedures are similar to that of the MUS except that there is no risk of vaginal mesh extrusion or mesh erosion into the urinary tract.

Retropubic Suspensions. Retropubic bladder neck suspensions, such as the Burch or Marshall-Marchetti-Krantz, are performed within the space of Retzius and create support for or otherwise prevent the descent of the tissues near the bladder neck and proximal urethra by securing these structures onto a fixed anatomic point, such as Coopers ligament or the symphysis pubis.[48] Open retropubic suspensions have an estimated cured/dry rate of 82% at 12 to 23 months, and this rate decreases to 73% at 48 months or longer.[45] Laparoscopic suspensions using the same principles have a short-term cured/dry rate of 69% and long-term data at 24 to 47 months that demonstrates a cured/dry rate of 74%.[45]

Future Therapies. A novel approach for treating SUI uses an intravesical air-filled balloon attenuation device to directly dampen the transient spikes in intravesical pressure related to the increases in abdominal pressure, which result in SUI. A medical grade polyurethane balloon device is inserted into the bladder and inflated with 25 ml of air, which is replaced every 90 days. A randomized controlled study evaluated the device and demonstrated an improvement in reduction of pad weight test and self-reported improvement in urinary leakage for those women who received the device compared with the control arm (50.8% vs 16.3%, $P < .001$).[49] This device could potentially provide women with a useful alternate treatment option for SUI.

Another exciting approach to the treatment of SUI involves tissue engineering. A cell-based approach using stem cells derived from the culture and expansion of autologous muscle-derived stem cells hold promise as a future bulking agent that could prove to be more effective and durable than existing bulking agents.[50,51]

Autologous muscle-derived cells for urinary sphincter repair begin with a needle biopsy of a striated muscle for cell harvest. Often the quadriceps femoris is biopsied under local anesthesia as an office-based procedure. These cells are then processed in a proprietary fashion, and a subpopulation of muscle-derived cells are expanded in culture. After additional processing, these cells are injected into the mid-urethral and proximal urethral walls, in the region of the striated urethral sphincter (rhabdosphincter)

often using ultrasound localization. Such injections are done in the office using local anesthesia. The theoretical benefits of using this treatment is that the bulking effect is completely compatible with the patients native tissues, and the therapeutic benefit is maintained in the long term as the autologous cells are incorporated and remain viable in the urethral wall.

In a study that pooled data from 2 phase I/II studies of women who received autologous muscle-derived cells for urinary sphincter repair demonstrated no adverse events at 12 months follow-up. There was a potential dose response, with higher dose groups having a greater percentage of patients with at least a 50% reduction in stress leaks and pad weight at 12 months.[52] Although autologous cell therapies appear to be an attractive treatment, there are challenges to commercialization, which include the tightly controlled manufacturing processes and the inherent variability in cell growth across patient samples.

Male Stress Incontinence Treatments. Conservative therapy with PFMT is considered the first-line therapy for early incontinence within the first 6 to 12 months after a prostatectomy because progressive improvement in continence can occur. For those patients with irreversible UI after prostatectomy, surgical treatment with either a male sling or an artificial urinary sphincter (AUS) is considered first-line surgical therapy. Factors to consider when choosing the best option for a given patient include severity of UI, previous surgical procedures, bladder function, manual dexterity, cognitive function, and patient preference. The AUS remains the treatment of choice for moderate-to-severe male stress incontinence, and the male sling provides an alternative treatment for those men with mild stress incontinence. Complete or improved continence is found in 88% to 89% of men who undergo an AUS and in 70% to 84% of men who undergo a male sling.[53]

Bladder Underactivity/Urethral Overactivity and Overflow Incontinence

The goal of therapy for individuals with chronic urinary retention and overflow incontinence is to achieve periodic and complete bladder emptying either by reducing outlet closure forces (surgically or pharmacologically), increasing bladder contractility to allow satisfactory emptying, or by bypassing the bladder outlet through catheterization or urinary diversion.

Pharmacologic therapy to reduce urethral closure forces consists of alpha-adrenergic blockers, 5-alpha reductase inhibitors (in men), and, rarely, agents that act on striated muscle, such as benzodiazepenes or onobotulinumtoxinA. Such therapy carries a risk of developing SUI.

Effective pharmacologic therapy to increase bladder contractility is not currently available although bethanechol has been used for this purpose in uncontrolled studies.

Intermittent Self-catheterization. The most effective management of bladder underactivity or urethral overactivity is intermittent catheterization performed by the patient or a caregiver 3 or 4 times per day. By serially

emptying the bladder at regular fixed intervals, usually between 4 and 6 hours, patients may maintain freedom from the nuisance and complications of indwelling catheters. If leakage occurs between catheterizations, the frequency can be increased and anticholinergics or other therapies can be added. The clean technique, popularized by Lapides and colleagues,[54] involves washing the catheter and hands with soap and water rather than relying on sterility. Although bacteriuria is common, symptomatic urinary infection is much less likely in patients undergoing clean intermittent catheterization (CIC) than in those with indwelling catheters, and there is a lower overall rate of complication when using CIC, such as upper tract infection and bladder calculi.[55,56] There is conflicting evidence comparing clean with sterile techniques, and patients who have recurrent symptomatic UTIs with CIC may benefit from sterile or low-friction catheters.[57]

Indwelling Catheters. An alternative method of management that is considered less satisfactory is the indwelling urethral or suprapubic catheter. The suprapubic tube (surgically placed in an infraumbilical position) can avoid the complications of urethral erosion, epididymitis, orchitis, prostatitis, and urethral stricture and is often more comfortable and manageable for the patient compared with a Foley (urethral) catheter. However, indwelling catheters of either type have been shown to be inferior to intermittent catheterization techniques in terms of rates of bacteriuria and urethral complications.[58] The irritation related to indwelling catheters can predispose to squamous metaplasia, which is a statistically significant risk factor for the development of squamous cell carcinoma of the bladder, a particularly aggressive form of cancer. Patients should undergo periodic urologic surveillance after placement of a chronic indwelling catheter.

Sacral Neuromodulation. The use of sacral neuromodulation, mentioned previously for bladder overactivity and UUI, has shown some limited benefit in permitting satisfactory bladder emptying in the setting of chronic, non-neurogenic, nonobstructive urinary retention. The exact mechanism by which it exerts its favorable effects in this setting is unknown but may involve "rebalancing" of pelvic floor hypertonicity. In a randomized prospective trial, 83% of patients who received a permanent implant had improvement of their symptoms, with 69% of treated patients able to discontinue intermittent catheterization.[59] The optimal patient population for this therapy is not well defined. Surgical approach and location of electrodes and pulse generator are the same as when used for the indication of UUI.

Urinary Diversion. A more invasive method of management is surgical treatment with urinary diversion. As mentioned previously, a vascularized segment of small bowel, colon, or stomach can be used as a continent or incontinent urinary conduit.

CONCLUSIONS

The main goal of therapy for UI is to minimize the signs and symptoms most bothersome to the patient and the use of pads and other ancillary supplies or devices. Understanding the etiology and type of UI facilitates the selection of the correct mode of therapy. Oral therapies for UI are limited by their modest efficacy and side effect profiles that lead to discontinuation by the patient. Several new therapies have advanced the treatment of UI over the past 10 to 15 years. Total elimination of UI signs and symptoms may not be possible in all cases, and patients and practitioners need to mutually establish realistic goals of therapy.

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