Advances in the Treatment of Urinary Incontinence in Women

Elizabeth T. Brown, William S. Reynolds, Melissa R. Kaufman and Roger R. Dmochowski

Department of Urologic Surgery, Vanderbilt University Medical Center, Nashville, TN, USA.

ABSTRACT: Urinary incontinence in women is quite prevalent today and management can be costly. Urinary incontinence can be minimal or quite bothersome, limiting activities of daily living. It is subdivided into urgency urinary incontinence, stress urinary incontinence, and mixed urinary incontinence. As such, treatment can vary immensely depending on the clinical presentations, ranging from behavioral modification to medicinal therapies to surgical procedures. First-line management for all urinary incontinence includes lifestyle and behavioral modifications. Historically, treatment options for urgency urinary incontinence were predominantly antimuscarinics, while more recent therapies include oral beta-3 agonist administration, sacral neuromodulation, onabotulinumtoxinA injection, and posterior tibial nerve stimulation. Stress urinary incontinence can be treated with a variety of urethral bulking agent injections or sling-based procedures using mesh, autologous fascia, or cadaveric fascia, as well as urethral intrasphincteric injections of autologous muscle-derived cells in new clinical trials. These recent advances that have been developed to help better curb urinary incontinence are discussed in this review.

KEYWORDS: urinary incontinence, urgency urinary incontinence, stress urinary incontinence, sling, vaginal mesh, bulking agent injection, autologous muscle-derived cell therapy, beta-3 agonist, onabotulinumtoxinA, sacral neuromodulation, posterior tibial nerve stimulation

CITATION: Brown et al. Advances in the Treatment of Urinary Incontinence in Women. *Clinical Medicine Insights: Urology* 2015:8 1–6 doi:10.4137/CMU.S13181.

RECEIVED: October 23, 2014. **RESUBMITTED:** January 14, 2015. **ACCEPTED FOR PUBLICATION:** February 2, 2015.

ACADEMIC EDITOR: Xiangyi Lu, Editor in Chief

TYPE: Review

FUNDING: Authors disclose no funding sources.

COMPETING INTERESTS: MRK is a national principal investigator for Cook Myosite and is a member of faculty for a resident cadaver course in association with American Medical Systems. RRD is a consultant for Allergan and Medtronic. ETB has received partial travel reimbursement from the Society of Women in Urology.

CORRESPONDENCE: elizabeth.t.brown@vanderbilt.edu

Paper subject to independent expert blind peer review by minimum of two reviewers. All editorial decisions made by independent academic editor. Upon submission manuscript was subject to anti-plagiarism scanning. Prior to publication all authors have given signed confirmation of agreement to article publication and compliance with all applicable ethical and legal requirements, including the accuracy of author and contributor information, disclosure of competing interests and funding sources, compliance with ethical requirements relating to human and animal study participants, and compliance with any copyright requirements of third parties. This journal is a member of the Committee on Publication Ethics (COPE). Provenance: the authors were invited to submit this paper.

Published by Libertas Academica. Learn more about this journal.

Introduction

Urinary incontinence (UI) is a common complaint in the female population, affecting at least 55% of women overall.[1] However, the reported number varies widely in the literature and is thought to be underreported as many women may fail to discuss incontinence with their health providers.[2] This may be either due to embarrassment or due to a preconceived notion that incontinence is a normal part of aging.[3] While the true prevalence of UI is unknown, the cost of health care dollars devoted to incontinence is considerable. It has been estimated that there were >1.1 million office visits in 2000 for the primary complaint of incontinence, resulting in indirect and direct costs of incontinence in the United States estimated to be $19.5 billion, which is surprisingly large relative to costs for many other chronic diseases.[4] There are actually multiple treatment options for women with UI depending on types of incontinence, particular clinical presentations, and the willingness of patients to undergo invasive procedures. Due to the prevalence, cost burden, and recent advances in understanding UI pathophysiology, newer and more innovative therapies are continuously being developed.

Urinary Incontinence

UI is defined by the International Continence Society (ICS) as involuntary leakage of urine,[5] which can be subdivided into stress urinary incontinence (SUI), urgency urinary incontinence (UUI), or mixed urinary incontinence (MUI). SUI is the voluntary loss of urine on effort, physical exertion, sneezing, or coughing, while UUI is defined as the involuntary loss of urine associated with urgency.[6] Although patients can present with MUI, treatment is typically targeted at the most bothersome symptoms. At times, patients can complain equally of both urge and stress components and both are targeted for therapy.

Urgency Urinary Incontinence

Initial management for UUI. UUI is a component of a larger symptom complex known as the overactive bladder (OAB) syndrome. OAB is a clinical diagnosis that is defined by the ICS as "the presence of urinary urgency, usually accompanied by frequency and nocturia, with or without UUI, in the absence of a urinary tract infection or other obvious pathology."[7] The American Urological Association (AUA)/Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) guidelines on OAB state that OAB is generally not life-threatening and that the benefits of treatment should be weighed against potential adverse events and that not offering any treatment is an acceptable choice.[7] However, patients with UI due to neurogenic bladder should be assessed formally with videourodynamics to evaluate the upper tracts and treated accordingly.[8]

Nevertheless, for healthy nonneurogenic patients with significant bother, first-line therapies include dietary and lifestyle modifications—primary care providers can typically implement these initially. For example, patients should limit their fluid intake, especially caffeinated and/or carbonated beverages such as colas, coffees, teas, and citrus drinks.[9] Bladder and bowel habits should also be addressed. Patients should be taught bladder training and delayed voiding, as well as timed voiding.[7] Constipation should be actively managed and avoided when possible as it has been consistently shown to contribute to lower urinary tract dysfunction.[10] Obesity can also contribute to UUI and OAB symptomatology—a weight loss of 8% in obese women showed a decrease in overall incontinence per week and UUI episodes by 47% and 42% vs 28% and 26% in controls, respectively.[7,11] Thus, behavioral modification can greatly improve UI in properly selected patients. In fact, a randomized controlled trial of 197 women with UUI randomized to oxybutynin, behavioral therapy, or placebo found 80.7% reduction in UI episodes with behavioral therapy compared to 68.5% reduction with oxybutynin and 39.4% reduction with placebo ($P = 0.04$).[12,13] Pelvic floor muscle training is also considered a standard first-line therapy in the AUA/SUFU guidelines on OAB.[7] This consists of learning exercises to strengthen the pelvic floor and contracting them to reduce leakage, thus improving symptoms of both SUI and UUI.[12] Pelvic floor training, or Kegel exercise, is also supported as an initial therapy as per the guidelines of the National Institute for Health and Care Excellence (NICE) for a trial of 3 months, with eight contractions performed three times daily.[14]

Oral medications for UUI. In addition to dietary and behavioral modifications, oral medications are another conservative noninvasive treatment option for UUI, considered to be second-line treatment by the AUA/SUFU guidelines on OAB.[7] Traditionally, UUI has been treated with antimuscarinic therapies, including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, or trospium. All antimuscarinics have been shown to be safe and effective treatment options for OAB with or without UI.[12] The primary difference between the medications lies in the side effect profiles, not in terms of differences in their efficacy. Typically, antimuscarinics can cause dry mouth, constipation, cognitive changes, and blurred vision. Using a long-acting drug formulation can reduce these side effects, which is a standard in the AUA/SUFU guidelines.[7]

Additionally, certain medications have shown differences in cognitive impairment. The AUA/SUFU guidelines recommend using caution when prescribing such medications to frail patients.[7] While caution is advised for all antimuscarinics, trospium is a quaternary amine that does not cross the blood–brain barrier, theoretically decreasing the potential risk for central nervous system side effects.[15] Darifenacin has also been shown to have a cognitive side effect profile that is decreased/favorable due to its selectivity for the muscarinic 3 receptor.[7,16] There is evidence that fesoterodine is generally well tolerated in the elderly as well, especially at the 4-mg dose.[17] The AUA/SUFU guidelines also advise extreme caution when prescribing antimuscarinics to patients with delayed gastric emptying or urinary retention and it should not be used in patients with narrow-angle glaucoma. Due to these limitations and the significant side effect profile, patient compliance is low. In fact, it has been shown that 43%–83% of women abandon antimuscarinic therapy by 1 month, and that at 1 year, <35% women are still taking the medication.[18,19]

Historically, antimuscarinics have been the only oral medication option for patients with bothersome UUI. However, in 2012, the US Food and Drug Administration (FDA) approved mirabegron for OAB. Mirabegron is a beta-3 agonist, which promotes relaxation of the detrusor muscle, thus reducing urgency and frequency. Recently, Chapple et al[20] conducted a post hoc analysis of pooled data from three randomized, double-blind, placebo-controlled, 12-week, phase III studies of mirabegron to evaluate the efficacy of mirabegron (50 mg) in incontinent OAB patients. Mirabegron (50 mg) resulted in statistically significant improvements from baseline to final visit versus placebo in mean number of incontinence episodes, micturitions, and urgency episodes per 24 hours and mean volume voided per micturition in the pooled incontinent population.[20]

As a beta-3-adrenoceptor agonist, however, mirabegron can also have a potential effect on the beta-receptors in the cardiovascular system, which theoretically can lead to increased cardiovascular side effects such as elevated blood pressure. Nevertheless, a pooled phase III clinical trial showed no significant increase in hypertension when compared to placebo.[12,19] Additionally, other adverse effects are uncommon, with the incidence of dry mouth and constipation being <2%.[19] Further reports show that the adverse effect rates are similar to those for placebo, making it a more desirable option than antimuscarinics for many patients.[20] However, these data are primarily derived from clinical trials, and further studies are needed to evaluate the long-term effectiveness and compliance with mirabegron in the UUI population, although recent studies are beginning to show significant benefits for women with OAB with or without UUI.[21]

Owing to the preliminary success of mirabegron in phase III trials and clinical practice, a combination tablet (solifenacin plus mirabegron) is currently in clinical trials. In a randomized, double-blind, phase II study, combination therapy demonstrated statistically significant improvement over monotherapy with solifenacin (5 mg) in mean voided volume, micturation frequency, and urgency.[22] The side effect profile was not increased compared with mirabegron or solifenacin monotherapy, although there may be a slightly increased risk of constipation. There was also no dose-related difference in pulse rate or blood pressure when evaluating the safety and efficacy of this new combination pill.[22]

Treatment options for refractory UUI. When the aforementioned conservative therapies fail, patients are usually

referred to a more specialized provider, such as an urologist or urogynecologist with specialized training in UI. Traditionally, augmentation cystoplasty or urinary diversion has been the surgical option for refractory UUI. However, several minimally invasive surgical procedures are now available as third-line therapies for refractory UUI, with none showing superiority relative to others as of now.[23] Additionally, receiving onabotulinumtoxinA injection, posterior tibial nerve stimulation (PTNS), or sacral neuromodulation does not preclude a patient from trying a different therapy if results are not desirable.[7]

OnabotulinumtoxinA. Intravesical onabotulinumtoxinA treatment is now an option as third-line therapy for patients with refractory OAB/UUI and for patients who are not candidates for, or cannot tolerate, oral medications. OnabotulinumtoxinA can be injected into the detrusor muscle cystoscopically either in an office-based setting under local anesthesia or in the operating room. It had previously been approved by the FDA for the management of neurogenic bladder and was recently approved in 2013 for the management of OAB with or without UI. The AUA/SUFU guidelines recommend a 100-unit injection for the indication of OAB, while the NICE guidelines recommend 200 units, unless the woman is worried about retention and willing to accept a lower success rate.[7,13] Patients receiving intravesical onabotulinumtoxinA therapy should be advised of the risk of incomplete emptying and urinary retention, as well as the potential need for catheterization. According to AUA/SUFU guidelines, these patients "must be able and willing to return for frequent post-void residual evaluation and able and willing to perform self-catheterization, if necessary."[7] However, the risk of incomplete emptying and urinary retention appears to be dose dependent. A randomized controlled trial of 557 patients randomized to 100 units or placebo showed a significant decrease (2.7%, $P < 0.001$) in incontinence episodes per day, with an overall retention rate of 5.4%.[24] Long-term benefits appear to be present, although repeat injections are required as the effect of the toxin dissipates. Currently, the total dose of onabotulinumtoxinA should not exceed 360 units in a 3-month period for any indications, including those outside the urinary tract.[25] Thus, in patients with OAB, repeat injections of onabotulinumtoxinA may be offered, and may sometimes be necessary, if leakage persists after injection of 100–200 units. A recent study by Sahai et al[26] showed that repeat injections can improve cystometric capacity and bladder compliance in patients with idiopathic detrusor overactivity but showed no difference in subjective quality-of-life questionnaire results at follow-up. The long-term efficacy and safety of onabotulinumtoxinA injection have been studied in the neurogenic population and the benefits appear to be sustainable with an excellent safety profile.[27] Recently, abobotulinumtoxin has been trialed in place of onabotulinumtoxinA, although there is paucity of data evaluating its efficacy. However, in a trial of bladder pain syndrome patients, intradetrusor injection of abobotulinumtoxin plus hydrodistention was compared with intradetrusor injection of saline with hydrodistention, showing mild improvement in the treatment group in a small number of patients but with no overall improvement when compared with placebo.[28]

Sacral neuromodulation. Another treatment option for refractory UUI is sacral neuromodulation. This is an excellent treatment option for patients who are either unwilling to accept the risk of urinary retention or who are unable to be catheterized after injection of onabotulinumtoxinA.[7] An electrode is placed in the S3 foramen, which provides nerve stimulation to the bladder and perineum. There are two approaches for placement of the electrode. A percutaneous approach can be performed in an office-based setting under local anesthesia to place a temporary lead. This typically provides stimulation for a short trial period (3–5 days), after which a permanent lead and generator are surgically implanted in the operating room. Another approach is a two-stage technique, conducted in the operating room, in which the permanent lead is surgically implanted and connected to an external generator. If the patient has successful results (>50% clinical improvement) after approximately 1 week, the permanent generator is then implanted in the patient in a separate setting in the operating room.[12] While the percutaneous approach obviates the need for a second anesthesia and operation, the two-stage technique has a higher rate of generator implantation (50.9% vs 24.1%) due to the stability of the permanent lead.[29] Sacral neuromodulation does have durable treatment effects, but there are adverse effects, including pain, lead migration, infection, electric shock, and the need for further procedures.[7,30] The current life of a generator is approximately 5 years and, currently, it requires surgical exchange after that time period. Patients must be cognitively capable of optimizing the device settings, which can be a limitation of this treatment. Another concern with generator implantation is the magnetic resonance imaging (MRI) compatibility—patients with UI requiring frequent MRIs, such as those with multiple sclerosis, should not be treated with neuromodulation. However, a retrospective study of nine patients with neuromodulation devices did not show any adverse events after undergoing MRIs of the pelvis, brain, or spine.[31,32] To date, sacral neuromodulation has been shown to be quite effective in treating refractory urgency and frequency. Noblett et al[33] studied 340 patients, 272 of whom were implanted with sacral neuromodulation after test stimulation. Of these, UI patients had 3.1 ± 2.7 leaks/day and urinary frequency patients had 12.6 ± 4.5 voids/day. The analysis, which includes all implanted patients with diary data at baseline and 12 months, showed an OAB therapeutic success rate of 85% at 12 months. UI patients had a mean reduction of 2.2 ± 2.7 leaks/day, while urinary frequency patients had a mean reduction of 5.1 ± 4.1 voids/day (both $P < 0.0001$).[33] These effects appear to be durable. A recent study evaluated the long-term follow-up of 217 patients (86%

female) who received sacral neuromodulation between 1996 and 2010.[34] Success was considered if the ≥50% improvement in any of the primary voiding diary variables persisted compared with baseline. The mean duration of follow-up was 46.88 months. Success and cure rates were, respectively, ≈70% and 20% for urgency incontinence, 68% and 33% for urgency frequency syndrome, and 73% and 58% for idiopathic retention. In patients with an unsuccessful therapy outcome, the mean time to failure was 24.6 months after implantation. There were 88 (41%) patients who had at least one device- or treatment-related surgical reintervention, with most of them (47%) occurring ≤2 years of follow-up.[34]

Posterior tibial nerve stimulation. PTNS is an office procedure whereby a small needle is placed into the peripheral tibial nerve, which modulates the sacral nerve plexus through the S2–S4 nerves.[12] This procedure consists of 12 weekly visits, each consisting of 30-minute treatments. The AUA/SUFU guidelines recommend PTNS as a third-line option for patients who are willing to comply with frequent office visits.[7] Long-term follow-up appears to be durable for patients who maintain compliance, and adverse events are mild and uncommon.[7] The NICE guidelines recommend PTNS as an option for patients who fail conservative therapy and for whom onabotulinumtoxinA injections or sacral neuromodulation is not an option. A recent study by Ammi et al[35] supported this recommendation, showing improvement in 53% of antimuscarinic refractory PTNS patients based on validated questionnaire results.

The efficacy and durability of PTNS were tested in phases I and II of the Overactive Bladder Innovative Therapy Trial,[36] which compared PTNS to extended-release tolterodine. This study showed comparative effectiveness between PTNS and tolterodine, but PTNS showed greater durability compared to the pharmacologic option.[36,37]

Stress Urinary Incontinence

Initial management for SUI. In the United States, there are no oral medications approved for the treatment of SUI.[38] Traditional conservative management for SUI consists of pelvic floor muscle training (Kegel exercises) and/or the use of incontinence pessaries.[12] Significant benefits can be seen with behavioral modification, including timed voiding and weight loss. Even a small reduction in weight loss has consistently been shown to reduce UI episodes with durable results.[39] In a randomized controlled trial of 40 women, a 5%–10% weight reduction decreased weekly incontinence episodes by 54%.[40] However, conservative therapies are often ineffective for bothersome SUI, leading patients to pursue more invasive surgical options.

Treatment options for SUI. For patients with SUI who have failed conservative management and desire surgical intervention, there are five approved therapies according to the AUA SUI Guidelines Panel: injectables, laparoscopic suspensions, midurethral slings, pubovaginal slings, and retropubic suspensions.[41] Artificial urinary sphincters are also listed as an option, but the data are limited and would likely be most useful in the Valsalva—voiding woman who must abdominally strain to empty the bladder.[41] While these procedures are all listed as options, these treatments are not equivalent.[41] There has been an overall trend away from open and laparoscopic suspensions, with the midurethral synthetic sling becoming the mainstay surgical option due to the minimally invasive approach and proven long-term efficacy. However, synthetic slings have received recent scrutiny due to the FDA public health notification on vaginal mesh, and this trend may evolve yet again.

Surgical slings. There are two types of slings: pubovaginal slings and midurethral slings. Traditionally, the pubovaginal sling using autologous fascia was considered one of the gold standard procedures for SUI. According to AUA guidelines, the estimated cured/dry rates for an autologous sling (rectus fascia or fascia lata) ranged between 90% at 12–23 months and 82% at 48 months or longer.[41] In more recent years, biologic grafts using cadaveric fascia have been developed, obviating the need for an autologous harvest site and thus avoiding the added morbidity. However, the long–term durability of these procedures has been questioned, with reports of graft failure and declining success rates over time.[41] As such, the midurethral synthetic sling has been developed, replacing the pubovaginal sling as the gold standard for SUI.[42]

Midurethral slings can be placed either retropubically or through a transobturator approach. The Trial of MidUrethral Slings (TOMUS) was a multicenter, randomized trial of 597 women. This trial was conducted by the Urinary Incontinence Treatment Networks and it showed both subjective and objective equivalence between the two surgical approaches.[43] A subsequent 2-year follow-up study showed a higher rate of bladder perforation and voiding dysfunction with retropubic sling placement, while transobturator placement resulted in more neuromuscular complaints such as leg weakness, pain, and groin numbness.[44] In the AUA SUI Guidelines Panel's meta-analysis, there was a de novo urge incontinence rate of 6% and retention rate of approximately 3% with midurethral slings.[41] The most common complication found in the meta-analysis was urinary tract infection (11%), which was also the most frequent complication in the TOMUS trial.[41,44] Nevertheless, success rates of midurethral slings are high. The AUA SUI Guidelines Panel's meta–analysis estimated cured/dry rates in patients without prolapse treatment ranging from 81% to 84% at all time points, which is comparable to the medium-term results for the Burch suspensions and autologous fascial slings, showing comparable efficacy between midurethral slings and autologous slings in the surgical treatment of SUI.[33] Nilsson et al[45] prospectively followed 90 women who received tension-free vaginal tape. At 17-year follow-up, 78% of women were assessable, showing a 90% objective continence rate, further supporting the long-term durability of midurethral slings.

In more recent years, a single-incision minisling has been developed as a smaller, synthetic midurethral sling, which is placed through a single vaginal incision, but preliminary data suggest lower cure rates and higher reoperation rates without long-term data.[41,45,46] In fact, a study by Basu and Duckett[47] supported this as well, showing that at 3-year follow-up, there was a significantly higher failure rate for the minisling versus the retropubic midurethral sling.

In 2008, the FDA issued a statement cautioning against the vaginal placement of mesh for both pelvic organ prolapse and UI. In 2011, an updated FDA warning stated that most mesh-related complications were associated with the transvaginal placement of mesh for pelvic organ prolapse and there were insufficient data to recommend against using mesh for SUI.[48] Nonetheless, patients are not necessarily aware of these differences and should be counseled appropriately before any surgical intervention, especially when voicing concerns about mesh placement.[49] As such, patients should be informed that synthetic slings are still considered a first-line treatment option for SUI. In fact, the American Urogynecologic Society and SUFU issued a joint statement in 2014 strongly supporting the use of polypropylene mesh for the treatment of SUI, stating that the midurethral sling procedure is safe, is effective, and remains the standard of care for the treatment of SUI.[12]

Urethral injection therapy. Injectable urethral bulking agents are options for patients, such as the elderly or those at a high anesthetic risk, who cannot undergo or do not wish to undergo an invasive surgery for the treatment of SUI.[41] These patients should understand that both efficacy and the resulting durability are inferior to the results from surgery, and it can often require multiple procedures to achieve a desirable effect. Bulking agent injections can result in an improvement in incontinence, but patients may not necessarily achieve dryness. Nonetheless, bulking agents can be quite effective in some patients and can be performed either as an office-based procedure or in the operating room. While the original injectable collagen is no longer available, a recent study showed that the newly developed polyacrylamide hydrogel was not inferior.[50] Of the 345 women included in the study, 229 were randomized to hydrogel and 116 were randomized to collagen gel. At 12 months, a decrease of ≥50% in leakage and incontinence episodes was seen in 53.2% and 55.4% of patients who received hydrogel and collagen gel, respectively.[50] At 12 months, 47.2% of patients with hydrogel and 50% with collagen gel reported zero stress incontinence episodes, and 77.1% and 70%, respectively, considered themselves cured or improved. However, there are several available injectables that appear to have similar efficacy, although each has unique biophysical properties.[51] Most clinical studies report modest efficacy of up to 75% improvement or cure over a short duration, but this tends to decrease over time and can show substantially less improvement at 1 year.[51] Currently, there is insufficient evidence regarding the use of bulking agents to guide clinical practice.[52]

Autologous muscle-derived cell therapy. An emerging innovative therapy for SUI is the use of autologous muscle progenitor cells, which are isolated from skeletal muscle biopsies and are then expanded ex vivo and subsequently injected into the urethral sphincter.[53] This is thought to improve SUI by augmenting urethral sphincter function.[53] In recently published pooled data from two phase I/II studies, a total of 80 women underwent injections of 10, 50, 100, or 200×10^6 autologous muscle-derived cells. Women were included in the study if they were ≥18 years of age with SUI refractory to previous treatment (including surgical) and had had no improvement of SUI symptoms for at least 6 months. Each woman underwent a needle biopsy of the quadriceps femoris, and this tissue was sent for ex vivo expansion. All dose groups had significantly less SUI-induced leakage at 12 months per voiding diary report ($P < 0.05$). Patients who received the 200×10^6 dose showed a significant reduction in mean pad weight, indicating a potential dose response ($P < 0.05$). There were few adverse events related to the biopsy or injection, and these were easily treated or self-resolved.[53] Currently, two phase III double-blind, randomized, placebo-controlled trials are ongoing.

Conclusion

UI can be a cumbersome complaint in women. While primary care providers can use empiric therapies such as oral medications and behavioral modification, UI is often refractory, requiring more invasive therapies by urologists or urogynecologists. The therapies include onabotulinumtoxinA injection, sacral neuromodulation, and posterior tibial nerve stimulation for UUI, as well as urethral bulking agent injections or sling-based procedures for SUI. The most recent development for SUI involves urethral intrasphincteric injection of autologous muscle-derived cells, and this is currently in clinical trial, with initial results suggesting that the treatment is safe and efficacious.

The advances in treatments for UI, as discussed in this review, have restructured the management of incontinence in women. Nevertheless, UI continues to be an extremely prevalent complaint in our aging female population, and new therapies are continually being developed to better help curtail UI.

Acknowledgment

This is an invited submission.

Author Contributions

Conceived and designed the experiments: ETB, WSR, MRK, RRD. Analyzed the data: ETB, WSR, MRK, RRD. Wrote the first draft of the manuscript: ETB. Contributed to the writing of the manuscript: ETB, WSR, MRK, RRD. Agree with manuscript results and conclusions: ETB, WSR, MRK, RRD. Jointly developed the structure and arguments for the paper: ETB, WSR, MRK, RRD. Made critical revisions and approved final version: ETB, WSR, MRK, RRD. All authors reviewed and approved of the final manuscript.

REFERENCES

1. Thom D. Variation in estimates of urinary incontinence prevalence in the community: effects of differences in definition, population characteristics, and study type. *J Am Geriatr Soc*. 1998;46:473–480.
2. Branch LG, Walker LA, Wetle TT, DuBeau CE, Resnick NM. Urinary incontinence knowledge among community-dwelling people 65 years of age and older. *J Am Geriatr Soc*. 1994;42:1257–1262.
3. Cheater FM, Castleden CM. Epidemiology and classification of urinary incontinence. *Baillieres Best Pract Res Clin Obstet Gynaecol*. 2000;14:183–205.
4. Chapple C, Milsom I. Urinary incontinence and pelvic prolapse: epidemiology and pathophysiology. In: Wein AJ, Kavoussi LR, Partin AW, Peters CA, Novick AC, eds. *Campbell-Walsh Urology*. (Chap. 63). St. Louis, MO: Saunders; 2012:1871–1895.
5. Abrams P, Cardozo L, Fall M, et al. The standardization of terminology in the lower urinary tract function report from the standardization sub-committee of the International Continence Society. *Urology*. 2003;61:37–49.
6. Haylen BT, deRidder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Int Urogynecol J*. 2010;21:5–26.
7. Gormley EA, Lightner DJ, Burgio KL, et al; American Urological Association; Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. *J Urol*. 2012;188:2455–2463.
8. Winters JC, Dmochowski RR, Goldman HB, et al; American Urological Association; Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction. Urodynamic studies in adults: AUA/SUFU guideline. *J Urol*. 2012;188:2464–2472. [Summary of the AUA guidelines on adult urodynamics].
9. Khan IJ, Tariq SH. Urinary incontinence: behavioral modification therapy in older adult. *Clin Geriatr Med*. 2004;20:499–509.
10. Kinnunen O. Study of constipation in a geriatric hospital, day hospital, old people's home and at home. *Aging*. 1991;3:161–170.
11. Fantl JA, Wyman JF, McClish DK, et al. Efficacy of bladder training in older women with urinary incontinence. *JAMA*. 1991;265:609.
12. Wood L, Anger J. Urinary incontinence in women. *BMJ*. 2014;349:g4531.
13. Burgio KL, Locher JL, Goode PS, et al. Behavioral vs drug treatment for urge urinary incontinence in older women: a randomized controlled trial. *JAMA*. 1998; 280:1995–2000.
14. National Institute for Health and Care Excellence. *Urinary Incontinence: The Management of Urinary Incontinence in Women*. London: NICE; 2013.
15. Gomelsky A, Dmochowski R. OAB update: focus on trospium. *Clin Med Insights Urol*. 2011;5:1–9.
16. Lipton RB, Kolodner K, Wesnes K. Assessment of cognitive function of the elderly population: effects of darifenicin. *J Urol*. 2005;173:493.
17. Dubeau CE, Kraus SR, Griebling TL, et al. Effect of fesoterodine in vulnerable elderly subjects with urgency incontinence: a double-blind, placebo controlled trial. *J Urol*. 2014;191(2):395–404.
18. Sexton CC, Notte SM, Maroulis C, et al. Persistence and adherence in the treatment of overactive bladder syndrome with anticholinergic therapy: a systematic review of the literature. *Int J Clin Pract*. 2011;65:567–585.
19. Chapple C, Cardozo L, Nitti V, Siddiqui E, Michel M. Mirabegron in overactive bladder: a review of safety, efficacy, and tolerability. *Neurourol Urodynam*. 2014; 33:17–30.
20. Chapple C, Khullar V, Nitti VW, et al. Efficacy of the B3-adrenoreceptor agonist mirabegron for the treatment of overactive bladder by the severity of incontinence at baseline: a post hoc analysis of pooled data from three randomized phase 3 trials. *Eur Urol*. 2015;67(1):11–14.
21. Sanford M. Mirabegron: a review of its use in patients with overactive bladder syndrome. *Drugs*. 2013;73(11):1213–1225.
22. Abrams P, Kelleher C, Staskin D, et al. Combination treatment with mirabegron and solifenacin in patients with overactive bladder: efficacy and safety results from a randomised, double-blind, dose-ranging, phase 2 study (symphony). *Eur Urol*. 2014.
23. Nambiar A, Lucas M. Chapter 4: guidelines for the diagnosis and treatment of overactive bladder (OAB) and neurogenic detrusor overactivity (NDO). *Neuro Urodyn*. 2014;33:21–25.
24. Balachandran A, Curtiss N, Basu M, Duckett J. Third-line treatment for overactive bladder: should mirabegron be tried before intravesical botulinum toxin A therapy? *Int Urogynecol J*. 2015;3(26):367–72.
25. Nitti VW, Dmochowski RR, Herschorn S, et al. OnabotulinumtoxinA for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. *J Urol*. 2013;189:2186–2193.
26. Sahai A, Dowson C, Khan M, et al. Repeated injections of botulinum toxin-A for idiopathic detrusor overactivity. *Urology*. 2010;75(3):552–558.
27. Rovner E. Chapter 6: practical aspects of administration of onabotulinumtoxinA. *Neurourol Urodyn*. 2014;33(suppl 3):S32–S37.
28. Manning J, Dwyer P, Rosamilia A, Colyvas K, Murray C, Fitzgerald E. A multicentre, prospective, randomized, double-blind study to measure the treatment effectiveness of abobotulinum A (AboBTXA) among women with refractory interstitial cystitis/bladder pain syndrome. *Int Urogynecol J*. 2014;25(5):593–599.
29. Kennelly M, Dmochowski R, Ethans K, et al. Long-term efficacy and safety of onabotulinumtoxinA in patients with urinary incontinence due to neurogenic detrusor overactivity: an interim analysis. *Urology*. 2013;81(3):491–497.
30. Cameron AP, Anger JT, Madison R, Saigal CS, Clemens JQ. Urologic diseases in America project. National trends in the usage and success of sacral nerve test stimulation. *J Urol*. 2011;185:970–975.
31. Starkman JS, Wolter CE, Scarpero HM, Milam DF, Dmochowski RR. Management of refractory urinary urge incontinence following urogynecological surgery with sacral neuromodulation. *Neurourol Urodyn*. 2007;26:29–35.
32. Chermansky CJ, Krlin RM, Holley TD, Woo HH, Winters JC. Magnetic resonance imaging following InterStim®: an institutional experience with imaging safety and patient satisfaction. *Neurourol Urodyn*. 2011;30(8):1486–1488.
33. Noblett K, Siegel S, Mangel J. Results of a prospective, multicenter study evaluating quality of life, safety, and efficacy of sacral neuromodulation at twelve months in subjects with symptoms of overactive bladder. *Neuro Urodyn*. 2014.
34. Peeters K, Sahai A, DeRidder D, et al. Long-term follow-up of sacral neuromodulation for lower urinary tract dysfunction. *BJUI Int*. 2014;113(5):789–794.
35. Ammi M, Chautard D, Brassart E, Culty T, Azzouzi AR, Bigot P. Transcutaneous posterior tibial nerve stimulation: evaluation of a therapeutic option in the management of anticholinergic refractory overactive bladder. *Int Urogynecol J*. 2014;25:1065–1069.
36. Peters KM, Macdiarmid SA, Wooldridge LS, et al. Randomized trial of percutaneous tibial nerve stimulation versus extended-release tolterodine: results from the overactive bladder innovative therapy trial. *J Urol*. 2009;182(3):1055–1061.
37. MacDiarmid SA, Peters KM, Shobeiri SA, et al. Long-term durability of percutaneous tibial nerve stimulation for the treatment of overactive bladder. *J Urol*. 2010;183(1):234–240.
38. Qaseem A, Dallas P, Forciea MA, Starkey M, Denberg TD, Shekelle P. Nonsurgical management of urinary incontinence in women: a clinical practice guideline from the American College of Physicians. *Ann Intern Med*. 2014;161(6):429–440.
39. Osborn D, Strain M, Gomelsky A, Rothschild J, Dmochowski R. Obesity and female stress urinary incontinence. *Urology*. 2013;82:759–763.
40. Subak LL, Whitcomb E, Shen H, Saxton J, Vittinghoff E, Brown JS. Weight loss: a novel and effective treatment for urinary incontinence. *J Urol*. 2005;174(1):190–195.
41. Dmochowski RR, Blaivas JM, Gormley EA, et al. Update of AUA guideline on the surgical management of female stress urinary incontinence. *J Urol*. 2010; 183:1906–1914.
42. Ogah J, Cody JD, Rogerson L. Minimally invasive synthetic sling suburethral sling operations for stress urinary incontinence in women. *Cochrane Database Syst Rev*. 2009;4:CD006375.
43. Richter HE, Albo ME, Zyczynski HM, et al. Retropubic versus transobturator midurethral slings for stress incontinence. *N Engl J Med*. 2010;362:2066–2076.
44. Brubaker L, Norton PA, Albo ME, et al. Adverse events over two years after retropubic or transobturator midurethral sling surgery: findings from the Trial of midurethral slings (TOMUS) study. *Am J Obstet Gynecol*. 2011;205:498.
45. Nilsson CG, Palva K, Aarnio R, Morcos E, Falconer C. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. *Int Urogynecol J*. 2013;24:1265–1269.
46. Abdel-Fattah M, Ford JA, Lim CP, Madhuvrata P. Single-incision mini-slings versus standard midurethral slings in surgical management of female stress urinary incontinence: a meta-analysis of effectiveness and complications. *Eur Urol*. 2011;60:468–480.
47. Basu M, Duckett J. Three-year followup from a randomized trial of a retropubic mid-urethral sling versus the Miniarc single incision sling for stress urinary incontinence. *Int Urogynecol J*. 2013;24:2059–2064.
48. Togami JM, Brown ET, Winters JC. Vaginal mesh-the controversy. *F1000 Med Rep*. 2012;4:21.
49. Koski ME, Chamberlain JC, Rosoff J, et al. Patient perception of transvaginal mesh and the media. *Urology*. 2014;84:575–582.
50. Sokol E, Karram M, Dmochowski R. Efficacy and safety of polyacrylamide hydrogel for the treatment of female stress incontinence: a randomized, prospective, multicenter North American study. *J Urol*. 2014;192(3):843–849.
51. Reynolds WS, Dmochowski RR. Urethral bulking: a urology perspective. *Urol Clin N Am*. 2012;39:279–287.
52. Kirchin V, Page T, Keegan PE, Atiemo K, Cody JD, McClinton S. Urethral injection therapy for urinary incontinence in women (review). *Cochrane Libr*. 2012;2:CD003881.
53. Peters KM, Dmochowski RR, Carr LK, et al. Autologous muscle derived cells for treatment of stress urinary incontinence in women. *J Urol*. 2014;192:469–476.