

# Can we create a valid treatment algorithm for patients with drug resistant overactive bladder (OAB) syndrome or detrusor overactivity (DO)? Results from a think tank (ICI-RS 2015)

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**AIMS:** To review and assess the definitions of drug resistance and the evidence supporting treatment for drug resistant overactive bladder/detrusor overactivity (OAB/DO).

**METHODS:** Evidence review of the extant literature and consensus of opinion was used to derive the summary recommendations.

**RESULTS:** Drug resistance or drug refractory status has been inconsistently defined and reported in current evident sources. Recent publications use some correlation of lack of efficacy and or experienced side effects to define drug resistance. Algorithms based upon these definitions largely relate to the appropriate use of neuro-modulation or botulinum neurotoxin, based upon patient selection and patient choice. Current treatment pathways are hampered by inability to consistently profile patients to optimize management, particularly after failure of initial pragmatic treatment.

**CONCLUSIONS:** Further research is recommended to better identify patient phenotype for purposes of directing optimized therapy for OAB/DO. Current treatment algorithms are influenced by extensive data generated from recent neuromodulation and botulinum neurotoxin trials.

## KEY WORDS

anticholinergics, antimuscarinics, augmentation cystoplasty, botulinum (neuro)toxin, detrusor myectomy, drug resistant, guidelines, management, neuromodulation, overactive bladder, percutaneous tibial nerve stimulation, refractory, treatment, urinary diversion

## 1 | INTRODUCTION

National and international guidelines as well as expert societies' recommendations deal with the line of available treatments for overactive bladder (OAB). EAU, AUA/SUFU, and NICE Guidelines as well as ICI recommendations propose that clinicians should offer behavioral therapies, such as bladder training, bladder control strategies, pelvic floor

muscle training, and fluid management as first line treatment to all patients with OAB.

There is, however, considerable variation with recommendations/guidelines regarding the use of oral pharmacotherapy, with antimuscarinics (AMs) currently being the mainstay of oral treatment for OAB (Table 1), which reflects the lack of adequate comparative head-to-head studies between AMs as well as of well-designed pharmaco-economic studies.<sup>1</sup> For example, the EAU Guidelines 2015 propose the use of either immediate release (IR) or extended release (ER) formulations as 1st

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**TABLE 1** Current guidelines on oral pharmacotherapy for OAB

	EAU-2015	AUA/SUFU-2014	NICE-2013
AMs	1. Either IR or ER preparations may be used initially	ER formulations should be preferred over IR, because of the lower rates of dry mouth	Oxy IR, tolterodine IR, or darifenacin should be used as 1st line drugs
	2. ER preparations should be used if initial trials of IR fail		All other preparations to be used as 2nd-line, the choice to be guided by local acquisition costs
	3. Consider using transdermal OXY if oral AMs cannot be tolerated due to dry mouth		
	4. Early review (of efficacy and side effects)		
Mirabegron	Use in patients with UUI Patients should be warned there is uncertainty about the long-term side effects	2nd-line treatment alternative to AMs Also, if a patient experiences inadequate symptom control and/or unacceptable AEs with one AM medication	3rd-line option in patients who have failed a trial of at least two AMs
Combination of AMs or AM + MIR	?	?	?

line drugs, while AUA/SUFU Guidelines (last updated 2014) favor the ER formulations over the IR ones and NICE Guidelines (last updated 2013) are largely cost-driven thus favoring mostly IR formulations. Similarly, there is no unanimity concerning the use of the new beta-3 agonist mirabegron, and no recommendations currently stand on combination pharmacotherapy.

## 2 | METHODS

At the International Consultation on Incontinence-Research Society (ICI-RS) in 2015, a panel of Functional Urologists and Urogynaecologists participated in a Think Tank (TT) discussing the development of a valid treatment algorithm for drug resistant OAB/DO. In the first part, the panelists presented and discussed extensively what is known and what is not known about defining drug resistance in patients with OAB/DO considering current Guidelines, published trials on treatment of “refractory” OAB and available data on the use of oral pharmacotherapy. In the second part, the panel discussed the literature data on approved treatments for drug resistant OAB and put forward proposals for further research and for a treatment algorithm. Both the algorithm and the manuscript were finalized following lengthy interactions after the end of the TT. The search terms overactive bladder, refractory, drug resistant, treatment, management, guidelines, antimuscarinics, anticholinergics, botulinum (neuro)toxin, neuromodulation, percutaneous tibial nerve stimulation, augmentation cystoplasty, urinary diversion, and detrusor myectomy were used for a literature search of both PubMed and Medicine, which served to set the basis for the discussion of the TT. However, the work of the TT does not represent a systematic review of the literature.

### 2.1 | Definition of drug resistant OAB: is there a consensus?

There is no widely accepted consensus on an appropriate definition for “refractory to pharmacotherapy” or “drug resistant” OAB. Furthermore, the management in this situation is inconsistently named; eg, second-line treatment, third line management, or step-up treatment. ICI guidelines state that after attempting to treat OAB for 3 months with an AM, taking the step toward “second-line” therapy is worthwhile and justified.<sup>2</sup>

AUA guidelines state that “third-line treatment” options, such as bladder botulinum toxin A (BTX-A) injections, posterior tibial nerve stimulation (PTNS), and sacral neuromodulation (SNM), may be offered in carefully-selected and thoroughly counselled patients who are “refractory” to first- and second-line OAB treatments.<sup>3</sup> However, the definition of refractory OAB has not been clearly stated, but implies non- or incomplete symptom responsiveness to a combination of behavioral and pharmacologic therapy. The possibility of medication intolerance due to side effect is also subsumed into this concept.

Regulatory authorities have also not been very specific when defining the concept of refractory OAB or even the failure of drug treatment. Indeed, the Food and Drug Administration (FDA) approved BTX-A injections for adults with OAB who “cannot use or do not adequately respond to a class of medications known as anticholinergics.”<sup>4</sup> The number of anticholinergics that patients have to fail and the minimum duration on oral treatment before being eligible for BTX-A injection is not clarified. Similarly, clinical and urodynamic criteria of inadequate response are missing.

Several studies evaluating the effects of SNM, BTX-A, and PTNS for patients with OAB have not reported the definition of first-line treatment failure.<sup>5-11</sup> On the other

hand, heterogeneous definitions for “refractory” OAB can be found in the literature, which include self-reported failures,<sup>12</sup> and inadequate response or intolerable side effects to one or more AM drugs during a variable or undefined time (usually 6 weeks to 12 months).<sup>13–20</sup>

### 2.1.1 | Antimuscarinic cycling

Numerous guidelines recommend switching from one AM to another if the first is not helpful, trialing two or three medications before escalating treatment.<sup>21</sup> However, a study with a mean follow up of 3.4 years suggests that patients with OAB continued to have bothersome symptoms and significant incontinence episodes (3.3–3.9 per day) despite cycling of 1–6 AMs. Discontinuation rates were high (71%) regardless of number of AMs previously used. The majority of patients (65%) only used one AM.<sup>21</sup>

Results are confirmed by prescription database studies. A systematic review<sup>22</sup> of 14 studies containing 190,279 unique patients reports median persistence rates 12.0–39.4% at 12 months, 8.0–15.0% at 18 months and 6.0–12.0% at 24 months. At 36 months, persistence rates ranged from 0.0% (darifenacin) to 16.0% (trospium). Poor efficacy, switch to a new medication, learning to get by without medication, and side effects have been some of the commonest reasons for discontinuation. In a large retrospective cohort study of 103,250 OAB patients in the United States,<sup>23</sup> the vast majority discontinued their medication as opposed to switching (5.8% only). One-third only filled one prescription, suggesting early failure within 30 days; 66.9% discontinued treatment within the first 6 months. After a treatment gap of at least 45 days, 34.6% re-initiated treatment with an AM. Of these patients 65.6% were with the same index AM.<sup>23</sup>

### 2.1.2 | Why do antimuscarinics fail?

It was discussed during the TT that chronic use maybe associated with lack of efficacy and that efficacy may dwindle over time (expert opinion). Examples were raised where efficacy had been maintained by introducing “rest periods” and re-challenging with AMs with some benefit in select cases. Long-term effects of this approach and/or of switching to alternate AMs or other agents such as beta-3 agonists are largely unknown.

Animal work has suggested that chronic administration of either oxybutynin or fesoterodine only led to an initial reduction in voids which normalized at 4 weeks.<sup>24</sup> The effect of an acute high dose of oxybutynin on the intermicturition interval in those exposed to chronic oxybutynin administration was abolished, suggesting some tolerance to AMs. In rats chronically exposed to AMs, expression of M3 receptors was reduced, as opposed to a trend for P2X1 increase. In addition, detrusor strip responses to carbachol were attenuated, by

contrast to enhanced ATP responses. Systemic administration of a purinergic blocker in rats chronically exposed to AMs led to significant increases in intermicturition intervals, implying a shift in transmission from muscarinic to purinergic.<sup>24</sup> What aspects are translational to humans are yet to be determined. It is unknown how long this potential alteration in neural transmission with chronic exposure to AMs would take to occur and whether there is sufficient plasticity when pharmacotherapy is stopped.

### 2.1.3 | Combination pharmacotherapy for OAB

Potential benefits of combining an AM with a beta-3 agonist have recently been assessed. In the Symphony trial, all combinations of various doses of mirabegron with solifenacin 5 or 10 mg significantly improved mean voided volume compared with solifenacin 5 mg monotherapy.<sup>25</sup> Three out of the six and five of six combinations, respectively, reduced micturition frequency and urgency episodes compared with solifenacin 5 mg. Incontinence episodes were reduced in all groups, including placebo. The lack of change compared to placebo in this regard was partly attributed to the low percentage of incontinent patients, significant baseline variation, and low severity. Apart from constipation there was no dose-related changes in adverse events when comparing combination to monotherapy arms of the trial.<sup>25</sup> Mirabegron 25 mg daily as “add on” therapy to solifenacin 2.5 mg or 5 mg<sup>26</sup> improved OABSS total score, OAB-q SF scores, number of micturitions/24 h, and number of urgency and urgency incontinence episodes/24 h for up to 16 weeks. In patients where mirabegron was increased to 50 mg, a further improvement was noted. Side effects were predominantly mild or moderate.<sup>26</sup> In an elderly population, combination of solifenacin 10 mg and mirabegron 50 mg daily was significantly better than monotherapy in reducing incontinence episodes.<sup>27</sup> Finally, patients who remained incontinent despite 4 weeks of solifenacin 5 mg treatment, were randomized to either solifenacin 5 mg, solifenacin 10 mg, or a combination of solifenacin 5 mg + mirabegron 50 mg in the BESIDE study.<sup>28</sup> In this study involving 2,174 patients, the combination group had significant improvements in incontinence episodes per 24 h (primary endpoint) as well as mean daily micturition episodes. Combination was non-inferior to solifenacin 10 mg for urinary incontinence episodes and superior with regards to mean daily micturitions. Combination therapy dry rate was 46% versus 37.9% for solifenacin 5 mg and 40.2% for solifenacin 10 mg. Dry mouth rates were similar in the combination and solifenacin 5 mg arms and lower than solifenacin 10 mg.<sup>28</sup>

## 2.2 | Current trends and considerations in the treatment of drug resistant OAB

When oral drug treatment of OAB fails, or when patients generally are dissatisfied with the adverse effects of oral

therapy, available options include: bladder BTX-A injections, Sacral NeuroModulation (SNM—InterstimII™), PTNS, and surgery (augmentation cystoplasty).<sup>29</sup>

**2.2.1 | Botox® versus Neuromodulation: unanswered questions in the rivalry for 2nd-line treatment of drug resistant OAB.**

Both OnabotulinumtoxinA (Botox®) and SNM have been approved for the treatment of drug resistant OAB (Table 2). Accumulating data attest to the efficacy of both treatments as they are becoming more widely available.

Several level of evidence 1 and 2 studies demonstrated the superiority of Botox® over placebo in all important clinical and urodynamic parameters (daily frequency  $P < 0.001$ , urgency episodes  $P = 0.02$ , incontinence episodes  $P < 0.001$ , maximum cystometric capacity  $P = 0.01$  and maximum detrusor pressure  $P = 0.04$ ).<sup>30</sup> Botox® is effective irrespective of the number of previous AM treatments and of the reason for AM failure.<sup>31</sup> In a direct comparison to AMs, Botox® was found to produce a similar reduction in numbers of urgency incontinence episodes, but was twice as effective as AMs in restoring complete continence (27% vs 13%).<sup>32</sup> Repeat injections seem to sustain the beneficial effect in those who continue with the treatment.<sup>33–35</sup> However, the treatment is associated with a risk of retention and need for clean intermittent self-catheterizations (12-16% in all studies, significantly higher with the 200 U than the 100 U—24-31% vs 7-10%) as well as urinary tract infections (14-21% in LOE1-3 studies),<sup>30</sup> which are the main reasons for treatment discontinuation while efficacy of the treatment

does not appear to be an issue—primary and secondary loss of efficacy are considered of secondary importance.<sup>36</sup> Discontinuation rates can vary between 25% and 63.8% at 60 months.<sup>35–37</sup>

SNM is superior to standard medical treatment<sup>31</sup> and combination of SNM with AMs is more effective than AMs alone.<sup>31</sup> Different studies are consistent that about 70-75% of OAB patients have a >50% symptomatic improvement after SNM.<sup>38–40</sup> Moreover, significant reduction has been shown in the number of incontinence episodes ( $P < 0.0001$ )<sup>38</sup> and the number of pads used ( $P < 0.0001$ )<sup>39</sup> with marked improvement in quality of life after SNM therapy.<sup>39</sup> Prospective multicenter trials confirm that both clinical and QOL improvements are sustained in the long term, with high patient-reported therapeutic outcomes (80%).<sup>41</sup> Device-related adverse events appear, however, to be quite high (47%), but the vast majority resolved (91%).

But in the case of an informed choice between the two treatments, which one should we propose to our patients first? Currently, no clear answer can be given. There is a paucity of direct long-term clinical studies comparing efficacy and safety of the two treatments. A short-term study comparing the outcomes of the two treatments at 6 months in women with refractory OAB suggested that SNM was more successful than Botox® (89.2% vs 68.2%,  $P = 0.003$ ), although no difference was found in the proportion of women who had to restart AMs.<sup>42</sup> The Refractory Overactive Bladder: Sacral NEuromodulation vs BoTulinum Toxin Assessment (ROSETTA) trial, a randomized, open-label, active-controlled trial comparing the effectiveness of 200 U Botox® versus SNM (InterStim®) therapy for refractory

**TABLE 2** Current guidelines on the use of treatments for drug-resistant OAB: PTNS, SNM, and BOTOX

	EAU 2015	AUA/SUFU 2014	NICE 2013
PTNS	Yes	Yes	No
	Women with UU1	Carefully selected populations	Only if patient declines
	Not curative		Botox and SNM
			Review by MDT needed
SNM	3rd-line option	3rd-line option	3rd-line option
	Before considering bladder augmentation or urinary diversion (Gr.A)	Carefully selected patient populations with severe refractory OAB who are not candidates for 2nd-line therapy and are willing to undergo a surgical procedure (Gr.C)	Similar to that of the AUA
BOTOX	3rd-line option	3rd-line option	Only in patients with proven DO, after MDT review, and if they are willing, capable, and have been taught the technique of CIC
	Starting at a dose of 100 U Botox (Gr A)	In carefully selected and thoroughly counselled patients who are refractory to both first and second-line therapies (Gr C)	Recommended dose is 200 U Botox. 100 U to be considered only if the patients wants to reduce the change of needing CISC, while accepting the possibility of reduced efficacy

Caution that patients must be willing and able to perform CIC and be warned of other risks, including UTI

urgency incontinence has been designed to answer which treatment is more effective.<sup>43</sup> Refractory urgency urinary incontinence was defined as a) persistent symptoms despite at least one or more conservative treatments (eg, supervised behavioral therapy, supervised physical therapy) and b) persistent symptoms despite the use of a minimum of two anticholinergics, or unable to tolerate medication due to side effects, or has a contraindication to taking anticholinergic/beta 3 agonist medication. At 6 months, 200 U OnabotulinumtoxinA were found superior to SNM in reducing urgency incontinence episodes, restoring complete continence (20% vs 4% only) and improving patient reported outcomes such as bother, satisfaction, and endorsement with the treatment, albeit not in Patient Global impression of improvement in urine leakage and bladder function.<sup>44</sup> Due to the limited follow-up time period, and as the 100 U dose of Botox® is currently the standard of care in refractory OAB as opposed to the 200 U used in the ROSETTA trial, it remains to be seen how results of the study will translate into current clinical practice.

Cross-over studies between the two treatments are also sparse. A study investigating the use of SNM as salvage treatment after Botox® failures found that 70% of the 20 study recruits responded to the test stimulation and received a definitive implant. However, at 1-year follow-up only 79% of them were satisfied with SNM treatment, minimizing response rate to 55% overall.<sup>45</sup>

Interestingly, although comparative and cross-over clinical studies between the two therapies are largely missing, there have already been several studies comparing their cost-effectiveness. Those studies are plagued by their dependence on costs which greatly vary between healthcare systems in different regions of the world. For example, in the United States all estimates of cost endpoints for SNM were greater than those for Botox® or surgery.<sup>46,47</sup> By contrast, in the Canadian, Italian, and the UK healthcare systems, SNM was estimated to be more cost-effective in the long term.<sup>48–50</sup> Furthermore, the use of different models based on a great variance of clinical parameters could also contribute to the conflicting results of comparative cost-effectiveness studies. A stark example is a study based on the Dutch healthcare system whereupon SNM was found to be more cost-effective than Botox® after 4 years of treatment but with a model using general anesthesia for both procedures. In different scenarios, however, where Botox® was done under local anesthesia as is commonly the case or peripheral nerve evaluation or bilateral testing were used for SNM, SNM was no longer cost-effective.<sup>51</sup>

To date, few randomized controlled trials have provided high levels of evidence on the efficacy of PTNS in OAB<sup>12,52</sup> showing marked differences between PTNS and sham treatment using various efficacy outcomes (changes in global response assessment, bladder diary parameters), while the method has been also shown to be more effective when compared to tolterodine alone<sup>53</sup> and have a lasting effect on

OAB symptoms.<sup>54</sup> Moreover, a randomized controlled crossover study of 40 women with OAB divided in two groups (Group A, first solifenacin followed by PTNS and Group B, first PTNS followed by solifenacin), showed a reduction in the number of daily micturitions, episodes of nocturia and urge incontinence in both groups. In this study, PTNS showed a greater effectiveness than Solifenacin in all parameters including patient perception of urgency and quality of life.<sup>55</sup> Another randomized study, however, found no difference in efficacy between PTNS and Tolterodine.<sup>56</sup>

### 2.2.2 | What do patients want?

The final decision is left to the adequately informed patient, so studies have started examining their preferences albeit with contradicting results. In a study of women with refractory OAB, 74% would choose Botox® over SNM. In the Botox® group, their decision was influenced by their dislike of the thought of having a foreign body in their back (54%), shorter waiting times (46%), and faster onset of effect for Botox® (43%), while in the SNM group the need for repeat Botox® injections at variable intervals (61.5%) and the risk of urinary retention with Botox® (46%) were the main reasons which pushed them toward SNM.<sup>57</sup> These results were quite different from other studies where only 9–50% of predominantly female OAB patients, having used AMs, would choose Botox® when considering efficacy, method of delivery and possible adverse events.<sup>58,59</sup> In the latter study, 57% would choose PTNS as opposed to 34% who preferred SNM and only 9% for Botox®.<sup>59</sup>

Such wide range of patient preferences may actually reflect differences in study designs, patient selection as well as local expertise. Clearly patients should make an informed choice based on adequately balanced presentation of available data on each method, but it is not rare for patients to depend on their treating physicians for choice.

### 2.2.3 | Augmentation cystoplasty for drug-resistant OAB/DO

The introduction of botulinum toxin in clinical urology during the last decade has dramatically affected the surgical indications for low compliance/low capacity bladders refractory to conservative treatment. This is reflected in the relevant literature which dates back to the late-1980s and -1990s, with only sparse publications on bladder augmentation after 2000.

So the question arises if there is still a role for AC in OAB treatment in 2016 and beyond. Is there a preferable procedure and which patient is the ideal candidate? When is the appropriate time in the course of OAB treatment for the step toward major surgery?

Various methods have been described to increase bladder capacity and to decrease bladder pressure by surgical means. Both bladder auto-augmentation via detrusor myectomy and the classical AC with the use of bowel have been mostly

applied in younger patients (median ages 33 and 38 years, respectively) with severe neurogenic DO failing conventional medical management. Success rates of 33-94%<sup>60-68</sup> and 58-100%<sup>69-75</sup> have been reported, respectively. Both methods achieve significant increases (>50%) of bladder capacity and decreases in storage pressure (>50%), but at the cost of increased residual urine and need for intermittent catheterisations (45-75% of detrusor myectomy patients, nearly all AC patients).<sup>63-76</sup> Complication rates are low for detrusor myectomy but considerably higher for AC (infections, incontinence, absorption disorders, stones, ileus, secondary malignancy, reservoir rupture, reinterventions).<sup>73-75</sup> Prior pelvic irradiation or extensive bladder fibrosis are contraindications for detrusor myectomy but not for AC.

To reduce these complications and spare the bowel alternative techniques like the interposition of commercially available small intestinal submucosa have been introduced.<sup>77</sup> For many years urological research is striving to substitute the whole bladder with cultured urothelial cells and extracellular matrix scaffolds, but this promising technique has not reached clinical practice, yet.

As this last resort of OAB treatment is today infrequently performed, the guidelines do not reflect high levels of evidence (Table 3). EAU guidelines, unchanged since 2011, denote

detrusor myectomy and clam cystoplasty as a valid option to decrease detrusor pressure and increase bladder capacity, whenever more conservative approaches have failed (grade B recommendation).<sup>78</sup> AUA guidelines (2014) consider AC or urinary diversion only as an additional treatment option in rare cases, for severe, refractory, complicated OAB patients on the level of expert opinion.<sup>3</sup> Likewise, NICE guidelines (2012) consider bladder augmentation using an intestinal segment for people with non-progressive neurological disorders and complications of impaired bladder storage and only after a thorough clinical and urodynamic assessment and discussion with the patient and/or their family members and carers about complications, risks, and alternative treatments.<sup>79</sup> Canadian guidelines (2012) also consider AC in special circumstances after failing all other options (level of evidence 3, grade C recommendation).<sup>80</sup>

The indication for AC is usually driven by poor bladder compliance (80%).<sup>81</sup> Other indications include immunity to botulinum toxin or unwillingness to have repeated injections and also poor access to healthcare. Prerequisites for AC are good renal function, the ability to conduct self-catheterization, and good compliance in the long term to avoid complications. In every patient, a careful follow-up is mandatory.

**TABLE 3** Current Guidelines on augmentation cystoplasty for drug resistant OAB

	EAU 2013/2015	AUA/SUFU 2014	NICE 2012
Augmentation cystoplasty	1. Only offer augmentation cystoplasty to patients with detrusor overactivity incontinence who have failed conservative therapy, in whom the possibility of botulinum toxin and sacral nerve stimulation has been discussed (GoR C)	Non-neurogenic LUTD: in rare cases, augmentation cystoplasty, or urinary diversion for severe, refractory, complicated OAB patients may be considered (Expert Opinion)	Neurogenic LUTD: consider augmentation cystoplasty using an intestinal segment for people with non-progressive neurological disorders and complications of impaired bladder storage (eg, hydronephrosis or incontinence) and only after a thorough clinical and urodynamic assessment and discussion with the patient and/or their family members and carers about complications, risks and alternative treatments
	2. Warn patients undergoing augmentation cystoplasty of the high risk of having to perform clean intermittent self-catheterisation; ensure they are willing and able to do so (GoR C)		
Detrusor myectomy	Non-neurogenic LUTD: do not offer detrusor myectomy as a treatment for urinary incontinence (GoR C)		
	Neurogenic LUTD: detrusor myectomy is an acceptable option for the treatment of overactive bladder when more conservative approaches have failed. It is limited invasive and has minimal morbidity (GoR B)		
Entero-cystoplasty	Neurogenic LUTD: bladder augmentation is an acceptable option for decreasing detrusor pressure whenever less invasive procedures have failed. For the treatment of a severely thick or fibrotic bladder wall, a bladder substitution might be considered (GoR B)		

Further research to classify augmentation cystoplasty into a valid treatment algorithm should include cost-effectiveness aspects beyond national levels. Patient databases would be desirable, therefore, strategies should be developed which data to collect and how such a platform could be established. Further clinical studies should determine the long-term effectiveness of AC in comparison to botulinum toxin treatment, but in many countries the feasibility of such studies is questionable due to ethical aspects. Further basic research concerning tissue engineering and biomaterials for bladder augmentation should enlighten the barriers for clinical applications.

### 3 | DISCUSSION

OAB is a well-defined symptom complex but not very specific for the pathophysiology. Symptoms improve in placebo arms of all published studies; not all patients with OAB show DO on cystometry and not all patients with DO respond well to pharmacotherapy. Moreover, several guidelines and studies report on “severe” OAB without a proper definition or a consensus about how to diagnose and or quantify OAB severity.

#### 3.1 | Proposal of a treatment algorithm (Fig. 1)

Initial management for OAB syndrome is usually “pragmatic”; treatment is initiated on the basis of symptoms and signs. This medical management strategy is known as *Diagnosis ex juvantibus*. With *ex juvantibus* management, treatment is started without more specialized laboratory, imaging, or other testing to precisely establish the presumed diagnosis. *Ex Juvantibus* management is possible in benign conditions when potentially more serious or life threatening diagnoses can be excluded. Usually awareness of a priori prevalence helps to support *ex juvantibus* management. Since LUT dysfunction is prevalent and usually not life threatening *ex juvantibus* management has been demonstrated to be very acceptable.

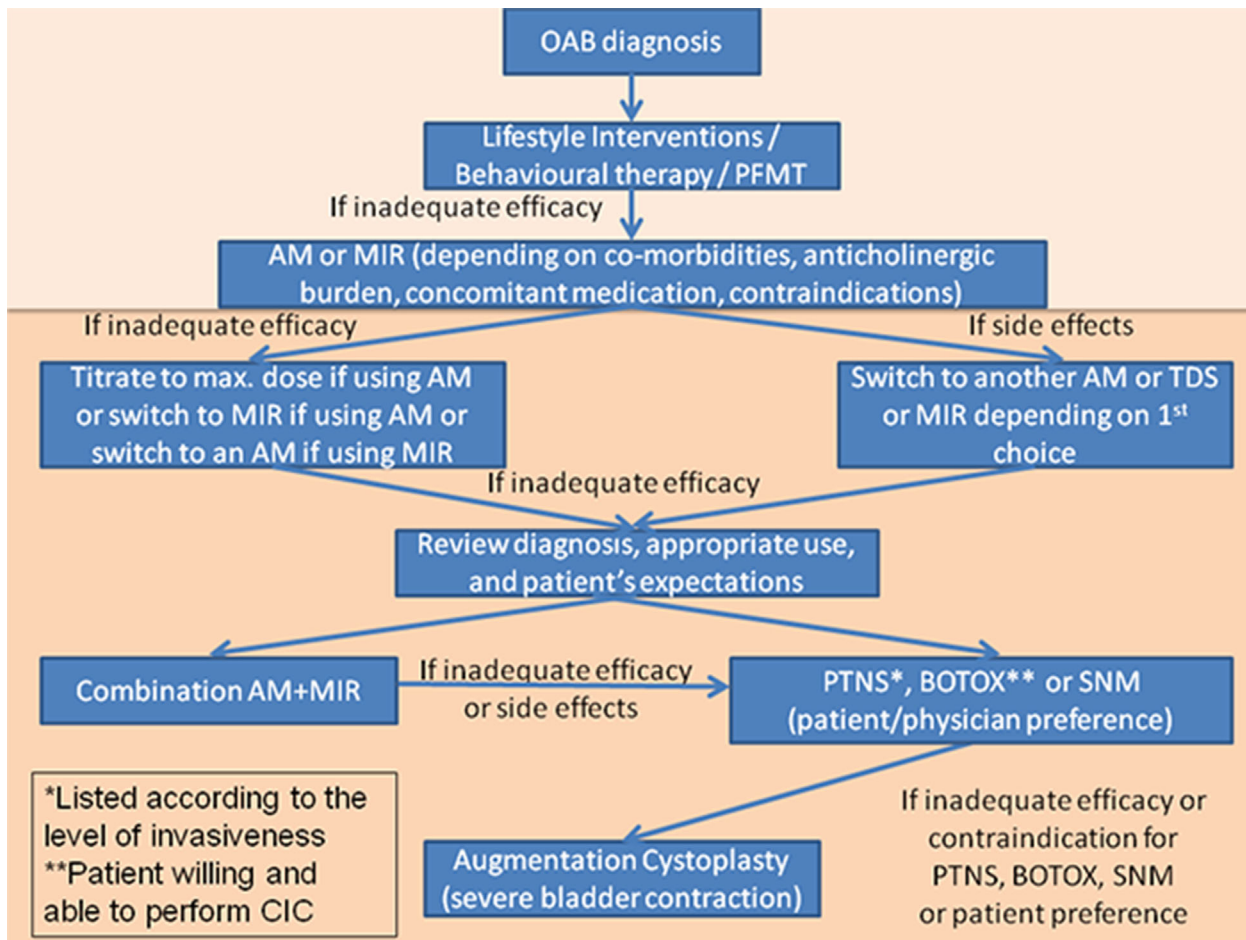
The consequence of *ex juvantibus* management is, however, that if it is ineffective, the initial diagnosis should be reconsidered first. It may also be good clinical practice to consider an alternative pathophysiology for the symptoms, which is infrequently reported and not included in the clinical practice guidelines. We should also consider that pharmacotherapy may be effective but not meeting treatment expectations. Moreover, the patient may assume that the perceived signs and symptoms are caused by some life-threatening disease and may be uncertain of the nature of the dysfunction, which was—in the case of *ex juvantibus* management—diagnosed by very simple means. A more precise diagnosis may help both the physician and the patient.

Further to the issues of an inappropriate first diagnostic process, it is imperative to define “drug resistant” OAB for the purposes of a treatment algorithm. While the debate on the efficacy of AMs has flared up again, now based on poor patient long-term adherence to the treatment as revealed by prescription databases and concerns on drug cycling with what appears to be a ceiling of efficacy with any of these agents, the addition of mirabegron may have opened new therapeutic windows with this novel class of drugs, which, however, have not been tested in the long-term yet. Nevertheless, there is good level of evidence for the use of either AMs or mirabegron, with emerging data also supporting the use of combination treatment between the two classes of drugs.

A number of aspects may be involved in “resistance” to OAB pharmacotherapy, including psychosocial parameters and physician-patient interaction, molecular variations, and comorbidities, which might shape variance in patient profiles of response to treatment. Apart from comorbid conditions which may affect the choice of drug but also its efficacy by increasing adverse events and changing absorption and bioavailability, data on psychosocial, and molecular factors are largely missing and could become wide fields of novel research in the area, contributing to the efforts towards more personalized medicine. The impact of patient initial perceptions of condition, their health literacy and the integrity of the informed decision making also affect the post therapy status of the OAB patient.

Lack of robust evidence as it is makes a consensus on the definition of drug-resistant OAB difficult. Help could be provided by similar conditions in other specialties. For example, depression is usually considered resistant or refractory when at least two trials with antidepressants from different pharmacologic classes (adequate in terms of dosage, duration, and compliance) fail to produce a significant clinical improvement. Resistant hypertension (definition by the American Heart Association) a BP that remains above goal in spite of optimal doses of three antihypertensive agents of different classes, one ideally being a diuretic. Drug resistant epilepsy is defined as failure of adequate trials of two tolerated, appropriately chosen, and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom. Consequently, OAB could be considered drug resistant when adequate (dosage, duration) trials of two different drug classes (either as monotherapies and/or in combination) fail to effectively improve OAB symptoms. Fig. 1 presents an expert consensus of a treatment algorithm, to serve as a basis for further development of an evidence base for patients who fail initial management.

Current evidence does not allow for a clear proposal on which 2nd-line treatment should be offered first to patients with drug resistant OAB. Comparative studies exist only on



**FIGURE 1** Proposed algorithm. PFMT, pelvic floor muscle training; AM, antimuscarinic; MIR, mirabegron; TDS, transdermal delivery system; PTNS, percutaneous tibial nerve stimulation; SNM, sacral neuro modulation; CIC, clean intermittent catheterizations.

cost-effectiveness and patients’ preferences but with contradictory findings. Patients’ choice can only be based on efficacy and adverse events data per single treatment, provided all techniques are available, reimbursed, and the treating physician adequately familiar and competent with the technique(s). All three techniques have level of evidence 1 data to support their use. PTNS is the least invasive of the three techniques and could be offered first in a step-by-step algorithm from the least to the most invasive option, but has the least published data compared to either Botox or SNM, is not widely available yet and carries a high clinical burden for the patient due to repeat hospital/office visits over short periods of time.

Botox bladder injections, although a newer technique compared to SNM, has become more widespread as it only requires a regular outpatient cystoscopic setting for its application, is relatively easy and quick to perform and has a fast onset of action. Again it is a more minimally invasive method compared to SNM, yet it requires repeat sessions every few months, is associated with increased risk of urinary infections and inadequate bladder emptying which eventually lead to high dropout rates. SNM is more invasive than the other two techniques, requires two-stage theater surgery and

high-complication rates, but has long-lasting effects, albeit with some decrease in efficacy over time. It may also be more cost-effective than Botox in the long term in several national healthcare systems.

Given the paucity of direct comparative studies between the three treatments and since results of current studies may be influenced by several factors such as physician’s expertise, patient selection, and the variance in local healthcare costs, it is rational to propose either of the three methods as 2nd-line treatment of OAB symptoms after failure of oral pharmacotherapy, in a valid treatment algorithm. Each technique could be suitable for select patient populations. Obviously availability of the technique and physician preferences could play a significant role in patients’ informed choice (Fig. 1). Presuming results of the ROSETTA trial are also reproducible with the approved 100 U Botox, then Botox detrusor injections should be offered before SNM at least in patients with refractory urgency incontinence as opposed to OAB-dry patients.

Augmentation cystoplasty has been seriously sidelined by the novel minimally invasive techniques, but also by strict indications, such as severe bladder contraction, and inferior efficacy in the non-neurogenic OAB population,



being now rarely performed in centers of excellence. It should be used in cases of inadequate efficacy or contraindication for the less invasive 2nd-line treatments or if patients prefer a more definitive solution to their problem (Fig. 1).

### 3.2 | Is patient profiling possible?

Successful conservative treatment for OAB relies on various factors, such as efficacy, tolerability, accessibility and convenience, patient's perception of the disease and expectation from treatment, costs, correct indication and quality of practitioner, as well as, effects on quality of life.<sup>82</sup> Due to the recent advances on drug development (eg, mirabegron) and on minimally invasive 3rd-line treatment options for OAB, a new treatment algorithm is needed to guide clinical practice. A practical example to illustrate this context is related to the relationship between efficacy and tolerability. As AMs have different tolerability profiles, another drug is often prescribed for patients who do not tolerate the initial index medication due to side effects. However, should we insist on another AM in case of lack of efficacy on full dose? When and how should mirabegron be incorporated in the algorithm? And how about combination therapy with AMs and beta-3 agonists? These issues have clinical importance and should be answered before addressing the term “drug resistant OAB.”

Additionally, several factors may affect the outcome of OAB treatments<sup>2</sup>:

- Comorbidities.
- Behavioral therapy in conjunction with drug therapy.
- Baseline symptom severity.
- Incorrect diagnosis.
- Mixed urinary incontinence.
- Intrinsic and extrinsic factors that may affect drug exposure.

Management of patient's expectations play an important role in clinical practice, as the most frequently reported reasons for poor compliance to AMs are “did not work as expected” and “side effects.”<sup>83</sup>

## 4 | FUTURE RESEARCH

- Long-term studies on efficacy and safety of oral pharmacotherapy as well as invasive treatments for drug-resistant OAB.
- Need for patient databases, particularly with regard to failure of pragmatic management and diagnosis of failure and subsequent management.

- Cross-over studies/comparative, head-to-head studies.
- Cost-effectiveness comparative studies: beyond national levels.
- Standardize quantification of OAB severity and definitions of efficacy of OAB management.
- Identify prognostic factors of efficacy.
- Benefit/risk ratio of second line management.
- Studies on patient perspective with regard to failure of treatment, diagnosis of dysfunction, and acceptance of invasive management.
- Combination studies for well-defined patient groups who failed initial management that include combinations of or with;  $\beta$ 3-agonists and AMs; AMs and desmopressin; estrogen and AMs
- Cost analysis of second line managements.
- Are all AM drugs the same in combination? Are there theoretical risks that are greater with some combinations?

## POTENTIAL CONFLICT OF INTEREST

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