

New technologies in the management of overactive bladder: current research and future prospects

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Abstract: Overactive bladder is characterized by frequency, urgency (wet or dry) and nocturia. These troublesome symptoms incur both a physiologic and economic cost, expected to be in excess of US\$82 billion in the USA and Europe by the year 2020. Second-tier medicinal oral therapies for overactive bladder abound, but the failure rate or discontinuation at 1 year exceeds 50%. Tertiary-tier therapies involve surgical alternatives including neuromodulation of sacral nerve 3 (S₃) or the posterior tibial nerve as a means to manipulate and ameliorate the above-described voiding symptoms. Sacral neuromodulation has been studied for more than 20 years, but newer, smaller, rechargeable implantable devices are in the forefront of current investigation. Hopes are that modifications to the device will eventually be possible at the patient's home, rather than the physician's office, with close urological/gynecologic supervision and guidance. Another means of surgical intervention for overactive bladder includes the use of a cystoscopy-guided radiofrequency probe by which energy disrupts the bladder floor neural voiding plexi. Stem cell therapy is also being evaluated for overactive bladder but is in the early stages of development.

Keywords: singular & combined specific M2/M3 anticholinergic/beta-agonist therapy, Botox-A, sacral neuromodulation, pudendal neuromodulation and posterior tibial stimulation

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Introduction

Economics and outline of tiered therapy

The troublesome overactive bladder (OAB) symptoms of frequency, urgency, and nocturia produce a plethora of healthcare concerns and a total projected cost of US\$82.6 billion in 2020.¹ The condition is estimated to involve more than 50 million Americans and Europeans (i.e. 15% of the combined population).¹ For research and clinical management purposes, the composite structure of therapy is a three-tiered approach. The first tier involves bladder training, with or without pelvic floor biofeedback, usually with 2–3 sessions weekly for 6 weeks. The second tier includes medicinal therapy, with a daily oral dose of an anticholinergic or one of the new beta agonists. Side effects often lead to discontinuation, however (>50% by 1 year). Finally, the third tier involves surgical options, namely sacral neuromodulation, intravesical Botox A, and tibial nerve neuromodulation.

On the horizon: medication for the management of OAB

B₃ agonist-mirabegron, vibegron, and combined oral therapy

Second-tier medicinal approaches to OAB management have long included anticholinergics. On the whole, anticholinergics are riddled with concerns, but most troubling is that, while more than 60% of these medications are utilized in the elderly, increasing evidence suggests that their use may lead to a reduction in cognitive function and potential dementia.² A meta-analysis³ and a longitudinal study⁴ corroborated a significant decline in cognitive function, with increasing anticholinergic primary or secondary effect. The latter study found an associated 0.33-point decline in the mini mental state examination and an increased risk of mortality after 2 years.⁴ Both studies may discourage prescribers from utilizing anticholinergics in the elderly and those with dementia.^{3,4} A 10-year

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total standardized daily dose response study also confirmed an increased risk of dementia and Alzheimer's with the highest anticholinergic dose.⁵ In the elderly, we must be cognizant of polypharmacy and the potential for medications with secondary anticholinergic effects to exacerbate the patient's cognitive function.⁶ The new family of OAB medications, β_3 -agonists, are now reshaping treatment alternatives. The first of this genre of medications is mirabegron, in either a 25 mg or 50 mg daily dose. Its primary improvement was curtailing the side effect of dry mouth, which encouraged increased fluid intake, exacerbating OAB symptoms. The 50 mg mirabegron rate of dry mouth was 2.3%, compared with 8.6% for 4 mg of the anticholinergic tolterodine ER. Similarly, elevation in systolic blood pressure was lower (0.4 mmHg) for mirabegron compared with tolterodine ER (0.5 mmHg) in a 12-month randomized controlled study.⁷ Mirabegron demonstrated equal efficacy in alleviating OAB symptoms compared with tolterodine ER (4 mg in particular) but with a significant improvement in nocturia.⁸ The newest potential β_3 -agonist completing phase III clinical trials is vibegron.⁹ A 2018 randomized study of 1232 patients assigned to a 12-week treatment group with vibegron (β_3 -agonist), imidafenacin (anticholinergic), or placebo demonstrated a safety profile with vibegron (50 mg or 100 mg) of 7.6% and 5.4%, which is similar to that of placebo at 5.1%. Efficacy was demonstrated with both vibegron 50 mg and 100 mg doses, with a $-2.08/\text{day}$ and $-0.03/\text{day}$ reduction in frequency episodes, compared with placebo at $-1.21/\text{day}$ and imidafenacin at $-2.06/\text{day}$. Urgency was similarly improved, with both vibegron doses at $-2.28/\text{day}$ and $-2.44/\text{day}$ while placebo was $-1.77/\text{day}$, and imidafenacin was $-2.15/\text{day}$. Nocturia and volume voided improved more significantly with vibegron at 33.55/29.96 ml voided volume *versus* imidafenacin at 20.80 ml, and placebo at 7.8 ml. Quality of life and patient global impression of improvement measures rose markedly with both vibegron doses and imidafenacin. The overall drug treatment emergent adverse events (TEAEs) were similar for all three categories, at 7.6%, 5.4%, 5.1% and 10.3%. Substantial mean changes in post-void residuals were not observed with this class 1 study. Additional comparative studies of vibegron are expected prior to the drug's introduction to market in 2019/2020 and will likely bring more substantive analysis for the interested clinician.

Benefits of combined oral therapies

Combination oral therapy may be a functional alternative when monotherapy produces unwanted side effects such as dry mouth and constipation, or less efficacy. Some combinations can work synergistically because they target different bladder receptor types (i.e. antimuscarinic and B_3 agonists¹⁰), or one medication can reduce the side effects of the primary medication (muscarinic antagonist and agonist).¹¹ Another receptor difference has been explored with an antimuscarinic and neurolytic/seizure medication.¹² The United States (US) Food and Drug Administration recently approved the concomitant use of mirabegron with the anticholinergic solifenacin. A 2017 randomized, prospective study evaluated the effectiveness of the combination of medications *versus* each utilized independently *versus* a placebo. This was the largest-scale study for overactive bladder medications conducted to date.¹⁰ The combination of solifenacin 5 mg and mirabegron 25 mg or 50 mg provided significant improvement in voiding symptoms when compared with monotherapy and placebo. Both medications work synergistically by modulating two separate β_3 -agonist and cholinergic receptors. Clinically significant improvements with combined therapy were noticeable by week 4, and the combined effect reduced frequency, urgency and nocturia by an additional 12%. TEAEs, such as dry mouth, constipation, and dyspepsia, were also lower with the singular combined therapy *versus* the two monotherapy cohorts.¹⁰ Another innovative therapy is THVD-201 (Tolenix-TheraVida, Durham, NC, USA) which combines the anticholinergic tolterodine and the synergistic muscarinic agonist pilocarpine, a salivary stimulant, the latter to moderate tolterodine's antimuscarinic side effects of xerostomia, or dry mouth. The phase II study demonstrates a statistically significant improvement of saliva production (and thus, decreased dry mouth) and reduction of overactive bladder symptoms, with twice daily dosing of tolterodine and pilocarpine (THVD-201).¹¹ THVD-202, the timed release, once-daily dosing of this combined therapy, is still under preliminary investigation. Tolterodine ER has also been recently paired with pregabalin,¹² an anticonvulsive medication which works by binding to calcium channels found on terminal nerve endings, reducing their efflux of a polyglut population of neurotransmitters. Marencak and colleagues¹² studied this drug combination in a 26-week, randomized, double-blind, placebo-controlled, three-period

crossover study, demonstrating statistically significant improvement in mean voided volume (MVV). The combination therapy improved MVV to 39.5 mls *versus* singular drug treatment at 27.4/15.5 mls and placebo at 11.9 mls ($p < 0.0001$). Discontinuation rates due to adverse events were 4, 2, 5, and 0% with combined therapy, pregabalin, tolterodine ER, and placebo. Pregabalin alone may improve symptoms in women with OAB.

New operative therapies for OAB

Onabotulinumtoxin A

When the performance or side effects from medicinal therapy are subtherapeutic or intolerable, onabotulinumtoxin A (BoNT-A) intravesical injection therapy has ascended into a leading role of alternative minimally invasive therapies. It works by binding to the intraneural synaptic vesical glycoprotein 2A, lysing its affiliated protein SNA25, thereby inhibiting the release of presynaptic acetylcholine. Secondly, purinergic receptor P2 × 3 and its related vanilloid receptor are downregulated, reducing symptomatic urgency. Unfortunately, the side effects of urinary retention or urinary tract infection remain problematic. Recently, the thought of delivering BoNT-A *via* liposome medium may reduce its penetrance through the urothelium, affecting more sensory nerves for frequency and urgency and potentially less detrusor contractility (hence, fewer urinary retention side effects). In 2002, Tyagi and associates developed the BoNT-A/liposome delivery system in an animal model. In 2014, Kuo and colleagues¹³ published results of a double-blind, randomized, parallel controlled pilot trial involving 24 overactive bladder patients at a tertiary medical center. Liposome-enhanced BoNT-A was instilled using a 60-minute noninjection intravesical technique. The control group had a normal saline instillation for the same duration. This new BoNT-A formulation and instillation technique demonstrated a statistically significant reduction in frequency, with a 3-day voiding diary of -6.5 voids ($p < 0.008$) and -12 urgency episodes ($p < 0.012$). However, only 50% of the BoNT-A group (12 patients) noted a therapeutic response at 1-month follow up, and only 28% at 3-month examination. There was no response to any of the urgency (wet) patients. All study non-responders were retreated after 1-month, but none realized any improvement. There were no episodes of urinary retention or urinary tract

infection. This is an innovative approach that may require additional study and refinement prior to mainstream utilization.

Sacral neuromodulation

Sacral neuromodulation is the most heavily studied, third-tier surgical therapy for OAB symptoms. Evidence-based analysis has demonstrated that it can have a high rate of adverse events, with many patients needing surgical revision. A recent study of the Interstim 2 device revealed that by 36 weeks of therapy, 11% of patients attained battery acquiescence and required its replacement.¹³ With duration of battery life a potential deterrent to sacral neuromodulation therapy, Axonics Modulation Technologies developed an alternative device in Europe in 2016. This rechargeable impulse generator (IPG) neurostimulator is 60% smaller than the Medtronic Interstim 2 device, and also utilizes a four-electrode tip lead for direct contact with the S₃ nerve.¹⁴ The new product's anticipated 15-year life span will reduce the need for battery replacement, thus reducing overall costs of OAB therapy. Another advantage of this device, compared with the Interstim 2, is the potential for whole body magnetic resonance imaging (MRI), while the Interstim 2 is only approved for head MRI with either a 1.5 or 3.0 T. Axonics Modulation Technologies is now seeking approval.¹³ A 3-month review of the device demonstrated that 31/34 patients (91%) achieved at least a 50% reduction in symptoms of OAB. 19.6% of patients did incur an adverse event, but no serious adverse events were reported. Overall, one patient required an explant secondary to an infection at the IPG site.¹⁵

Variations in existing surgical techniques can also substantially improve symptoms. Through an unknown method, sacral neuromodulation modulates neural activity of the sacral nerve number 3, ameliorating symptoms of overactive bladder and urinary retention. A 2018 retrospective observational study explored the tenet that electromyographic studies should be performed at the lowest amount of voltage, with the hope that closer proximity to the stimulated nerve will minimize and conserve energy source expenditure.¹⁶ Researchers theorized that stimulating the sacral nerve at 3 or less volts *versus* the traditional 6–8 volts would improve placement of the tined lead, improving objective voiding parameters including standardized questionnaires. The study included 284 women with OAB or urinary retention who were treated with sacral neuromodulation at ≤ 3

or ≥ 4 volts. Successful conversion of stage 1 to stage 2 showed statistically significant improvement for both ≤ 3 -volt groups (A: overactive bladder and C: urinary retention). Group A had a 93.5% (174/186) conversion rate *versus* Group B at 72.3% (110/152; $p < 0.001$). Group C had a 94% (34/36) conversion rate compared with Group D's 70% (21/30; $p < 0.017$). Success was defined as at least a 50% reduction in frequency, urgency, urgency incontinence, nocturia, and the Urogenital Distress Inventory (UDI-6) and Incontinence Impact Questionnaire (IIQ-7). The success rate for Group A was 82.1% (143/174) and for Group B was 63% (69/110), ($p < 0.001$). Mean battery life improved in both < 3 -volt cohorts ($p < 0.001$), adding a mean of 18 months to battery life. Annual reprogramming sessions were reduced in Group A and Group C to fewer than 1. These data represent a significant 20–40% improvement in most common voiding parameters, including frequency, urgency, and nocturia. This is a method that should be further investigated with randomized studies.¹⁶

Pudendal neuromodulation

Pudendal afferents are instrumental in inhibiting the voiding reflex.¹⁷ While sacral neurostimulation excites a select few pudendal nerve afferents, direct neurostimulation of the pudendal nerve itself may suppress this voiding reflex.¹⁶ Overall, three studies reviewed the application of direct pudendal neurostimulation with an implantable pulse generator.^{18–21} In a study of 15 patients, Spinelli and colleagues noted a decrease in urgency incontinence from a mean of 7 ± 3.3 to 2.6 ± 3.3 ($p < 0.02$) while cytometric capacity increased from 153.3 ± 49.9 mls to 331.4 ± 110.7 mls ($p < 0.01$). Additionally, maximum detrusor pressure decreased 66 ± 24.3 to 36.8 ± 35.9 cm H₂O. In a crossover trial of sacral *versus* pudendal neurostimulation in 30 patients with interstitial cystitis, Peters and associates¹⁷ found an overall reduction in voiding symptoms of 63% for pudendal stimulation (baseline to post-procedure), compared with 46% for sacral neurostimulation ($p < 0.02$). On a 7-point standardized patient improvement of symptoms scale from 'markedly worse' to 'markedly better', the pudendal approach was deemed more satisfactory for pelvic pain reduction ($p = 0.02$), frequency reduction ($p = 0.007$), urgency improvement ($p = 0.005$) and bowel function symptom relief ($p = 0.04$). Time of lead placement was not

significantly different for pudendal and sacral neurostimulation, with both under 30 min ($p = 0.57$). Possover²⁰ described similar results, but with lead placement approached intra-abdominally with laparoscopy. He reported frequency reduction from 25 \downarrow 10.18 daily voids, nocturia 5.82 \downarrow 2.18 nightly episodes, daily pad use reduction 7.3 \downarrow 1.6, while cystometric capacity increased from 159 \uparrow 312 ml. Mean follow up for this study was 18 months. We would be remiss if we failed to discuss the small rechargeable, implantable neurostimulator device called Bion (Advanced Bionics Corporation, Valencia, CA, USA). This was a 28×3.3 mm, 0.7 g neurostimulator placed with a delivery device directly into one side of either Alcock's canal for stimulatory interaction with the pudendal nerve. Groen²¹ found that, after failed medicinal therapy, 6 of 14 patients achieved statistical improvement in most voiding symptoms using the Bion, but the device was discontinued and never reached market in the USA. We speculate that the small device required frequent charging, impeding its adoption by the patient community. My personal experience with pudendal neuromodulation has found it to be a welcome addition for failed sacral neuromodulation patients, 26 of which have achieved a 78% success rate, with at least a 50% reduction in voiding symptoms with a 5-year follow up. This demonstrates a need for pudendal neuromodulation to be prospectively studied, with approval sought for its implementation for both tertiary and, potentially, secondary overactive bladder symptom failures.

Dorsal genital nerve stimulation

A variation of direct pudendal nerve stimulation through vaginal or posterior approach is neuro-modulation of the most anterior branch, the dorsal genital nerve (DGN).²² Its suspected mode of influence is through post-synaptic or presynaptic inhibition of bladder afferents.^{23,24} Somatic nerve inputs may adjudicate sympathetic outflow to the bladder which directly inhibits excitatory parasympathetic transmission to the bladder *via* vesical ganglia and detrusor smooth muscle.²⁵ Goldman and associates²⁶ reported their prospective multicenter experience involving 21 women with non-neurogenic urgency incontinence who underwent temporary, percutaneous prepubic clitorally-directed electrode placement to the dorsal genital nerve. The nerve was then stimulated by an external pulse generator. Results

demonstrated, without a sham control, that 76% of respondents had a 50% or more reduction in pad weight, while 47% were completely dry at the end of 1 week's stimulation. Their 89% reduction in incontinence episodes/day was much higher than the 30–46% reductions seen in similar studies using oral tolterodine (4 mg), solifenacin (10 mg) and trospium chloride (20 mg). Another small-scale DGN study, conducted by the van Breda group,²⁷ involved patient-controlled, on-demand stimulation of the nerve for non-neurogenic, mediated urgency incontinence. The implantation ranged from 10 to 40 min duration, but in 4/7 patients, the electrode dislodged and had to be replaced. A total of six of seven patients completed the study, with one discontinuing after 2 days, as constant stimulation (electrode migration) required electrode removal. Overall, two of six patients had complete resolution of their incontinence episodes, while four of six had an 80% reduction in heavy incontinence episodes. The authors did stress a need for improvement of the implantable lead hardware to prevent lead migration, as well as a more easily controlled stimulator. Both enhancements would make the device more appealing to physicians and their patients.

Posterior tibial neuromodulation

Another approach to the nerves of the bladder is through the posterior tibial nerve (PTN). Current practice involves 12 weekly, physician-led sessions in which a needle is placed near the medial malleolus to stimulate the PTN. After this introductory phase, an unspecified maintenance program of stimulation is employed, with patients' improvements monitored using 3-day voiding diaries.²⁸ An office-placed lead is implanted under a local anesthetic to stimulate the PTN. The lead receives wirelessly-communicated energy and programs *via* an external pulse generator and a disposable electrode patch Bioness StimRouter PNS. There are no current evidence-based data regarding efficacy other than for patients with chronic pain;²⁸ however, there is active enrollment for a prospective, randomized study to assess its use in patients with OAB. The treatment protocol involves in-home stimulation from 3 to 7 days a week for at least 30 min for 6 consecutive months. Results have not yet been presented, but a randomized, 12-week 2019 study²⁹ has made the comparison with posterior tibial neuromodulation (*via* a TENS URO stim

2101454) *via* two approaches: (a) less invasive transcutaneous procedure, with an easy stick-on and quickly removable temporary lead; and (b) invasive percutaneous needle approach for overactive bladder symptoms. Both study groups had failed conservative pelvic floor exercise and medicinal therapy. The results demonstrated equivalent improvements for frequency, urgency (wet and dry) but overall improvements were modest. For example, daytime frequency with comparison between temporary and percutaneous showed a baseline of 8.9 ± 2.7 and 8.4 ± 1.9 improving to 7.6 ± 1.6 and 8.0 ± 2.1 : very modest improvements. All voiding parameters improved, but the patient population was not really a moderate or worse symptomatic group from the onset. To have this procedure performed for weekly, 30-minute sessions for 3 months for a reduction of 1.6 voiding episodes/24-hour and 0.8 reduction in urgency incontinence episodes would likely not interest most patients and clinical investigators. A trial in which frequency is above 12/day and urgency above two daily episodes would provide a clearer picture as to whether this mode of therapy has any clinically significant value.

BlueWind Medical Company (Israel) is developing a miniaturized PTN implant, the Renova iStim, which is battery-less and is powered by a wireless ankle belt stimulator. It is presented in two forms for either a straight surgical implantation or percutaneous injection method. In August 2018, the company published results of a study with a minimum 36-month follow up, noting that 75% of patients demonstrated at least a 50% reduction in overactive bladder symptoms. As importantly, they demonstrated a 50% reduction in urgency incontinence leaks and an 80% reduction in large leaks. No severe adverse events were reported throughout the study. This wireless, external programmable device, worn as an ankle bracelet, manages therapeutic parameters. The company recommends daily, self-administered, 30-minute therapeutic sessions. There is no available information regarding use of the device for urinary retention.

Radiofrequency device therapy

Radiofrequency waves are noted to cause controllable disruption of bladder nerve signaling, and this method may improve the symptoms of frequency, urgency and nocturia. General detrusor

contractions during the filling phase are initiated by multicentric bladder nerve pacemakers and conduct their activities through the body of the bladder muscle so contraction occurs. New Uro's transurethral bladder partitioning device is an office-based, disposable radiofrequency transurethral-placed catheter and is inflated once in the bladder. Once properly positioned, its programmable generator can apply radiofrequency energy, sectionally ablating the nerve conduction systems of the bladder wall. The hypothesis is that disruption of multiple sectional bladder pacemakers and their congruent nerve microcircuits may lead to OAB symptom improvement. Amphora Medical (amphoramedical.com/technology) has designed a cystoscopic radiofrequency device for the ablation of bladder nerve circuitry. The cystoscope will optimize both bladder visualization and concomitant application of programmable radiofrequency wave energy. It is currently undergoing concurrent phase I and II studies in the USA and Europe, but there are no available study data at the current time.

Treatment costs

Mirabegron

Mirabegron has been determined to be the preferred medication with regards to reduced adverse events and clinical efficacy. In fact, 45% of patients continue its utilization at 1 year.³⁰ Oxybutynin, on the other hand, has a 23.9% continued utilization rate at the 1-year interval.³⁰ Persistence of patient utilization is an important consideration for clinicians because it is a direct result of symptom improvement and drug tolerability. Cost is also an important factor, as many patients have a fixed income. Mirabegron is estimated to have a yearly drug-only cost of US\$3312 while the less tolerated oxybutynin is US\$636.³⁰

Botox A

Several studies evaluated the cost of onabotulinumtoxin A for neurogenic bladder conditions, finding a drug-only annual cost of US\$582.^{30,31} Shepherd and associates estimated that a representative successful onabotulinumtoxin A patient may require 1.12 annual therapy sessions to elicit therapeutic efficacy.³² This annual estimate does not consider the additional costs of cystoscopic administration of this medication or anesthesia.

PTN stimulation and sacral neuromodulation

Martinson³³ and others in 2013 wrote a detailed description of the costs to the patient for both PTN and sacral nerve stimulation. For PTN, the initial cost was US\$1999 but an additional US\$3815 was required for maintenance therapy. Each successive year would require approximately US\$2358 for maintenance therapy. For sacral nerve neuromodulation, initial testing costs US\$2094, with therapy adding US\$26,586 annually. An average of US\$616 is required for treatment each year thereafter. Martinson's cost analysis is comprehensive and a valuable resource for both physicians and patients. No peer-reviewed cost analysis exists for the remaining therapy options.

Conclusion

With debilitating symptoms of frequency, urgency (wet or dry), and nocturia, OAB afflicts tens of millions of American and European citizens, necessitating billions of US dollars/Euros in treatment costs. Medical therapy has been the primary means of symptom amelioration, but bothersome side effects remained until the introduction of β_3 -agonists. Refinements are being made in sacral neuromodulation surgical technique, improving symptoms 20–50% over traditional methods. New, disposable, portable means of home neuromodulation are also being developed that are showing promise in symptom improvement and ease of use. Radiofrequency energy for nerve circuitry disruption are in development, and we await results. Stem cell therapies have yet to be applied for overactive bladder symptoms, but are sure to be investigated as accessibility, applicability, and science improves. The future holds great promise for new and improved treatment methods for this pervasive, costly condition.

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Conflict of interest statement

The author declares that there is no conflict of interest.

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