Overactive Bladder

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Overactive bladder (OAB) is an umbrella term that includes the symptoms of urinary urgency, frequency, nocturia, and/or urgency incontinence. Prevalence of this condition is reported to be higher in women and also reported to increase with age, with estimates extending up to 40 % after 70 years [1, 2]. OAB has a significant impact upon quality of life [3], as well as having a significant impact on the healthcare system with annual costs ranging from 66 billion US dollars. These costs are related to the routine costs of pads and diapers to patients, as well as the costs associated with the increased risk for falls and fractures, infections, and physical compromise [1]. Asking patients if they suffer these symptoms and tailoring an appropriate and effective treatment regimen is of great value not only for the patient but also for the healthcare system.

In 2010, the International Urogynecological Association (IUGA)/International Continence Society (ICS) formalized a joint report updating the definitions/nomenclature of symptoms surrounding overactive bladder [4].

1. Increased daytime urinary frequency: Complaint that micturition occurs more frequently during waking hours than previously deemed normal by the woman.
2. Nocturia: Complaint of interruption of sleep one or more times because of the need to micturate. Each void is preceded and followed by sleep.
3. Urgency: Complaint of a sudden, compelling desire to pass urine which is difficult to defer.
4. Overactive bladder (OAB, Urgency) syndrome: Urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence, in the absence of urinary tract infection (UTI) or other obvious pathology.
5. Urgency (urinary) incontinence: Complaint of involuntary loss of urine associated with urgency.

The most common etiology for overactive bladder is idiopathic. Neurologic conditions including multiple sclerosis, Parkinson's, and spinal cord injury can lead to similar symptoms and are termed neurogenic detrusor overactivity. Detailed treatment and diagnostic issues specific to these conditions are beyond the scope of this chapter.

This chapter will serve to review the evaluation of OAB and the algorithm of treatment options for nonneurogenic overactive bladder and the current supporting literature.

Evaluation

The evaluation of patients with overactive bladder includes a thorough medical, surgical, gynecological, medication, and past therapy history.

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Detailing symptoms of voiding frequency, urgency and urinary leakage and importantly the level of bother to the patient are the key to diagnosis and ultimately the management.

The physical examination should include a pelvic examination with emphasis on pelvic masses, significant prolapse, and/or assessment for urinary retention (post void residuals >200 cc). Urinalysis and culture should also be evaluated to rule out an infection as this can mimic or exacerbate symptoms. Voiding diaries, typically for 72 hrs, are another useful tool to assess excess fluid intake, exacerbating factors, voiding and leakage patterns. Urodynamics and cystoscopy should not be included in the initial evaluation of uncomplicated patients, but can be considered in complicated or refractory cases [5].

Treatment

Based on extensive review of the literature, the American Urological Association (AUA)[1] published guidelines for a treatment algorithm in 2012 consisting of the following therapy recommendations [5]:

1. *First-line*: Behavioral therapy (fluid management, bladder retraining, pelvic floor therapy) with a potential for combination with antimuscarinics.
2. *Second-line*: Antimuscarinic medication (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, trospium, or transdermal preparations). No specific preference between these medications with the exception that extended release medication should be used preferentially if possible.
3. *Third-line*: Sacral neuromodulation, peripheral/percutaneous tibial nerve stimulation, intravesical botulinum toxin.
4. *Additional*: Rare cases for indwelling catheters, diversion, or augmentation cystoplasty.

[1] This AUA review does not address the role of β3-agonists.

Behavioral Modification

Bladder retraining (progressive delay in frequency to an interval of approximately every 2–3 hrs) and fluid management (moderation/avoidance of alcohol, caffeine, and normalization to approximately 1.5–2 l daily) are commonly cited as starting recommendations for patients and important points of discussion. Also, for those who have the primary complaint of nocturia, assessing voided night time volumes and amount of fluid intake after 6 pm may be useful parameters to help guide therapy. For example, if a patient complains of getting up three to four times a night, but each time they void, they are going 300–400 ml, it would indicate someone with nocturnal polyuria that would be addressed in a very different way than if it were drinking a large amount of fluid before bed and/or voiding only small amounts each time.

Pelvic floor physical therapy or muscle training (PFMT) is another commonly employed, low-risk tool. Data on efficacy is somewhat mixed [6, 7]; however, a recent Cochrane review on the subject concluded "the differences in likelihood of cure or improvement after PFMT compared to control are sufficient to be of interest to women" [8]. There is some evidence, however, that the benefit for stress urinary incontinence (a commonly combined measure in these studies) may be greater than that for overactive bladder and urgency incontinence.

Weight loss is a behavioral modification that has received attention as a means to decrease incontinence. A small cohort study demonstrated that a modest 5 % weight reduction decreased incontinence episodes by 50 % [9]. More recently, in the PRIDE (Program to Reduce Incontinence by Diet and Exercise) study, 338 women who were overweight or obese with at least 10 leakage episodes/week were randomized to a 6-month intensive weight-loss program or to four general educational sessions [10]. The intervention group experienced 8 % vs. 1.6 % weight loss, and a 47 % vs. 28 % reduction ($p=0.01$) in incontinence (this included either stress or urgency leakage) when compared to controls. Of note, women

with urgency leakage, specifically, experienced reduction of leakage from 42 % vs. 26 % which trended toward, but did not reach significance ($p = 0.14$) [10].

Pharmacologic Therapy

Antimuscarinics

Historically, the mainstay of pharmacological treatment for urgency incontinence was antimuscarinic medications. Antimuscarinic medications target and block intravesical receptors that promote bladder contractions. Typical efficacy is modest with symptom reduction ranging between 40 and 60 %. Rates of achieving continence range from 5 to 59 % [11]. Additionally, due to common side effects of dry mouth, dry eyes, and constipation, only approximately 25 % of users continue the medication by 1 year [12].

When choosing an antimuscarinic, there is data to support the use of extended over immediate release formulations. The OBJECT trial (Overactive Bladder: Judging Effective Control and Treatment), a multicenter randomized and double-blind study, demonstrated that oxybutynin 10 mg ER was superior to tolterodine 2 mg IR [13] . Solifenacin, in 5 and 10 mg extended release doses, was also shown to be superior to 2 mg immediate release dosing of tolterodine [14].

Additional comparisons include the OPERA and STAR trials. The OPERA (Overactive bladder: Performance of Extended Release Agents) directly compared extended release oxybutynin and extended release tolterodine. Oxybutynin was superior in reduction of urinary frequency, but had higher rates of dry mouth (23 % vs. 17 %) [15] The STAR trial compared solifenacin 5 or 10 mg to extended release tolterodine 4 mg [16]. Findings from this study of 1,177 patients, randomized with an ability for increased dosage in the solifenacin group, demonstrated a significantly greater improvement in the solifenacin group with respect to the number of urgency episodes, urge incontinent episodes, all incontinent episodes, and increases in mean-voided volumes [16].

Table 6.1 Anticholinergic preparations

Drug name	Dosage range
Oxybutynin	2.5–5 mg IR daily thrice daily 5 or 10 or 15 mg ER daily
Tolterodine	4 mg ER daily
Solifenacin	5 or 10 mg daily
Trospium	20 mg nightly, increase to twice daily
Darifenacin	7.5 or 15 mg daily
Fesoterodine	4 or 8 mg daily
Oxybutynin transdermal	3.9 mg patch every 4 days
Oxybutynin gel	84 mg of 3 % gel daily 100 mg of 10 % gel daily

However, as some data provide evidence of modest benefit of one over another, clear superiority is lacking. The recent AUA guidelines do not preferentially distinguish between any of the anticholinergic medications [5]. (An outline of available preparations is listed in Table 6.1.)

When considering side effect profiles, oxybutynin (which has a higher affinity for the parotid gland receptors) has higher rates of dry mouth (up to 61 %), while darifenacin has higher rates of constipation (up to 17 %) [5]. Transdermal preparations of oxybutynin in a patch or gel formulation may decrease these side effects while maintaining efficacy [17, 18]. Of note is the oxybutynin transdermal system (Oxytrol patch (3.9 mg)) recently approved for and is now available over the counter in the United States. In a recent meta-analysis compiling data regarding "trade-offs" between efficacy and side effect profiles, authors concluded that 40 mg/day trospium, 100 mg/g per day Oxybutynin gel, and 4 mg/day fesoterodine were the most favorable formulations [19]. However, acceptance of clear superiority of one antimuscarinic is lacking, and the AUA guidelines do not endorse the favoring of one over another antimuscarinic.

While side effect profiles have been a limitation, overall safety profiles of anticholinergics are good. The main contraindication for antimuscarinics is untreated narrow-angle glaucoma. Caution should also be maintained in patients with poor gastric emptying, frailty, and/or cognitive impairment [5].

β3-Agonists

The first in its class, and the first new class of medications for the treatment of OAB in over 30 years, mirabegron, a β3-agonist, was FDA approved for overactive bladder in June 2012. In contrast to antimuscarinics, this class of drugs targets the β3 receptors in the bladder dome that promote detrusor relaxation. It represents an exciting alternative to the antimuscarinics that have had poor continuity rates of only 25–50 % at 1 year, secondary to side effects [12].

Four phase III trials with mirabegron have demonstrated efficacy and safety [12, 20–22]. These studies included comparisons to placebo in three of the four as well as to tolterodine in two of the four studies. Regarding efficacy among these studies, mirabegron was superior to placebo and similar to tolterodine. Regarding side effects, mirabegron was better tolerated with lower rates of dry mouth compared to tolterodine (2.3–2.8 % vs. 8.6 %) [20]. Specifically, among 1,329 patients randomized to mirabegron 50 mg, 100 mg, or placebo, decreases in incontinence episodes were −1.47 (±0.11), −1.63 (±0.12) and −1.13 (±0.11) respectively. Similarly, the decrease in voids between active and placebo arms was −1.66 (±0.13), −1.75 (±0.12), and −1.05 (±0.13). Both findings were statistically significant [12]. In another randomized, double-blind study, doses of 25 and 50 mg were compared to placebo. Among these 1,306 patients randomized, mean incontinence episodes and number of micturitions were both significantly reduced in the mirabegron groups. The 50 mg dose, but not the 25 mg, also significantly increased the mean-voided volume over placebo [22] (for additional details see Table 6.2).

The safety and tolerability profile of mirabegron has been excellent. Some small, but clinically insignificant increases in pulse rate (0.8–0.9 bpm) and blood pressure (1.5 mmHg SBP and 1.0 mmHg DBP) have been noted [22]. Still, rates of hypertension in another study in both 50 and 100 mg mirabegron dose group were actually lower than placebo [21] . No studies demonstrated significant increases in cardiac events [12, 20–22]. The main consideration for an alternate drug recommendation remains uncontrolled hypertension (blood pressures >180/110). Still, while blood pressure monitoring is indicated, again, the actual clinical impact has not typically been significant.

Intravesical Botox

Onabotulinum Toxin-A (BTX-A), a serotype of the neurotoxin produced by *Clostridium botulinum*, is increasingly utilized as a safe and effective treatment option for refractory overactive bladder. Proof of concept of BTX-A use in the lower urinary tract stems from neurogenic bladder literature and has expanded its use into non-neurogenic cases [23].

BTX-A blocks acetylcholine release at the presynaptic neuromuscular junctions, decreasing detrusor overactivity and incontinence. It is additionally believed to alter urothelial sensory afferent pathways and help alleviate hypersensitivity responses, an explanation as why BTX-A is also effective in decreasing urinary urgency and frequency and increasing bladder capacity [23, 24].

Efficacy and safety of BTX-A have been demonstrated in multiple studies [25–30]. Efficacy typically defined as >50 % reduction in symptoms ranges at 60–80 %, with continence seen in approximately 22 % [24, 28, 29]. Doses of 200 or 300 units are often used in neurogenic cases. However, the literature in nonneurogenic overactive bladder points to an optimal risk/benefit dose of 100 units [27]. Higher doses have been associated with higher rates of retention and need for catheterization, and in one study with 200 units used in 28 women, this rate was as high as 43 % [31].

A recent, larger randomized trial of 242 women directly compared antimuscarinic therapy with intravesical BTX-A in the ABC trial: Anticholinergic versus Botulinum Toxin-A Comparison Trial for the Treatment of Bothersome Urge Urinary Incontinence [26]. Refractory patients with idiopathic overactive bladder were randomized to antimuscarinic therapy plus a saline intravesical injection vs. 100

Table 6.2 Results from phase III clinical trials, mirabegron

Author/year	Comparison groups (*n*)	Study time	Decrease incontinence episodes/24 h	Decrease in voids/24 h	Increase mean voided volume (ml)	Adverse outcomes/additional
Nitti et al. (2013) [12]	Placebo vs. 50 mg vs. 100 mg mirabegron (*n*=1,329)	12 weeks	−1.47/−1.63 in 50 and 100 mg groups vs. −1.13 in placebo ($p<0.05$)	−1.66/−1.75 in 50 and 100 mg groups vs. −1.05 in placebo ($p<0.05$)	18.2/18.0 in 50 and 100 mg groups vs. 7.0 in placebo ($p<0.05$)	Well tolerated. 1–2 bpm elevation in HR in mirabegron group. No difference in cardiovascular events
Chapple et al. (2012) [20]	50 mg or 100 mg mirabegron vs. tolterodine 4 mg ER (*n*=2,444)	12 months	−1.01/−1.24 for 50 and 100 mg mirabegron and −1.26 for tolterodine (no formal statistical comparison)	−1.27/−1.41 for 50 and 100 mg mirabegron and −1.39 for tolterodine (no formal statistical comparison)	17.5/21.5 for 50 and 100 mg mirabegron and 18.1 for tolterodine (no formal statistical comparison)	Tolterodine group with more dry mouth. Rates of hypertension, headache and constipation similar among all. No increased cardiovascular adverse events
Khullar et al. (2013) [21]	Placebo vs. 50 mg or 100 mg mirabegron or tolterodine 4 mg ER (*n*=1,978)	12 weeks	−1.57/−1.46 for 50 and 100 mg mirabegron vs. −1.17 placebo ($p<0.05$) Tolterodine −1.27 vs. placebo (ns) *no direct comparisons between mirabegron and tolterodine	−1.93/−1.77 for 50 and 100 mg mirabegron vs. −1.37 placebo ($p<0.05$) vs. tolterodine −1.57 (ns) *no direct comparisons between mirabegron and tolterodine	Mean increase vs. placebo in 50 mg/100 mg mirabegron/tolterodine =11.9/13.2/12.6 ($p<0.05$)	Changes in systolic and diastolic BP <1.5 mmHg were similar across treatment groups. No significant increase in cardiovascular events
Herschorn et al. (2013) [22]	Placebo vs. 25 or 50 mg mirabegron (*n*=1,306)	12 weeks	−1.36/−1.38 in 25 and 50 mg mirabegron vs. −0.96 placebo ($p<0.05$)	−1.65/−1.60 in 25 and 50 mg mirabegron vs. −1.18 placebo ($p<0.05$)	12.8 in 25 mg (ns); 20.7 in 50 mg dose ($p<0.001$)	No increase in cardiovascular events. Increase in BP: 1.5 mmHg SBP and 1.0 mmHg DBP with 0.8–0.9 bpm. Increase in HR in mirabegron groups

units BTX-A plus a placebo pill. At 6 months, those receiving BTX-A were more likely to be continent: 27 % vs. 13 % ($p=0.003$), with otherwise similar decreases in the number of incontinence episodes daily (initially a baseline of 5 decreased by 3.4 and 3.3/day). Expectantly, urinary tract infection rates (33 %) and intermittent self-catheterization at 2 months (5 %) were both higher in the BTX-A group. However, symptom control at 6 months was also significantly higher in the BTX-A group [26].In a recent cost analysis, the cost comparison was similar between the two treatments over the first 6 months, however, after that time (assuming average efficacy of BTX-A being 9 months), the cost profile favors BTX-A [32].

With BTX-A use, important contraindications/considerations remain: current urinary tract infection, malignancy, obstruction, pregnancy, and neuromuscular junction disorders such as myasthenia gravis (auto-antibodies to acetylcholine receptors) and Lambert–Eaton Syndrome (failure of nerves to release acetylcholine).

Sacral Nerve Stimulation (InterStim Therapy)

InterStim is a form of sacral nerve neuromodulation that is currently FDA approved for: urgency/frequency, urgency incontinence, nonobstructive urinary retention and fecal incontinence. It consists of a lead wire with four electrodes that are positioned along the sacral nerve roots—most commonly S3. This is then attached to an implantable pulse generator (IPG) that is surgically placed in the upper buttocks and provides a nonpainful electrical stimulation. Procedurally, this involves a two-step process (either in office percutaneous nerve evaluation (PNE) or stage I in the operating room) where the patient is able to test the efficacy (reduction in symptoms >50 %) prior to final IPG placement. Proof of concept for InterStim was devised in animal models by Tanagho and Schmidt in the 1970s, and it has been FDA approved in the United States for bladder indications since 1997 [33].

Several advances have been introduced including: a tined lead that has decreased invasiveness of the procedure, and a smaller IPG battery that has improved comfort. Evidence regarding how the tined lead is placed has also resulted in procedural improvements. Use of the curved vs. straight stylet in a randomized crossover trial demonstrated a clear intraoperative superiority with the use of the curved stylet [34]. Furthermore, the safety profile of InterStim, in light of these advances, is excellent. Major complications and morbidity have been uncommon, and estimates of infection (previously up to 10 %) have been closer to 3 % and of chronic pain (previously up to 16 %) have been closer to 8 % in more recent studies [35–41].

Theories on how InterStim works include modulation of the somatic afferents in the pudendal nerves which could both aid inhibitory mechanisms or revive an ability to void by relieving abnormal guarding reflexes—both of which would normalize voiding function [42, 43]. Additionally, recent work has demonstrated that InterStim modulates learning center regions of the CNS [42]. Still, a precise understanding of how InterStim functions remains unclear.

The efficacy of sacral nerve neuromodulation is well supported in multiple clinical trials. The literature demonstrates success for urgency/frequency and urgency incontinence to range between 56 and 68 % (up to 80 %). Efficacy in patients with urinary retention is approximately 70 %, and in fecal incontinence approximately 85 % [35, 36, 44–47]. Success is being defined as 50 % or greater reduction in symptoms.

The recent InSite Trial compared InterStim directly to standard medical therapy (antimuscarinic medications) [48]. In 147 patients with an overactive bladder randomized to these modalities, those receiving InterStim had significantly higher-efficacy rates: 61 % vs. 42 % ($p<0.05$). Quality of life measures were also significantly improved with InterStim compared to medications. 86 % of InterStim subjects compared to 44 % of those undergoing standard medical therapy reported “improved” or “greatly improved” urinary symptoms ($p<0.001$) [48].

Peripheral/Percutaneous Tibial Nerve Stimulation (PTNS)

PTNS is another form of neuromodulation for the treatment of overactive bladder. Procedurally it involves a 34-gauge needle placed 5 cm above the medial malleolus in order to access the posterior tibial nerve and enables stimulation of L4 to S3 nerve roots. This stimulation occurs in an office setting for 30 min on a weekly basis for 12 weeks, with subsequent monthly treatments from then on.

The SUmiT (Study of Urgent PC vs. Sham Effectiveness in Treatment of Overactive Bladder Symptoms) [49] compared active to sham stimulators. Women were randomized ($n=220$) between the two groups and after 13 weeks, the PTNS group demonstrated 54.5 % (vs. 20.9 % in the sham) efficacy defined as "moderately or markedly" improved symptoms. Voiding diaries also demonstrated statistically significant reductions in all overactive bladder parameters [49]. This study additionally supported safety measures of this modality with only 6 of the 110 reporting adverse events which included bruising, tingling, bleeding at the needle site, or discomfort.

Sustainability of this response after the initial 12 weekly treatments with continued monthly sessions has been supported. When 33 PTNS successes were continually treated with monthly sessions for 1 year, efficacy was maintained [50]. When compared to antimuscarinic therapy, PTNS has also demonstrated superiority. Among 100 adults randomized to PTNS or tolterodine 4 mg daily, success was demonstrated in 79.5 % of PTNS vs. 54.8 % in tolterodine ($p=0.01$) [51]. Of note, however, there was no placebo or sham treatment, and no blinding in this study, which may have impacted results.

Conclusion

Overactive bladder represents a chronic, common condition that significantly impacts the quality of life, but multiple treatment options exist. While prudent to initiate conservative options before moving to more invasive therapies (as outlined in the AUA guidelines [5]), a knowledge base and employment of the breadth of these options are valuable. It is important to discuss realistic expectations with patients, as many therapies define success as symptom reduction rather than cure. Regular follow-up to assess and reassess their progress and satisfaction level is essential to ensure compliance. Often it is not through one but through a combination treatment plan that optimal results are achieved.

References

1. Milsom I, Coyne KS, Nicholson S, Kvasz M, Chen CI, Wein AJ. Global prevalence and economic burden of urgency urinary incontinence: a systematic review. Eur Urol. 2014;65:79–95.
2. Coyne KS, Sexton CC, Bell JA, et al. The prevalence of lower urinary tract symptoms (LUTS) and overactive bladder (OAB) by racial/ethnic group and age: results from OAB-POLL. Neurourol Urodyn. 2013;32:230–7.
3. Coyne KS, Payne C, Bhattacharyya SK, et al. The impact of urinary urgency and frequency on health-related quality of life in overactive bladder: results from a national community survey. Value Health. 2004;7:455–63.
4. Haylen BT, de Ridder 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.
5. Gormley EA, Lightner DJ, Burgio KL, et al. Diagnosis and treatment of overactive bladder (non-neurogenic) in adults: AUA/SUFU guideline. J Urol. 2012;188:2455–63.
6. Burgio KL, Goode PS, Richter HE, Markland AD, Johnson TM, Redden DT. Combined behavioral and individualized drug therapy versus individualized drug therapy alone for urge urinary incontinence in women. J Urol. 2010;184:598–603.
7. Kaya S, Akbayrak T, Beksac S. Comparison of different treatment protocols in the treatment of idiopathic detrusor overactivity: a randomized controlled trial. Clin Rehabil. 2011;25:327–38.
8. Dumoulin C, Hay-Smith J. Pelvic floor muscle training versus no treatment, or inactive control treatments, for urinary incontinence in women. Cochrane Database Syst Rev. 2014;5:CD005654.
9. Subak LL, Johnson C, Whitcomb E, Boban D, Saxton J, Brown JS. Does weight loss improve incontinence in moderately obese women? Int Urogynecol J Pelvic Floor Dysfunct. 2002;13:40–3.
10. Subak LL, Wing R, West DS, et al. Weight loss to treat urinary incontinence in overweight and obese women. N Engl J Med. 2009;360:481–90.

11. Shamliyan T, Wyman JF, Ramakrishnan R, Sainfort F, Kane RL. Benefits and harms of pharmacologic treatment for urinary incontinence in women: a systematic review. Ann Intern Med. 2012;156(861–74):W301–10.
12. Nitti VW, Auerbach S, Martin N, Calhoun A, Lee M, Herschorn S. Results of a randomized phase III trial of mirabegron in patients with overactive bladder. J Urol. 2013;189:1388–95.
13. Appell RA, Sand P, Dmochowski R, et al. Prospective randomized controlled trial of extended-release oxybutynin chloride and tolterodine tartrate in the treatment of overactive bladder: results of the OBJECT Study. Mayo Clin Proc. 2001;76:358–63.
14. Chapple CR, Rechberger T, Al-Shukri S, et al. Randomized, double-blind placebo- and tolterodine-controlled trial of the once-daily antimuscarinic agent solifenacin in patients with symptomatic overactive bladder. BJU Int. 2004;93:303–10.
15. Diokno AC, Appell RA, Sand PK, et al. Prospective, randomized, double-blind study of the efficacy and tolerability of the extended-release formulations of oxybutynin and tolterodine for overactive bladder: results of the OPERA trial. Mayo Clin Proc. 2003;78:687–95.
16. Chapple CR, Martinez-Garcia R, Selvaggi L, et al. A comparison of the efficacy and tolerability of solifenacin succinate and extended release tolterodine at treating overactive bladder syndrome: results of the STAR trial. Eur Urol. 2005;48:464–70.
17. Dmochowski RR, Sand PK, Zinner NR, Gittelman MC, Davila GW, Sanders SW. Comparative efficacy and safety of transdermal oxybutynin and oral tolterodine versus placebo in previously treated patients with urge and mixed urinary incontinence. Urology. 2003;62:237–42.
18. Goldfischer ER, Sand PK, Thomas H, Peters-Gee J. Efficacy and safety of oxybutynin topical gel 3 % in patients with urgency and/or mixed urinary incontinence: a randomized, double-blind, placebo-controlled study. Neurourol Urodyn. 2014. doi: 10.1002/nau.22504.
19. Buser N, Ivic S, Kessler TM, Kessels AG, Bachmann LM. Efficacy and adverse events of antimuscarinics for treating overactive bladder: network meta-analyses. Eur Urol. 2012;62:1040–60.
20. Chapple CR, Kaplan SA, Mitcheson D, et al. Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a beta(3)-adrenoceptor agonist, in overactive bladder. Eur Urol. 2013;63:296–305.
21. Khullar V, Amarenco G, Angulo JC, et al. Efficacy and tolerability of mirabegron, a beta(3)-adrenoceptor agonist, in patients with overactive bladder: results from a randomized European-Australian phase 3 trial. Eur Urol. 2013;63:283–95.
22. Herschorn S, Barkin J, Castro-Diaz D, et al. A phase III randomized, double-blind, parallel-group, placebo-controlled, multicentre study to assess the efficacy and safety of the beta(3) adrenoceptor agonist, mirabegron, in patients with symptoms of overactive bladder. Urology. 2013;82:313–20.
23. Schurch B, Stohrer M, Kramer G, Schmid DM, Gaul G, Hauri D. Botulinum-A toxin for treating detrusor hyperreflexia in spinal cord injured patients: a new alternative to anticholinergic drugs? Preliminary results. J Urol. 2000;164:692–7.
24. Schmid DM, Sauermann P, Werner M, et al. Experience with 100 cases treated with botulinum-A toxin injections in the detrusor muscle for idiopathic overactive bladder syndrome refractory to anticholinergics. J Urol. 2006;176:177–85.
25. Sahai A, Khan MS, Dasgupta P. Efficacy of botulinum toxin-A for treating idiopathic detrusor overactivity: results from a single center randomized double-blind placebo controlled trial. J Urol. 2007;177:2231–6.
26. Visco AG, Brubaker L, Richter HE, et al. Anticholinergic versus botulinum toxin A comparison trial for the treatment of bothersome urge urinary incontinence: ABC trial. Contemp Clin Trials. 2012;33:184–96.
27. Dmochowski R, Chapple C, Nitti VW, et al. Efficacy and safety of onabotulinum toxin A for idiopathic overactive bladder: a double-blind placebo controlled randomized dose ranging trial. J Urol. 2010;184:2416–22.
28. Nitti VW, Dmochowski R, Herschorn S, et al. Onabotulinum toxin A for the treatment of patients with overactive bladder and urinary incontinence: results of a phase 3, randomized, placebo controlled trial. J Urol. 2013;189:2186–93.
29. Chapple C, Sievert KD, MacDiarmid S, et al. Onabotulinum toxin A 100 U significantly improves all idiopathic overactive bladder symptoms and quality of life in patients with overactive bladder and urinary incontinence: a randomized, double-blind, placebo-controlled trial. Eur Urol. 2013;64:249–56.
30. Flynn MK, Amundsen CL, Perevich M, Liu F, Webster GD. Outcome of a randomized, double-blind, placebo controlled trial of botulinum A toxin for refractory overactive bladder. J Urol. 2009;181:2608–15.
31. Brubaker L, Richter HE, Visco A, et al. Refractory idiopathic urge urinary incontinence and botulinum A injection. J Urol. 2008;180:217–22.
32. Zyczynski H for the PFDN. Comparison of cost-effectiveness of onabotulinum toxin A and anticholinergic medications for the treatment of urgency urinary incontinence. Female Pelvic Med Reconstr Surg. 2013;19(5 Suppl):S45–S190.
33. Tanagho EA, Schmidt RA. Bladder pacemaker: scientific basis and clinical future. Urology. 1982;20:614–9.
34. Jacobs SA, Lane FL, Osann KE, Noblett KL. Randomized prospective crossover study of interstim lead wire placement with curved versus straight stylet. Neurourol Urodyn. 2014;33(5):488–92.
35. van Kerrebroeck PE, van Voskuilen AC, Heesakkers JP, et al. Results of sacral neuromodulation therapy for urinary voiding dysfunction: outcomes of a prospective, worldwide clinical study. J Urol. 2007;178:2029–34.

36. Siddiqui NY, Wu JM, Amundsen CL. Efficacy and adverse events of sacral nerve stimulation for overactive bladder: a systematic review. Neurourol Urodyn. 2010;29 Suppl 1:S18–23.
37. White WM, Mobley 3rd JD, Doggweiler R, Dobmeyer-Dittrich C, Klein FA. Incidence and predictors of complications with sacral neuromodulation. Urology. 2009;73:731–5.
38. Wexner SD, Hull T, Edden Y, et al. Infection rates in a large investigational trial of sacral nerve stimulation for fecal incontinence. J Gastrointest Surg. 2010;14: 1081–9.
39. Spinelli M, Sievert KD. Latest technologic and surgical developments in using InterStim Therapy for sacral neuromodulation: impact on treatment success and safety. Eur Urol. 2008;54:1287–96.
40. Blandon RE, Gebhart JB, Lightner DJ, Klingele CJ. Re-operation rates after permanent sacral nerve stimulation for refractory voiding dysfunction in women. BJU Int. 2008;101:1119–23.
41. Washington BB, Hines BJ. Implant infection after two-stage sacral nerve stimulator placement. Int Urogynecol J Pelvic Floor Dysfunct. 2007;18: 1477–80.
42. Amend B, Matzel KE, Abrams P, de Groat WC, Sievert KD. How does neuromodulation work? Neurourol Urodyn. 2011;30:762–5.
43. de Groat WC, Kawatani M. Reorganization of sympathetic preganglionic connections in cat bladder ganglia following parasympathetic denervation. J Physiol. 1989;409:431–49.
44. Siegel SW, Catanzaro F, Dijkema HE, et al. Long-term results of a multicenter study on sacral nerve stimulation for treatment of urinary urge incontinence, urgency-frequency, and retention. Urology. 2000;56: 87–91.
45. Hassouna MM, Siegel SW, Nyeholt AA, et al. Sacral neuromodulation in the treatment of urgency-frequency symptoms: a multicenter study on efficacy and safety. J Urol. 2000;163:1849–54.
46. Mellgren A, Wexner SD, Coller JA, et al. Long-term efficacy and safety of sacral nerve stimulation for fecal incontinence. Dis Colon Rectum. 2011;54: 1065–75.
47. Hull T, Giese C, Wexner SD, et al. Long-term durability of sacral nerve stimulation therapy for chronic fecal incontinence. Dis Colon Rectum. 2013;56: 234–45.
48. Siegel S, Noblett K, Mangel J, et al. Results of a prospective, randomized, multicenter study evaluating sacral neuromodulation with InterStim therapy compared to standard medical therapy at 6-months in subjects with mild symptoms of overactive bladder. Neurourol Urodyn. 2014. doi: 10.1002/nau.22544
49. Peters KM, Carrico DJ, Perez-Marrero RA, et al. Randomized trial of percutaneous tibial nerve stimulation versus Sham efficacy in the treatment of overactive bladder syndrome: results from the SUmiT trial. J Urol. 2010;183:1438–43.
50. 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;183:234–40.
51. 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;182:1055–61.