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**Authors**

Farhan, Bilal  
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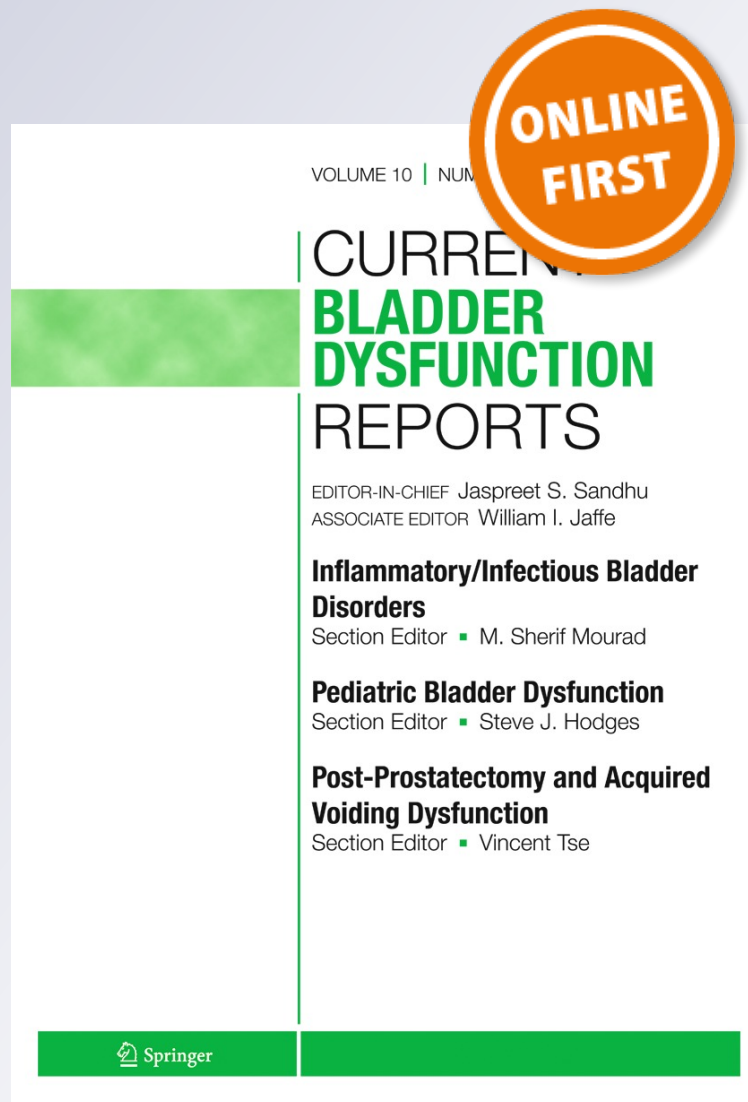
# *Clinical Pathways of Third-Line Treatment of Overactive Bladder in the Elderly*

**Bilal Farhan & Gamal Ghoniem**

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# Clinical Pathways of Third-Line Treatment of Overactive Bladder in the Elderly

Bilal Farhan<sup>1</sup> · Gamal Ghoniem<sup>1</sup>

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**Abstract** Overactive bladder (OAB) is a syndrome of urinary urgency, usually accompanied by frequency, nocturia, and sometimes urinary urgency incontinence. There are many guidelines for the OAB treatment which are constructed on a stepwise fashion starting from the least invasive to the more invasive therapy. The emergence of third-line therapy (AUA/SUFU guidelines) has resulted in significant decrease of more invasive surgery and improved patients' quality of life. The aim of a clinical pathway is to improve the quality of care, reduce risks, increase patient satisfaction, and increase the efficiency in the use of resources. The available options for the third-line OAB treatments include intravesical injection of botulinum toxin A, percutaneous tibial nerve stimulation (PTNS), and sacral nerve stimulation (SNS). The available evidence confirms that all three treatment approaches are well tolerated and effective, although only botulinum toxin type A (BoNTA) and SNS can achieve nearly a cure of urgency urinary incontinence (UUI). The choice among the different third-line treatment depends on patient preference, availability, and local expertise. The application of these pathways can improve incontinence care by letting physicians adequately communicate with patients and select individualized therapy at an early stage especially for elderly patients.

**Keywords** Overactive bladder · Clinical pathways · Third line treatment · Onabotulinum toxin A · Sacral neuromodulation · Percutaneous tibial nerve stimulation

## Introduction

Idiopathic overactive bladder (I-OAB) is defined by the International Continence Society (ICS) as symptom complex of “urinary urgency that is frequently accompanied by urinary frequency (voiding eight or more times in a 24-hour period) and nocturia (awakening two or more times at night to void), with or without urgency urinary incontinence (UUI), in the absence of a urinary tract infection or other obvious pathology” [1]. Symptoms may or may not be associated with detrusor overactivity (DO) [2–4]. Patients with neurologic disorders often experience voiding dysfunction. When this voiding dysfunction is consistent with OAB, it is termed neurogenic overactive bladder (N-OAB) [5]. OAB is a common chronic condition with its prevalence increases with age in both women and men, and it should not be considered as part of normal aging process [6–8].

OAB has a significant burden for patients and healthcare providers such as negative impact on the social, physical, psychological, financial, and sexual aspects of quality of life but generally do not affect survival [9].

In general, a clinical pathway is a structured method for the patient-care management of a well-defined group of patients during a well-defined period of time. A clinical pathway clearly states the goals and key elements of care based on evidence-based medicine (EBM) guidelines, best practice, and patient expectations. The aim of a clinical pathway is to improve the quality of care, reduce risks, increase patient satisfaction, and increase the efficiency in the use of resources. This includes facilitating the communication and coordinating roles and

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✉ Gamal Ghoniem  
gghoniem@uci.edu  
Bilal Farhan  
farhanb@uci.edu

<sup>1</sup> Department of Urology, University of California, Irvine, 333 City Blvd. West, Ste 2100, Orange, CA 92868, USA

sequencing the activities of the multidisciplinary care team, patients, and their relatives. It also requires documenting, monitoring, and evaluating variances and providing the necessary resources and outcomes.

This article may help to provide a practical clinical pathway regarding the third-line treatment for the elderly population who suffer from refractory lower urinary tract symptoms. The application of these pathways can improve incontinence care by letting physicians to adequately communicate with patients and select individualized therapy at early stage especially for elderly patients. This is a patient-centric approach that improves efficacy of treatment and quality of life and safety. Keeping patients informed of the plan of care and on schedule improves their compliance and potentially eliminates unnecessary testing and achieves cost savings. Also, by having a clear pathway communicated to the patient can gain early acceptance of third-line therapies and avoid the high drop-out noticed with medical therapy.

The treatment of OAB as recommended by the International Consultation on Incontinence (ICI) and AUA/SUFU [10•, 11] are as follows:

*First-line therapy:* First-line treatments include conservative measures such as adjustment of fluid habits, review of drug treatment, timed voiding, bladder retraining, and pelvic floor muscle therapy. Behavioral therapies and education should be offered first; starting antimuscarinic therapies at the same time as behavior therapies may prove clinically beneficial. This line should be offered to all patients.

*Second-line therapy:* Pharmacotherapy for minimum 3 months with either antimuscarinics (extended-release preparations should be used instead of immediate-release preparations when possible) or oral beta-3 adrenoceptor agonist (mirabegron) should be offered too. Despite the proven efficacy of pharmacotherapy treatment, it is difficult to predict the response in the individual patient, the adverse effects, and lack to adherence for long period, especially for elderly “frail” patients [12, 13], who should be use with caution as they have a lower therapeutic index and higher adverse effects (AE) such as dizziness, dry mouth, blurred vision, and constipation and the effects of multiple medications should be considered [10•]; the elder “frail” can be define as “elder person who have combining impaired physical activity, balance, muscle strength, cognition, and nutrition.”

*Third-line therapy:* Intradetrusor botulinum toxin type A (BoNTA) and neuromodulation therapies such as sacral neuromodulation (SNM) or percutaneous tibial nerve stimulation (PTNS) for carefully selected *patients* with severe refractory OAB symptoms or those who are not respond to or don not tolerate the second-line therapy and are willing to undergo a surgical procedure [10•].

The AUA/SUFU guidelines state that after attempting to treat OAB for 4 to 8 weeks with medications, taking the step towards third-line therapy is worthwhile and justified.

## Third-Line OAB Treatment

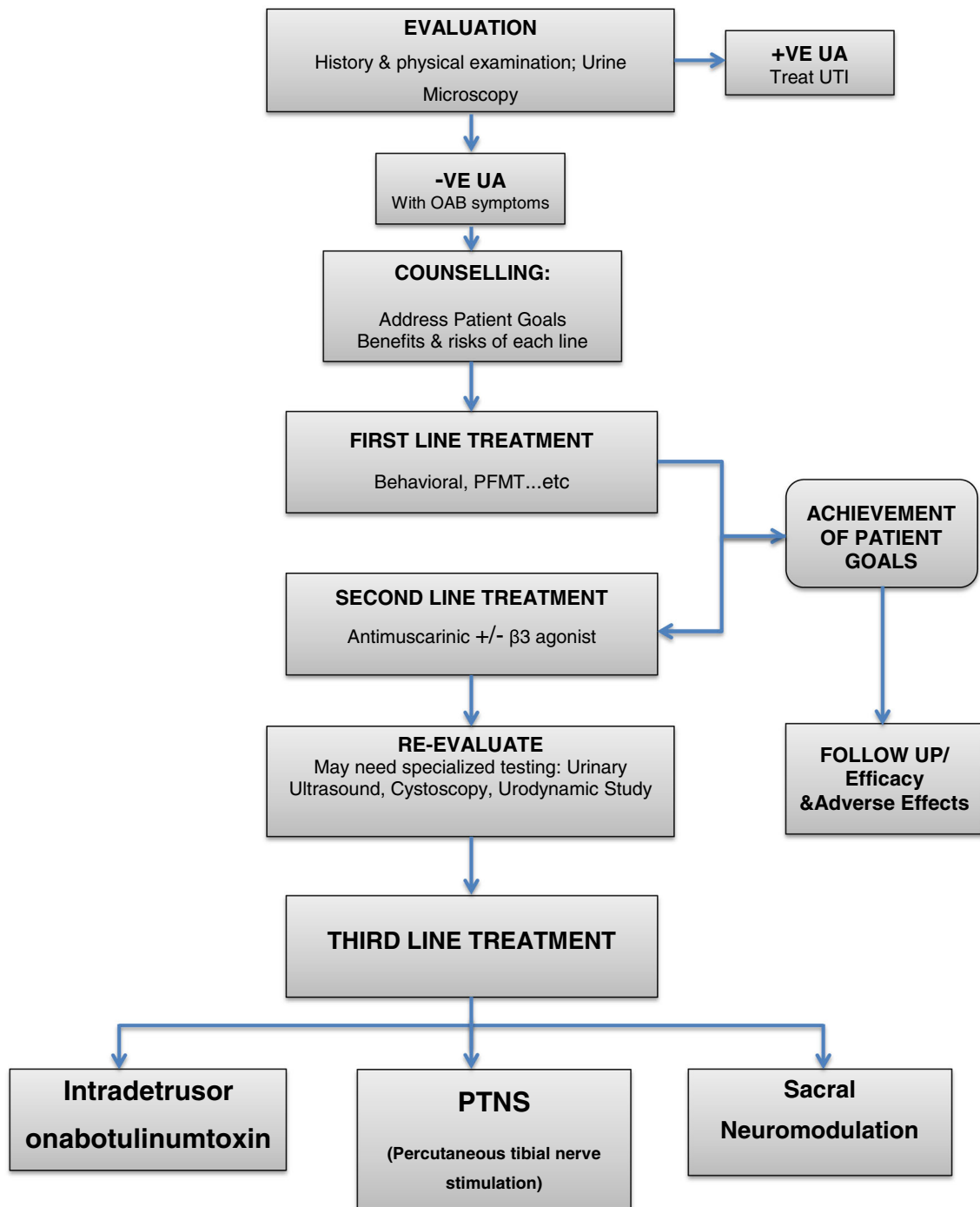
### General Principle

The importance of understanding patient expectations, goals, and satisfaction is increasingly recognized as an important element in the decision to treat OAB. For either I-OAB or neurogenic detrusor overactivity (N-OAB), eliciting patient perceptions and sharing the best available evidence with relevant options are important in achieving patient satisfaction [14•, 15]. Typically, when the patient goals are defined, outcomes should be correlated with relief of symptom(s), patient satisfaction, and goal achievement expectations as a result of treatment.

We believe that the approach treatment to the patient with OAB in the standard step-wise algorithm pathway is reasonable (Fig. 1), but in some occasions may subject patients to unnecessary cost and delay in treatment. The general principle for pharmacotherapy of the elderly patient is to start with a low dose and increase it slowly, depending on the agent's pharmacokinetics and pharmacodynamics and adverse effects.

Treatments of OAB at early stage may help to improve patient care and minimize overall use of healthcare resources. There is considerable evidence of delay in diagnosis, which may be related to embarrassment, belief that certain bladder symptoms as normal aging process, and assumption that will get little benefits with the treatment. In addition, failure to adhere to medical therapy due to lack of response or adverse effects of pharmacotherapy usually leads to frustration and abandoning of medications. The inadequate follow-up after treatment with poor communication between patients and physician has been identified as important factor to non-adherence [16]. It has been shown that 10 % of patients with OAB do not start the medication 12 months after prescription [17]. Motivation of the patient with regular follow-up visits to monitor treatment effects and adherence may be useful [18].

Patient satisfaction with treatment is directly related to improvement of symptoms and expectations, which need adequate follow-up after initial treatment (good motivation). Discussion of the patient's goals and expectation before starting treatment should be realistic and agreed upon by the patient and physician. Patients should be aware that OAB especially when severe is a chronic complex condition that can be improved, but is unlikely to be cured [19].



**Fig. 1** Algorithm clinical pathway for initial management of OAB treatment. It should take 4–8 weeks to reach third-line treatment

### Refractory OAB

Refractory OAB could be defined as persistent urgency, frequency, with or without incontinence that remains bothersome despite adequate behavioral and medical therapy for 8 to 12 weeks with at least one medication administered for 4 to 8 weeks [10, 11]. However, there is no current consensus on appropriate definition of such concept neither inclusion of failure secondary to intolerable side effects [20, 21].

The term “failed” or refractory OAB can be applied if the patient expectations and satisfaction are not achieved with second-line OAB treatment due to lack of efficacy or AE. Physicians should be aware that factors such as psychological well-being and emotional and sexual health outcomes affect patient perceptions of the value of treatment, perceived treatment efficacy, and treatment expectations [20, 22, 23].

The reasonable indications for the third-line OAB treatment are as follows: (a) failure of pharmacotherapy of OAB



due to lack of efficacy and loss of efficacy; (b) intolerable side effect; (c) contraindications to pharmacotherapy initiation; (d) inability to achieve patient's expectations by dose titration, switching medications to different anti-muscarinic or B3 agonist drug. The theoretical benefits of extended release antimuscarinic medications are not well established in elderly population as most of clinical trials had limited number of patients above 65 years of age and frail elderly [24, 25].

### Re-evaluation of Patients with Refractory OAB

Although OAB can be diagnosed by the patient symptoms, refractory OAB (R-OAB) patients require a basic assessment in order to exclude any other underlying causes for lower urinary tract dysfunction before the third-line OAB treatment which can be corrected. For example, bladder outlet obstruction (BOO) in men with BPH or women who have history of anti-incontinence surgery should be excluded since BOO is a known cause for OAB symptoms. Full detailed history and examinations including neurological and urogynecological examination should be performed. Clean catch urine should be sent for analysis and culture; significant post void residual urine should also excluded by ultrasound or catheterization. Patients who have high residual urine volumes have higher risk of retention following BoNTA injections. Simple diary for frequency/volume is useful to document and support the diagnosis of OAB and exclude other causes of urinary symptoms such as nocturnal polyuria.

Most R-OAB patients require functional and anatomical studies of the lower urinary tract. Urodynamic or better videourodynamic study is essential to make an accurate diagnosis specially to rule out neurogenic dysfunction prior to get on more invasive or perhaps irreversible therapy.

Cystourethroscopy could be helpful for many elderly patients with R-OAB especially those with hematuria and painful bladder syndrome to exclude any other causes for the LUTS such as a bladder tumor or calculus.

Treatment approach in the elderly depends on the patient's goals, social setting, and the mental status of the patient.

### Botulinum Toxin A (BoNTA)

BoNTA have been studied as intradetrusor injection for the treatment of detrusor overactivity since 2000 [26]. Although the mechanism of action of BoNTA in urinary bladder has already described in details [27], new information becomes available every year. It was approved by the US FDA for use in adults with overactive bladder in January 2013 and by European Union in 2011.

There are many publications that provide a good useful summary for the use and the effectiveness of BoNTA in the management of OAB and urgency incontinence [28, 29]. The level of evidence of effectiveness continues to build with time. Such

randomized, controlled studies have proven that BoNTA 100 U was well tolerated and produced significant clinical improvements in all OAB symptoms, patient-reported outcome, and quality of life (QoL) in patients inadequately managed by anticholinergics [30–32]. Other interesting evidence of randomized controlled trial on BoNTA vs placebo is in male patient with refractory OAB; although it did not reach significant statistical results, but it showed improvement of daily frequency [33].

Published reviews showed the evidence of BoNTA injection in the management of N-OAB due to multiple sclerosis and spinal cord injury. The efficacy of treatment reach 75–90 %, but training for clean intermittent self-catheterization is mandatory before starting treatment [3]. A systematic review of BoNTA for both N-OAB and I-OAB supported a level A recommendation for its use in these patients [34]. The efficacy of BoNTA that has been investigated using patient expectations and satisfactions was found to have high patient-reported outcome especially with repeated treatments [4].

According to the AUA guidelines for the available evidence on BoNTA in OAB, clinician may offer intradetrusor Bonita 100 U as third-line OAB treatment [10], while NICE guidelines recommend that 200 U should be used, unless the woman is concerned about retention and accepted lower success rate, in which case 100 U is acceptable [35]. We developed clinical pathway for intradetrusor BoNTA injection for OAB in general, helping the clinician and the patient as guidance and for motivations and to increase the success rate for treatment (Fig. 2). The cost-effectiveness has been studied between BoNTA with supportive care versus supportive care alone. It confirmed that BoNTA with supportive care is cost effective with 100 % probability [36].

### Counselling and Adverse Outcomes

It is important that patients should be counseled about the risks and benefits of BoNTA injections, which include urinary retention and urinary tract infections which usually due to incomplete voiding. Such retention is usually temporary which may require an indwelling catheter or the need to self-intermittent catheterization temporarily. Patients treated with BoNTA have approximately ninefold increased risk of a post-void residual complication, such as urinary retention [37]. In phase 3 study when a dose of 100 U is used, retention requiring catheterization was about 5 % [38]. A more helpful evidence to use in counselling is that at 1 month post-BoNTA injection, about one in four patients will have high residual urine [39]. The patient must be able and willing to return for frequent post voiding residual urine volume evaluation and to perform self-catheterization if necessary.

The patient should be aware that the effects of BoNTA injection have been shown to last approximately 6–9 months, so the patients may require repeat injections to continue their therapeutic benefits.

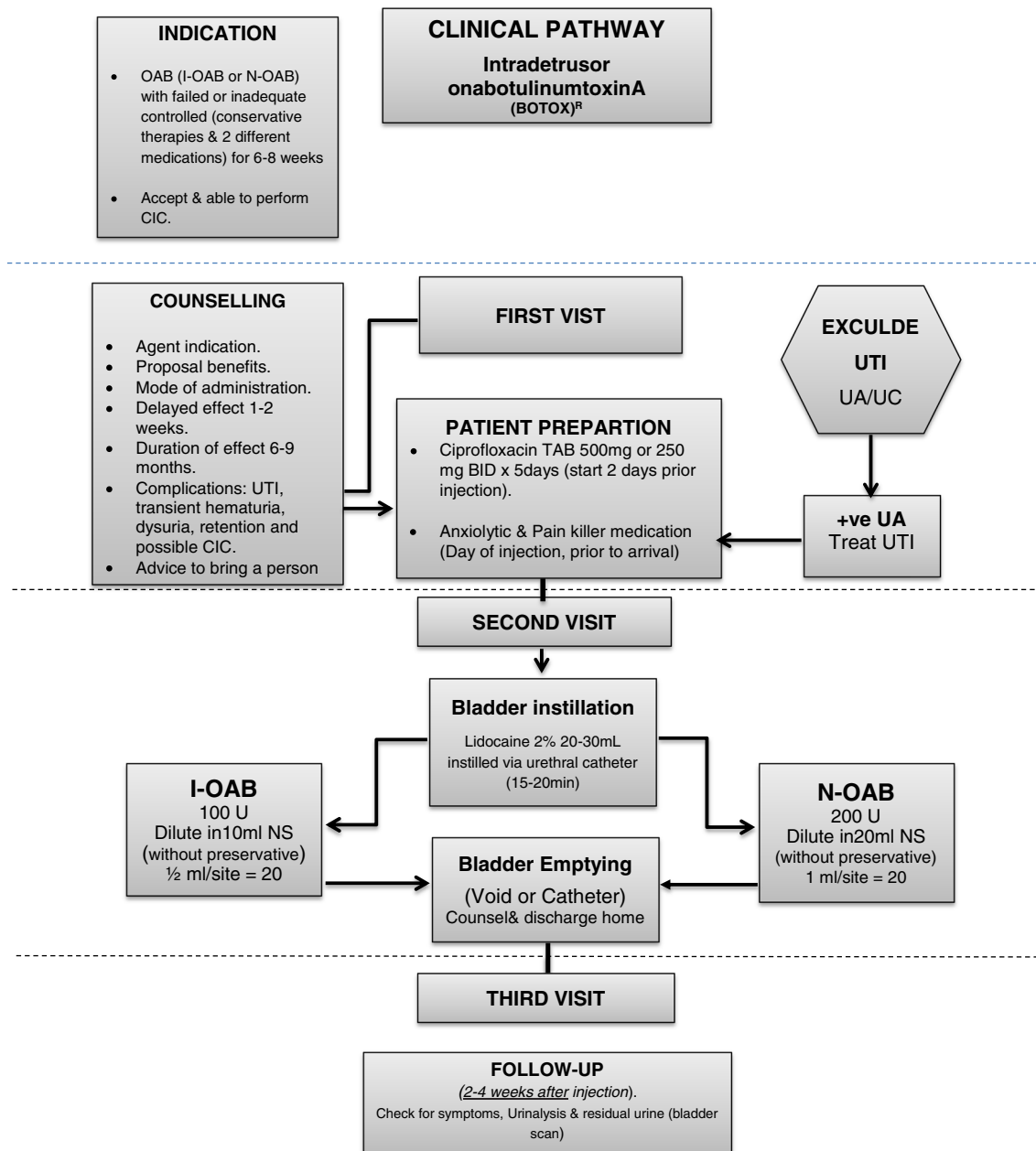


Fig. 2 Algorithm for Botox injection

BoNTA injection should not be performed in case of positive urinalysis and culture for urinary tract infection (UTI). In such case, the UTI should be treated and the injection postponed.

While the use of antibiotics is not indicated with cystoscopy in normal patients, it can be used in cases with voiding dysfunction. We use routinely prophylaxis antibiotics in the form of ciprofloxacin for 5 days, starting 2 days prior to BoNTA injection.

**Procedure Considerations**

BoNTA injection into the bladder wall was originally described by using a rigid cystoscopy and an endoscopic needle to inject 1 mL just beneath the detrusor mucosa at 20–30 sites

sparing the trigone [40]. Later, the technique was changed using a flexible cystoscopy [41].

We usually offer a minimally invasive technique which was performed by instillation of 20–40 mL of 2 % lidocaine into the bladder through a urethral catheter 15–20 min prior to cystoscopy [42, 43]. Oral mild anxiolytic agent and pain killer are taken 1 h prior to the procedure. Therefore, BoNTA injection can be performed in the office with either a rigid or flexible cystoscopy, depending on surgeon’s preference. For treatment of patients with refractory I-OAB, we inject intradetrusor at 20 sites, sparing the trigone, with 100 U of Botox<sup>®</sup> diluted in 10 mL normal saline solution without preservative at 0.5 mL/site.



## Post-Procedure Follow-up

The patient must be monitored until void urinations are normal. After the first injection, a patient must be seen 2 to 4 weeks following the injection, in order to evaluate the treatment's efficacy. This evaluation involved a urinary diary, post-void residual urine measurement, and urinalysis. A post-void residual greater than 200 mL and/or symptomatic must be counseled about the use of self-catheterization. A repeated injection can be indicated when the clinical benefit of the preceding injection wears off (typically after a period of 6 to 9 months). In all cases, a delay of 3 months must be respected between each injection [10••, 12].

## Neuromodulation

Neuromodulation techniques have been applied to the sacral nerve roots or their more distal branches like pudendal and posterior tibial. There are essentially two types of stimulation that can be used for neuromodulation.

The first is central/high frequency stimulation (sacral nerve stimulation) that uses electrodes which were inserted at the level of the third sacral nerve (S3), which is connected to the implantable pulse generator. The second one is peripheral/low frequency stimulation to activate inhibitory pathways in the spinal cord and inhibit detrusor contraction (percutaneous tibial nerve stimulation).

SNM is FDA-approved since 1997 for urinary frequency and urgency, and idiopathic non-obstructive urinary retention. Since then, the acceptance and use of SNM have been growing [44].

PTNS and SNM are other options as third-line treatment that may be offered to selected patient with refractory OAB [10••]. Both are neuromodulatory therapies presumed to improve or restore normal control of an imbalanced voiding reflex by affecting the central afferents [45].

## Sacral Neuromodulation

### *Patient Selection*

Patient selection has played an important role on the success rate of SNM. In one study, a success rate of 64 % at 2 years was demonstrated in patients with I-OAB, while all patients with N-OAB who responded initially relapsed within 2 months [46]. Although it is controversial, the role of SNM in patients with neurogenic bladder was also investigated and success rates were similar to those in patients with I-OAB [47, 48]. Poor results have been reported in elderly cognitively impaired patients and patients with spinal cord injuries [49]. Failure of pharmacotherapy does not appear to indicate a poor response to SNM [46].

Patients with refractory OAB and non-obstructive urinary retention are considered suitable for SNM once they have failed or could not tolerate more conservative treatments [50, 51]. Patients must be cognitively capable of optimizing their device settings and compliant with the long-term treatment protocols (Fig. 3).

However, there is still significant variability in use according to a standardized treatment algorithm for urinary dysfunction.

### *Procedure Considerations*

SNM requires a preliminary, percutaneous nerve evaluation (PNE), a screening stimulation test that is performed to assess the clinical effect and the integrity of sacral nerve.

Such test help the patient and physician to decide whether the benefits of permanent implantable pulse generator (IPG) implantation is worthy, evaluating the benefits, risks, and costs of the therapy.

There are two approaches for stimulation test, PNE or stage one out of two-staged implantation.

### *PNE*

The PNE test uses a temporary test lead placed into the S3 foramen and connected to an external pulse generator (EPG). The procedure is usually performed in an outpatient setting under local anesthesia and prone position. The procedure is done by stimulating the S3 sacral nerves bilaterally and the side prompting the desirable response and comfort for the patient is selected for the temporary lead insertion. The patient's electrode will be connected to an external pulse generator that gives the patient the ability to control the stimulation intensity. The patient is discharged home with 5–7-day voiding diary.

Based on the patient's subjective experience and the objective data obtained from the voiding diary, a final decision can be made to proceed or not with permanent implantation. If the patient had the desired response, he/she usually will undergo the permanent implantation of the tined lead and IPG, i.e., full implantation. On the other hand, if they do not respond to PNE and there is a question about wire migration, they may have an excellent outcome when they undergo two-staged implantation [52].

Complications such as migration of the temporary lead or failure of this test help to identify patients who will respond to permanent SNS leading to the development of a two-stage implant technique [53].

### *Two-Staged Procedure*

If the patient is not a candidate for test stimulation or did not respond to the outpatient PNE test, stimulation may be performed

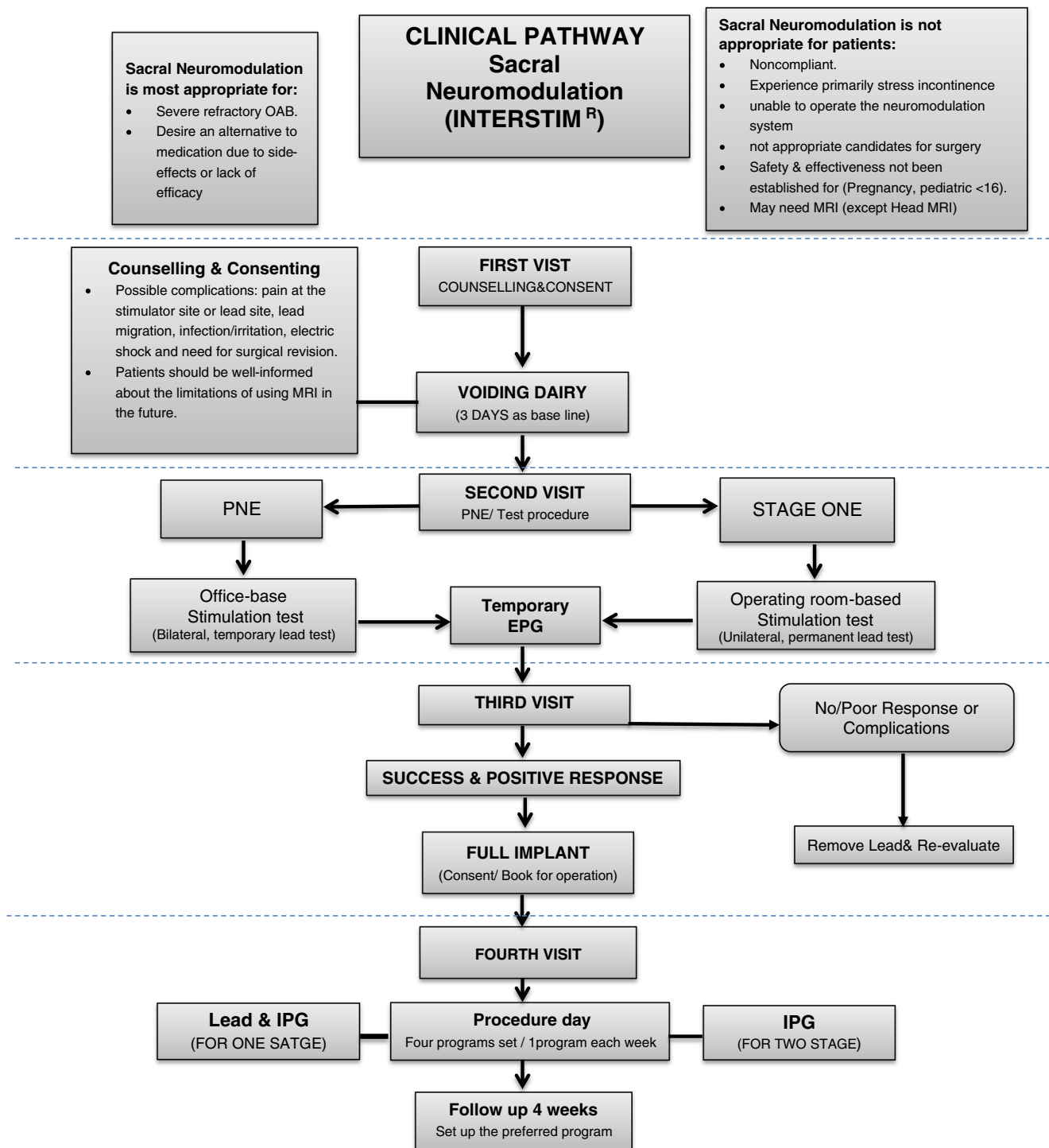


Fig. 3 Algorithm for SNM in OAB

in the operating room (OR) using the tined lead. In fact, the two-stage procedure decreases the technical-related test failure.

The advantage of this procedure is that the same responses should be obtained once the external generator is replaced by the permanent IPG as the lead site does not change. The permanent tined lead has self-anchoring tines that reduce the risk of migration.

This procedure extends the test periods of up to 2–4 weeks. If the patient has a good response during the test, the present lead is then connected to an IPG.

Due to the decreased risk of migration and the longer test duration, this test has a higher response rate [44, 47, 54].

The choice of PNE or first stage testing depends on patient's and physician's preference. Postoperatively, the IPG will be

turned on and programming the SNM with different settings. The patient is taught to set the unit at a comfortable setting at which the stimulation can be felt but it is not painful and advised to try different programs to control symptoms [55•].

### Percutaneous Tibial Nerve Stimulation

PTNS is a peripheral neuromodulation that may be offered by Stoller [56], to nearly any patient with OAB who has not achieved their treatment goal with medication, excluding those with a pacemaker and who are pregnant [10••]. The elderly, the frail, patients with non-neurogenic detrusor overactivity, those with milder symptoms or partial responders, and patients with medication adverse effects are all excellent candidates for PTNS.

PTNS is postulated to achieve detrusor inhibition by acute electrical stimulation of afferent somatic sacral nerve fibers. The rationale for this treatment modality is based on the presence of spinal inhibitory systems that are capable of interrupting a detrusor contraction. Inhibition can be achieved by electrical stimulation of the pelvic nerve afferent sensory fibers in the pudendal nerve and muscle afferents from the limbs [57, 58]. Most of these afferent somatic fibers reach the spinal cord via the sacral spinal nerves and dorsal roots of the sacral nerves.

AUA/SUFU guidelines recommend PTNS as a third-line therapy for highly motivated patients who are willing to comply with the frequent office visits required [10••]. PTNS may be better for those with less refractory, mild to moderate symptoms. PTNS treatment needs up to 3 months to determine success and, if so, 12 to 18 sessions and visits to the doctor's office annually to maintain benefit, each session lasts 30 min once weekly as common protocol that is used in clinical practice [59–61].

Several studies have been published evaluating the effects of PTNS on OAB [56, 62]. PTNS was found to be effective in reducing urinary frequency, incontinence episodes, and detrusor overactivity in 37–100 % of patients with OAB [63••].

Improvements are reported not only in OAB symptoms but also in urodynamic observations such as reduction of detrusor overactivity, increase of the cystometric capacity, and of the threshold of appearance of involuntary detrusor contractions [59].

There is a lot of data that support the efficacy and safety of PTNS which strongly and notably reflect what one sees in clinical practice [64]. Durability of effectiveness of PTNS has been demonstrated after 12 and 36 months of therapy with valuable long-term treatment option to sustain clinically significant OAB symptom control [60, 65].

### Conclusion

The evidence of the third-line OAB treatment continue to develop which make the guidelines and clinical pathways provide more solid base recommendations where optimal management can lead to improvement in the patient outcomes and QoL.

When it comes to third-line therapy, the patient should be in the center of decision making. Treatment success is usually based on patient expectations. Communicating with and explaining all appropriate options to the patient, based on differing efficacy and AE profile of the treatments available for OAB, as well as eliciting patient input, can enhance outcome.

Most published researches on the management of OAB have been focused on which treatment is more effective, but may be should look on what is the best treatment option available for each patient. Eventually, patients do not necessarily choose the more effective treatment, rather the best one that fit their needs, and this remains one of their fundamental rights.

### Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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