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# Medical and Surgical Treatment for Overactive Bladder

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Additional information is available at the end of the chapter

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## Abstract

In this chapter, we focus on the medical treatment of overactive bladder (OAB) syndrome. The treatment of choice of the OAB syndrome is still the anticholinergic therapy, although we must consider  $\beta_3$ -agonists with almost the same evidence. No drug has been shown to be clearly superior to the rest. The use of oxybutynin transdermal should be considered when the side effects due to the oral administration are intolerable. In elderly patients, first efforts should be directed to use non-drug therapies, such as behavioural therapy. In patients suffering from cognitive dysfunctions, the use of antimuscarinic with caution is recommended. Mirabegron, a  $\beta_3$ -agonist, can be offered, although it should be noted that the long-term effects are still unknown. The logical second-line treatment is the intravesical injection of botulinum toxin A, considering its temporary effectiveness and the possibility of retention. In some centres, sacral nerve stimulation may be an option. Surgical treatment should be reserved when conservative therapies fail.

**Keywords:** medical treatment, overactive bladder, antimuscarinics

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## 1. Introduction

Overactive bladder or detrusor overactivity is characterized by the presence of involuntary detrusor contractions that may be spontaneous or provoked [1]. Clinically, idiopathic detrusor overactivity is manifested as the urgent desire to urinate, with or without incontinence, generally associated with frequency and nocturia, which severely affect patients' quality of life. This combination of symptoms is included in a more general term that we know of as overactive bladder (OAB) [2].

When designing a treatment algorithm, the balance between the risks and benefits of each option must be taken into account regarding effectiveness and invasiveness, and the duration, severity and reversibility of adverse effects, more so than the evidence available. Behavioural treatment or hygienic-dietetic measures, that is, pelvic floor rehabilitation exercises and bladder training, are considered to be the first line of treatment for OAB syndrome, although they require great amount of time and effort from both the physician and the patient [3]. Oral and transdermal drugs are the second line of treatment, where antimuscarinic agents, in spite of their effectiveness, present a high percentage of side effects (all reversible). The third line of treatment includes intra-bladder treatment with onabotulinum toxin A, which entails risks of urinary retention with delayed resolution, and the different options of neuromodulation and nerve stimulation, which are more invasive and require greater motivation on behalf of the patient. And finally, surgery, the last therapeutic option due to its irreversible side effects [4] is surgery such as augmentation enterocystoplasty or urinary derivation.

The medical treatment of idiopathic OAB syndrome is the main objective in this chapter.

## 2. Oral medication

Medical treatment is the second line of treatment of OAB syndrome. It should be highlighted that the efficacy of said treatment is subject to the associated side effects of the drugs implemented, which are usually frequent and intense, leading many patients to abandon treatment.

In an attempt to inhibit the contractions of the detrusor muscle that occur in OAB syndrome, different drugs have been used including anticholinergics, calcium antagonists (nifedipine, flunarizine and terodiline hydrochloride),  $\beta$ -adrenergic agonists (clenbuterol),  $\alpha$ -adrenergic blockers (prazosin), prostaglandin-synthetase inhibitors (indomethacin) and muscle relaxants (flavoxate hydrochloride and dicyclomine) [5]. Of all the aforementioned, the most frequently used are the antimuscarinic anticholinergic drugs. Recently, a new group of drugs has become available, known as  $\beta_3$ -agonists, which present a competitive efficacy and tolerability when compared with the classical treatment.

### 2.1. Antimuscarinic drugs

Antimuscarinic or anticholinergic drugs are currently used as the primary treatment of OAB syndrome. The differences among them are based on their pharmacological profiles (muscarinic receptor affinity and other routes of action), the pharmacokinetic properties (liposolubility) and the formulations available.

Antimuscarinic drugs act by blocking the muscarinic receptors that are stimulated by acetylcholine, which is simultaneously released by the parasympathetic nervous system's activity, inhibiting the contraction of the detrusor muscle. The muscarinic receptors are primarily found in smooth muscle fibres, including the detrusor muscle, and in glands. Five types of muscarinic receptors have been described in human bladders; the most frequent are M2 and

M3, with M2 predominant to M3 in a 3:1 ratio. The M2 receptors are responsible for relaxing the detrusor muscle. The M3 receptors control the contraction of the detrusor muscle. Close to 90% of the muscarinic receptors in the salivary glands are of the M3 type [6]. The concomitant stimulation of these receptors by the antimuscarinics explains the well-known adverse effects of dry mouth and constipation.

The antimuscarinics can be divided into the following groups:

- Tertiary amines (atropine, oxybutynin, propiverine, darifenacin, tolterodine and solifenacin), which are well absorbed in the gastrointestinal tract, and depending on their lipophilic nature, they present a greater or lesser capacity to pass through the blood-brain barrier.
- Quaternary amines (propantheline, trospium chloride), which are not well absorbed in the digestive tract but have a lower incidence of side effects affecting the central nervous system.

Antimuscarinic drugs are metabolized by the cytochrome P450 enzyme system, fundamentally by the CYP2D6 and CYP3A4 enzymes, with the respective risk of pharmacological interaction by enzymatic induction or inhibition.

Establishing solid criteria regarding the resolution or improvement of urinary urgency associated with OAB is difficult. The absence of a standard definition of improvement or worsening impedes the possibility of creating a concept of resolution as a primary objective. Generally, systematic reviews assert that the effect of pharmacological treatment is weak but significantly superior than that of the placebo.

Antimuscarinics lack complete selectivity at the bladder level and produce side effects in other organs and systems that may limit their use [7]. Dryness of the mouth is the most frequent side effect, although constipation, blurry vision, tachycardia, fatigue or altered cognitive function may also occur. These side effects are dose-dependent and thus patients should start with a minimal dose and gradually increase depending on the efficacy and the patient's tolerance.

The immediate release (IR) formulation of oxybutynin is the prototype drug for urinary urgency. It provides adequate flexibility regarding the maximum dose, even when used as needed 'off label'. However, due to its pharmacokinetic properties, the IR drugs have a greater risk of side effects than the extended release (ER) versions. The transdermal release system or topical gels provide an alternative formulation to be taken into consideration.

## 2.2. Dosage: pharmacokinetics

The dosage and pharmacokinetics of the primary antimuscarinics used in daily clinical practice are presented in **Table 1**.

All antimuscarinics are contraindicated in patients with closed-angle glaucoma. On the other hand, the use of any antimuscarinic must be taken into account during breastfeeding as it may inhibit the production of milk due to its direct effect on the mammary glands.

	Dosage	Half life	Bioavailability	Stable concentration time	Excreted in urine	Excreted in faeces	Other
Oral oxybutynin*1	IR—5 mg/8–12 h ER—10 mg/24 h	2–3 h	2–11%	8 days	50%	50%	–
Transdermal oxybutynin*2	36 mh/3–4 days (patch)	2–3 h	–	48 h	<0.1%	99%	No first hepatic pass
Tolterodine*3	IR—2 mg/1–2 h ER—4 mg/24 h	6–10 h	17–65%	4 days	77%	17%	–
Solifenacin*4	5 mg/2–4 h (max 10 mg)	50 h	90%	24 h	70%	23%	–
Fesoterodine*7	4 mg/24 h (max 8 mg)	7 h	52%	24 h	70%	7%	No first hepatic pass

\*1 **Oral oxybutynin.** Oxybutynin has been the most used drug for many years to treat OAB. Along with its anticholinergic effect, it acts as an antispasmodic agent, muscle relaxant and even as a local anaesthetic, if using intra-bladder administration (*Oral Oxybutynin data sheet*).

\*2 **Transdermal oxybutynin.** The transdermal route is one of the tested forms of administration to minimize side effects along with the rectal route [8, 9]. The transdermal administration of oxybutynin avoids gastrointestinal metabolism and the hepatic first-pass effect, which reduces the formation of the N-desethyl metabolite, whose plasmatic concentration is directly related with the incidence of side effects associated with antimuscarinics. Its side effect profile is similar to the placebo except for the incidence of cutaneous reactions. This leads to a high degree of compliance (90–95%) [10] (*Transdermal Oxybutynin data sheet*).

\*3 **Tolterodine.** Tolterodine is an anticholinergic agent with greater selectivity on the bladder than on the salivary glands, due to its more selective antimuscarinic effect on the M2 receptors, although it seems that the M3 glandular receptors are more sensitive to blocking [11, 12].

The half-life of oral tolterodine is approximately 6 h in fast metabolizers, and around 10 h in slow-metabolizing patients (those lacking CYP2D6). The absolute bioavailability of tolterodine is 17% in fast metabolizers, which includes most patients, and 65% in slow-metabolizing patients (*Tolterodine data sheet*).

\*4 **Solifenacin.** The in vitro and in vivo pharmacological studies indicate that solifenacin is a competitive inhibitor specific to sub-type M3 muscarinic receptors (*Solifenacin data sheet*).

\*5 **Fesoterodine.** Fesoterodine is rapidly and extensively hydrolysed by unspecific plasmatic esterases, without undergoing the hepatic first-pass effect, producing 5-hydroxymethyl derivatives, which is the main active metabolite and which makes it responsible for the pharmacological action of fesoterodine (*Fesoterodine data sheet*).

**Table 1.** Dosage and pharmacokinetic characteristics of the primary antimuscarinic drugs.

### 2.3. Evidence: clinical efficacy

The efficacy of antimuscarinic drugs has been supported by five systematic reviews of different drugs compared to placebos [13–17]. Most of the studies include patients with an average age of 55–60 years, both men and women, where no results can be extrapolated based on sex. According to the evidence, and with significant consistency between the different studies, only moderate short-term improvement of symptoms is observed with the use of antimuscarinic drugs compared to placebo. See **Table 2**.

	Number of studies	N	Relative Risk (95% CI)	Number of patients needed to treat NNT for a cure (95% CI)
Oxybutynin (IR-ER)	4	992	1.7 (1.3–2.1)	9 (6–16)
Tolterodine (IR-ER)	4	3404	1.2 (1.1–1.4)	12 (8–25)
Solifenacin	5	6304	1.5 (1.4–1.6)	9 (6–17)
Fesoterodine	2	2465	1.3 (1.1–1.5)	8 (5–17)

**Table 2.** Summary of the cure rate of the principal clinical trials [18].

The best indicator of the relevance of the side effects is the rate of abandonment due to intolerance, although this is not reflected in routine clinical practice. All of the formulations of fesoterodine, oxybutynin, propiverone, solifenacin, tolterodine, darifenacin and trospium offer a greater rate of improvement or resolution and a greater rate of side effects (dryness of the mouth) compared to placebo (Evidence Level (EL) 1a and 1b, respectively). Likewise, transcutaneous oxybutynin has shown a significant improvement in the number of episodes of incontinency and nocturnal urination per day compared to placebo, with improvement in urinary urgency, similar to its gel formulation [13].

### 2.4. Comparison between antimuscarinic drugs

The comparisons between the different antimuscarinic drugs, both in effectiveness and in side effects, are important for decision making in daily practice.

Forty randomized and controlled clinical trials have been published along with five systematic reviews [13–15, 19, 20]. Almost all of them are studies supported by the pharmaceutical industry. Generally, the titration schemes of the dose are included in the protocols for the experimental group, but not for the comparison group. They are short studies (12 weeks) and the primary objective is the modification of the symptoms of OAB more than its cure or improvement in urinary urgency, generally analysed as a secondary objective. The clinical applicability of these studies in daily clinical practice is questionable as most of the studies are of low to average quality [16].

There is not enough evidence to confirm that one antimuscarinic drug is better than another to cure or improve urinary urgency (EL 1a). However, oxybutynin ER is superior to tolterodine

IR and ER (EL 1b), solifenacin is more effective than tolterodine IR (EL 1b) and fesoterodine is more effective than tolterodine ER (EL 1b), regarding improvement of urinary urgency. None of the antimuscarinic drugs have shown to improve the related quality of life better than the others (EL 1a) [16]. In general, it is accepted that if one antimuscarinic IR drug is not effective, an ER version is offered (grade of recommendation (GR A)).

The ER formulations cause less side effects than the IR formulations (EL 1b) [16, 20]. Oxybutynin IR produces more dryness of the mouth than tolterodine and trospium ER, but less than darifenacin [16, 20]. Oxybutynin ER generally produces more dryness of the mouth than tolterodine ER, although the incidence of moderate to severe dryness of the mouth is similar (EL 1a). Transdermal oxybutynin has a lower rate of dryness of the mouth than oxybutynin IR and than tolterodine ER, but a greater rate of abandonment due to cutaneous reactions (EL 1b) [16]. In fact, the use of transdermal oxybutynin is recommended when oral antimuscarinic drugs are not tolerated due to dryness of the mouth (GR A). Solifenacin of 10 mg daily has a greater rate of dryness of the mouth than tolterodine four daily [21, 22]. The same rate of abandonment is generally observed, regardless of the incidence of dryness of the mouth. The primary comparative studies regarding the efficacy and adherence are shown in **Table 3**.

Performing an early check-up of the efficacy and side effects after 1 month of treatment with these patients (GR A) is recommended. On the other hand, physicians should be able to manage and treat the side effects inherent to antimuscarinic drugs (**Tables 4 and 5**). Patients must be informed regarding said effects before starting treatment.

**2.5. Adherence: persistence**

Most studies on antimuscarinic drugs have a short follow-up period (12 weeks), considering that adherence in clinical trials is much higher than in routine practice [23].

The adherence rate at 2 years varies from 49 to 84% according to two clinical trials with fesoterodine at 8 mg [24, 25]. The principal drugs studied regarding adherence are oxybutynin and tolterodine. The abandonment rate was very high after 12 months with tolterodine, but even higher with oxybutynin (68–95%).

	Number of studies	N	Relative risk (95% CI)
<i>Effectiveness</i>			
Oxybutynin ER vs. tolterodine ER	3	947	1.11 (0.94–1.31)
Solifenacin vs. tolterodine ER	1	1177	1.2 (1.08–1.34)
Fesoterodine vs. tolterodine	2	3312	1.1 (1.04–1.16)
<i>Abandonment due to side effects</i>			
Solifenacin vs. tolterodine ER	3	2755	1.28 (0.86–1.91)
Fesoterodine vs. tolterodine	4	4440	1.54 (1.21–1.97)

**Table 3.** Comparison of the effectiveness and abandonment rate due to side effects of the principal antimuscarinic drugs [13].

Symptomatic treatment of dry mouth
<ul style="list-style-type: none"><li>• Drink small sips of water</li><li>• Suck on sugar-free hard candies or gum</li><li>• Avoid mouthwashes with alcohol</li><li>• Oral lubricants<ul style="list-style-type: none"><li>- Anethole trithione (sialogogue)—one tablet three times per day (50% success rate)</li><li>- Bromhexine hydrochloride (sialogogue)—30 drops three times per day (60% success rate)</li><li>- Eledoisin (drops)—three drops under tongue when needed</li><li>- Artificial saliva—nebulizations when needed (94%)</li><li>- Squeezed lemon (sialogogue) — when needed</li></ul></li></ul>

Table 4. Symptomatic treatment of dry mouth.

Symptomatic treatment of constipation
<ul style="list-style-type: none"><li>• Diet rich in fibre and liquids</li><li>• Fibre supplements</li><li>• Regular exercise</li><li>• Normal intestinal habits</li></ul>

Table 5. Symptomatic treatment of constipation.

The average number of days before the drug is discontinued varies from 30 to 50 days [26]. In this sense, more than half of all patients will abandon treatment with antimuscarinics within the first 3 months due to lack of effectiveness, side effects or cost (EL 2).

Several randomized and controlled clinical trials have attempted to identify factors associated with a lower adherence rate. In this sense, the low level of efficacy (41.3%), adverse effects (22.4%) and cost (18.7%) [26] is associated with a lower adherence/persistence, along with IR formulations, age (young people), unrealistic expectations about treatment, gender (male) or race (Afro-Americans and other minorities).

2.6. Cognitive effects in old age—anticholinergic load

Few studies in the elderly population with OAB are available and they present various limitations including the multi-factorial aetiology of urinary urgency at this age, the presence of co-morbidities such as cognitive deficit, the effect of concomitant medications or the high risk of suffering side effects. However, it can be confirmed that all antimuscarinic drugs are effective in elderly patients (EL 1b).

The evidence is not conclusive regarding the cognitive effects of antimuscarinic drugs [27]. Few studies specifically study the cognitive changes associated with treatment using

antimuscarinics; in fact, there are no studies conducted on patients who are vulnerable to suffering cognitive deficit.

Regarding the primary antimuscarinic drugs used, the effects on the elderly population and on cognitive function are explained as follows:

- **Oxybutynin.** There is sufficient evidence to confirm that oxybutynin IR may cause or worsen cognitive deterioration, although there is no current consensus on this topic (EL 2) [28–34].
- **Tolterodine.** No differences in the efficacy or side effects have been reported regarding age [35–38], although a greater rate of abandonment has been reported in elderly patients compared with placebo [28]. On the other hand, the post hoc analysis showed a slight negative effect on cognitive function. That said, there is no evidence that tolterodine causes deterioration of cognitive function (EL 3).
- **Solifenacin.** A cluster analysis [33] has shown that treatment with solifenacin does not increase cognitive function in elderly patients. No pharmacokinetic differences have been demonstrated between the different age groups, although a greater frequency of side effects has been observed in patients over 80 years of age, without any cognitive effects identified in healthy volunteer patients [34]. In patients with moderate cognitive deterioration, over 65 years of age, there were no differences in the efficacy between the different age groups, with a lower incidence of side effects in comparison with oxybutynin IR [33, 39]. Therefore, it can be confirmed that solifenacin has not shown to cause deterioration in cognitive function in elderly patients (EL 1b).
- **Fesoterodine.** There is no evidence in the comparison of the efficacy and side effects of fesoterodine between young and elderly patients. The cluster analysis of the different clinical trials confirmed the efficacy of fesoterodine at 8 mg but not at a dose of 4 mg in patients over 75 years of age. Adherence is lower in patients over 75 years of age; however, the effect on their mental state has not been documented [24, 40, 41]. There are no differences with the placebo regarding cognitive function in younger elderly patients [42]. Therefore, fesoterodine has not shown to cause deterioration in cognitive function in elderly patients (EL 1b).

Currently, extrapolating these data to the general elderly population is a risk. Conducting prevalence studies based on the community regarding the side effects of antimuscarinics could be very helpful in the future [43]. When antimuscarinic treatment is started in elderly patients, it is recommended that their mental function be evaluated objectively and monitored (GR C) [44]. Nonetheless, there is no consensus regarding which is the best test to evaluate mental function and detect changes in cognitive function [45, 46]. On the other hand, taking into account the so-called ‘anticholinergic load’ (GR C) is important in older adults. Drugs with anticholinergic properties are commonly prescribed for a variety of medical illnesses [47–50]. It has been estimated that 20–50% of older people have been prescribed at least one medication with anticholinergic activity [49, 51]. This could be long-term prescribed for conditions such as asthma or to manage the side effects of medicines used to treat psychiatric disorders [51]. That is why it is important to consider the anticholinergic load before starting a

treatment with anticholinergic drugs. In this aspect, the list of potentially inappropriate medications (PIMs) determined by Beers Criteria in collaboration with the American Geriatrics Society [47] should be considered. These medications cause many problems, which are costly and often preventable in older adults and lead to poor outcomes. Some anticholinergic drugs, such as first-generation antihistamines (dexchlorpheniramine, doxylamine and hydroxyzine), antiparkinson agents (benztropine and trihexyphenidyl) and antispasmodics (scopolamine and propantheline) are considered to be avoided in this population with moderated quality of evidence and strong recommendation [47], due to the wide spectrum of central effects such as the onset of dizziness, sedation, confusion, in addition to increasing delirium, causing a decline in cognitive and physical function [49–51]. In relation to urological anticholinergic drugs such as darifenacin, trospium, fesoterodin and solifenacin, these recommendations are softer, and they are usually associated to peripheral adverse effects such as chronic constipation, dry mouth, dry eyes, blurred vision and increased heart rate [50]. Nevertheless, it is very important to estimate the anticholinergic load of each patient, in order to avoid the synergistic effect of several anticholinergic drugs, related to their tolerance and their well-known side effects [47]. Furthermore, attention should also be paid when these drugs are combined with cholinesterase inhibitors, especially in elderly patients [45].

### 3. $\beta$ 3-agonist: mirabegron

Mirabegron is the first clinical  $\beta$ 3-agonist available. The  $\beta$ 3-adrenergic receptors are the predominant  $\beta$ -receptors in the smooth muscle cells of the detrusor muscle and their stimulation leads to the relaxation of said muscle.

The clinical effectiveness of mirabegron is shown in two systematic revisions [52, 53], which demonstrate that the doses of 25, 50 and 100 mg reduce episodes of incontinency, episodes of urgency and urinary frequency in 24 h compared to placebo (EL 1a), with no differences in the frequency of side effects [52]. The continence rate (dryness) for the placebo is 35–40%, compared to 43–50% with mirabegron. In all of these studies, the significant statistical difference is observed in relation with improved symptoms, and not resolution (EL 1b). The effectiveness is similar both in those patients without previous treatment and in those that previously received treatment with antimuscarinics.

The effectiveness compared with extended release tolterodine 4 mg is practically identical with a continence rate (dryness) of 43–45% (EL 1b) [54].

The adrenergic side effects are somewhat frequent, without reaching levels of clinical relevance (EL 1a). The most frequent side effects are hypertension (7.3%), symptoms of nasopharyngitis (3.4%) and lower urinary tract infections (3%) [52]. No risks have been demonstrated with the prolongation of the QTc in electrocardiograms (ECGs) [55] nor with increased intra-ocular pressure [56] observed with the dose of 100 mg. There are no significant differences in the rate of side effects depending on the different doses of mirabegron [54]. However, it is recommended that patients be informed of the possible long-term side effects, which remain unknown (GR B).

Evaluation of urodynamic parameters in patients with OAB together with obstructive symptoms of bladder voiding concludes that mirabegron (50 or 100 mg) does not negatively affect said urodynamic voiding parameters compared with the placebo [57].

Regarding adherence, at 12 months, mirabegron presents a rate similar to that of tolterodine (5.5 vs. 3.6%, respectively) (EL 1b), although the frequency of dry mouth is significantly greater in the tolterodine group [54]. There are no studies published on its use in elderly patients with OAB.

To summarize, mirabegron seems to provide a similar efficacy as that of the antimuscarinic drugs with a clearly lower rate of dry mouth and constipation. The low incidence of uncomfortable side effects for the patient may make this the drug of choice in patients who have previously suffered from dry mouth and/or constipation and/or who are currently being treated with antimuscarinics but are unable to tolerate them [4].

If symptom control is not adequate with antimuscarinic treatment or the side effects are intolerable, along with regulating the dose, changing to a different antimuscarinic may be a suitable alternative [4]. There are various observational studies on this topic, where unsatisfied patients treated with oxybutynin [58, 59] and tolterodine [58, 60, 61] showed greater effectiveness and/or greater tolerance with solifenacin [59, 60], fesoterodine [61] or darifenacin [58]. Also, these patients could also change to a  $\beta_3$ -adrenergic receptor antagonist such as mirabegron, with an efficacy profile similar to that of the antimuscarinic drugs but with less side effects.

The combination therapy with mirabegron and solifenacin has been evaluated previously [62]. Through a randomized, double-blind, dose-ranging, phase 2 study (called 'SYMPHONY'), it was observed that different combination therapies, mirabegron 25 and 50 mg and solifenacin 2.5, 5 and 10 mg, show significant improvements over monotherapy, solifenacin 5 mg, in relation to the mean volume voided, number of micturitions per 24 h, incontinence episodes per 24 h and urgency episodes per 24 h. All treatments were well tolerated and concordant with the known safety profile of mirabegron and solifenacin monotherapy. No dose-related trends in blood pressure, pulse rate, post-void residual volume or laboratory or ECG parameters were observed between groups, although the incidence of constipation was slightly increased with combination therapy. The lack of supra-additive effects on safety parameters demonstrated that the mild pharmacokinetic interaction between mirabegron and solifenacin that was recently described [63] did not appear to be clinically relevant. So, the combination of mirabegron and solifenacin may provide an attractive therapeutic approach to maximize efficacy and minimize the side effect burden [62].

#### 4. Botulinum toxin

Botulinum toxin is a presynaptic neuromuscular blocker that induces a selective and reversible muscle weakness that lasts up to 6 months. Botulinum toxin exercises its paralyzing effect by inhibiting the release of acetylcholine from the motor nerve to the neuromuscular junction.

It also decreases the afferent signals from the muscle spindles, which leads to it directly decreasing nerve activity that produces spasticity [64, 65].

The toxin marketed in Europe is onabotulinum toxin A (onabotA; BOTOX®), which is used at a dose of 100 IU dissolved in 10 ml of saline solution and injected in 20 spots on the bladder wall (0.5 ml per puncture site), over the trigone. It is indicated for the treatment of OAB with persistent or refractory urinary urgency in both sexes, in spite of the scarce number of male patients included in pre-marketing trials [66, 67]. Other doses of onabotA and other formulations of botulinum toxin A, abobotulinum toxin A and incobotulinum toxin A, have not been licensed for use in urinary urgency. Repeated injections are effective, with no decreased efficacy with repeated treatment (LE 3), but the percentage of patients who abandon treatment is high (EL 2). The most important side effects include episodes of lower urinary tract infection and increased post-urination and post-voiding volume that may require the intermittent use of a bladder catheter [68].

By studying the effect of a staggered dose, it has been established that the ideal dose of onabotA is 100 IU. The effectiveness of onabotA was shown in two randomized (1:1) phase III trials with a total of 1105 incontinent patients with OAB whose symptoms were not previously controlled with antimuscarinic treatment. In these studies, at the beginning, the population had an average of more than five episodes of urgent urinary incontinence (UUI), around 12 urinations per day and a scarce post-voiding volume. Twelve weeks after the endoscopic injection of onabotA, the episodes of UUI were reduced by half in treated patients, and to more than two, the number of urinations per day, with a total of 22.9% of patients completely dry, compared with 6.5% of the group that received injections of saline solution (EL 1a). Also, the patients' quality of life was substantially improved in the group treated with onabotA compared to the control group (EL 1a) [69]. On the other hand, the cohort studies have demonstrated the effectiveness of the injections in the bladder wall of onabotA in elderly patients [70], although the success rate was lower and the post-voiding volume was greater (>150 ml) (EL 3).

One recent clinical trial compared the injection of 100 IU of onabotA compared with solifenacin and showed similar improvement in both groups regarding UUI after 6 months [71]. The patients who received onabotA were more inclined to resolution of the UUI (27% vs. 13%,  $p$  0.003) (EL 1a), but with greater rates of urinary retention in the first 2 months (5% vs. 0%) and urinary tract infection (33% vs. 13%). The patients who received solifenacin were more prone to suffer dry mouth.

In summary, offering endoscopic injections in the bladder wall with onabotulinum toxin A (100 U) in patients with refractory UUI after treatment with antimuscarinics (GR A) is recommended. The patients should be informed of the limited duration of the response, the risk of urinary tract infection and the possible need for posterior self-catheterizations (GR A).

## 5. Sacral nerve stimulation

Nerve stimulation by means of the electrical stimulation of the sacral nerve roots is currently an accepted therapeutic alternative to treat chronic urinary dysfunction when other more conservative options have failed. The development of nerve stimulation techniques has provided

a more physiologic and functional vision of functional disorders of the lower urinary tract by enabling the application of electric impulses that modify the behaviour of a specific affected neuronal system.

According to the Federal Drug Administration (FDA), the indications for sacral nerve stimulation are as follows:

- UUI, due to idiopathic, post-surgical non-obstructive hyperactivity bladder overactivity, associated with faecal incontinence or urethral overactivity.
- Voiding dysfunction, due to lack of contractility of the detrusor muscle, absence of relaxation of the pelvic floor or Fowler's syndrome.
- Frequency-urgency syndrome associated or not with pelvic pain, sensorial hyperactivity or chronic cystopathies.
- Interstitial cystitis and chronic urinary dysfunction from a neurological cause, spinal cord lesions, bladder sphincter dyssynergia and stable multiple sclerosis.

Although the mechanism of action of sacral nerve stimulation is yet to be completely established, it is known that the stimulation of the sacral nerves regulates the function of the detrusor muscle and the external urinary sphincter through the inhibition or disinhibiting of the ventral inter-neurons, modulating the sacral-pontine reflexes that control urination. This is regulated through the efferent type A- $\beta$ - and A- $\beta$ -somatic myelinated fibres that transmit the sensorial impulses from the metameres of the S2–S4 sacral roots [72–74].

Adequate evaluation of the patient is essential before taking into consideration the use of an implant to initiate nerve stimulation, with a basic neurourological examination and a urodynamic evaluation including a flowmetry, cystomanometry and electromyography of the surface of the perineum. This study should be performed before starting treatment, during the temporary stimulation test and after the definitive insertion of the implant.

The nerve stimulation implant is inserted in two surgical times, with the establishment of three phases in the initiation of the sacral nerve stimulation:

1. Evaluation of the sacral nerves. The percutaneous insertion is carried out with fluoroscopic control using a stimulation electrode in the sacral foramen next to the sacral nerve, normally in S3. In the past, an electrode that was connected to an external stimuli generator with a cable was used for 5–7 days. Currently, a tined electrode is used that allows for a longer test phase as it avoids mobilization of the system itself [75]. At this point, the integrity of the somatic motor and sensorial fibres of the sacral roots is evaluated. The motor response in S3 is the contraction of the pelvic floor as well as plantar flexion of the first toe of the foot. The sensitive response is a tingling sensation in the perineum and external genitals.
2. Sub-chronic phase or test phase. In this phase, the therapeutic effect of the stimulation is determined through the daily urination of the patient during the stimulation. The patients who are candidates for the second surgical time for completion of the

insertion of the pulse generator are those in which the UUI is reduced by more than 50% during the test phase [76]. It has been found that the use of the serrated electrode in the initial implant increases the number of patients who end up with the definitive implant (EL 4).

3. **Definitive implant.** This consists of the percutaneous insertion of an electrode with four stimulation points that is implanted over the sacrum, fixing it to the periosteum and connecting it to the impulse generator placed in a subcutaneous pocket in the superior-external quadrant of the gluteus, or in the lower abdominal region [75]. The intervention is performed under general anaesthesia using short-acting muscle relaxants to reproduce the responses obtained in the evaluation of the sacral roots. The programming is performed within the first 24 h after the surgery using a telemetric programmer and selecting the individualized electric stimulation parameters of amplitude, frequency, pulse length and polarity. Also, the patient is given a hand programmer to activate or deactivate the generator and adjust the amplitude if needed.

All of the relevant randomized studies are affected by the limitation that neither the evaluators nor the patients were blinded for the active treatment decision, as all of the patients recruited for the implant had to have responded in the test phase prior to randomization.

Three clinical trials have been published regarding sacral nerve stimulation. One of them compared the implant with a control group that continued with medical treatment and delayed the implant by 6 months. Fifty per cent of the patients who were initially implanted experienced improvement of more than 90% in their UUI after 6 months compared to 1.6% of the control group [77]. Another clinical trial produced similar results; however, the effect on quality of life, evaluated using the SF-36 questionnaire, was not conclusive, with differences between groups in only one of the eight domains [78].

Reviewing a total of 17 studies of a series of cases of patient with UUI treated in the beginnings of the use of sacral nerve stimulation [79], we obtained the following results: after a follow-up period of 1–3 years, approximately 50% of the patients experienced a reduction of more than 90% in their urinary urgency, 25% showed an improvement of 50–90% and another 25% improved in less than 50%. In studies with a follow-up period of at least 4 years, the continued effectiveness of the treatment was observed, with an improvement of more than 50% of the initial symptoms in approximately 50% of the patients and a sustained resolution of symptoms in 15% (LE 3) [80, 81]. The resolution rate of UUI was 15% [81].

The incidence of adverse effects in relation with the implant is 50% [80, 81]. The most frequent adverse effect is the presence of pain at the site where the impulse generator is implanted (15.3%) followed by newly appearing pain (9%) and the migration of the electrode (8.4%) with the respective stimulation of undesired fibres and lack of effectiveness. These effects require surgical revision in 33–41% of cases [80, 81].

We can conclude that sacral nerve stimulation is more effective than maintaining conservative treatment to cure UUI (EL 1b). If available, sacral nerve stimulation should be offered to patients with UUI refractory to conservative therapies.

## 6. Posterior tibial nerve stimulation

Electro-stimulation is included within the conservative therapies used to treat OAB by acting on the afferent nerves of the pelvic floor. When conducting a systematic review, two clinical trials compared the action of the electro-stimulation with oxybutynin in patients with UUI, showing a similar efficacy between the two treatments [82].

Posterior tibial nerve stimulation is performed using a neuromodulator that utilizes the peroneal nerve for afferent access to the S3 spinal cord region. The mechanism that makes the neuromodulation of the bladder-urethra reflexes possible is based on the fact that the nerve fibres of the posterior tibial region share sensitive inputs with the S3 root. Current indications include overactive bladder with or without UUI and chronic pelvic pain.

The stimulation can be done in a percutaneous manner with a thin 34 G needle inserted just below the medial malleolus of the ankle (P-PTNS), although it can also be done in a transcutaneous manner (T-PTNS). Adequate stimulation applied using the neuromodulator, regarding the frequency, intensity and length of the impulses, is demonstrated when the big toe is observed flexing or the remaining toes show extension or flexion. The normal treatment scheme consists of 12 weekly sessions of 30 min.

Regarding P-PTNS and based on two clinical trials [83, 84], the results in women with refractory OAB are consistent. The results suggest that this treatment improves UUI in women who have previously received treatment with antimuscarinics that was not effective or tolerable (EL 2b) (GR B). However, there is not enough evidence to confirm that P-PTNS cures UUI or offers a long-term solution for symptoms of OAB as the therapeutic effects dissipate when the treatment ends. On the other hand, P-PTNS does not seem to be more effective than tolterodine in women (EL 1b) [85]. In men, there is no sufficient evidence to extract conclusions about its effectiveness.

Regarding T-PTNS, a small clinical trial compared T-PTNS together with standard treatment (rehabilitation of the pelvic floor and bladder training) with standard treatment used alone in elderly women. The group that received T-PTNS showed more improvement of symptoms at the end of treatment [86]. However, the evidence on T-PTNS is limited (EL 2a).

The side effects associated with this technique are infrequent and mild. The most common include cases of a painful feeling and transitory bleeding or bruising at the puncture site [87].

In routine clinical practice, finding patients on second-line (drugs) or even third-line treatment (botulinum toxin, PTNS or sacral nerve stimulation) that have not been correctly evaluated before starting said treatment, or that have never tried previous behaviour therapies, is common. Finding patients who have had little success with pharmacological treatment or with different combined simultaneous treatments without any clear evidence on the individual efficacy of each therapy is also common. Patients must be reminded about the importance of persisting over time with a new treatment (from 4 to 8 weeks if the treatment is pharmacological and from 8 to 12 weeks for behavioural therapies) to be able to clearly evaluate the efficacy and associated side effects before trying another line of treatment [4].

## 7. Surgical treatments

Surgical treatment is reserved when all the non-invasive therapies have not been effective. The first option is usually the augmentation cystoplasty, where a detubularized segment of bowel is inserted into the bivalved bladder wall. The distal ileum is the bowel segment most often used but any bowel segment can be used if it has the appropriate mesenteric length [88]. There are no randomized control trials comparing bladder augmentation to other treatments for patients with OAB. Most often, bladder augmentation is used to correct neurogenic OAB or small-capacity, low-compliant, bladders caused by fibrosis, tuberculosis, radiation or chronic infection. The largest case series of bladder augmentation in a mixed population of idiopathic and neurogenic OAB included 51 women [89], where only 53% were continent and satisfied with the surgery, whereas 25% had occasional leaks and 18% continued to have disabling OAB. It seems that the results for patients with idiopathic OAB (58%) seemed to be less satisfactory than for patients with neurogenic OAB (90%). Adverse effects were common and many patients may require clean intermittent self-catheterization to obtain adequate bladder emptying.

Another option is the detrusor myectomy. This technique aims to increase bladder capacity and reduce storage pressures by incising or excising a portion of the detrusor muscle, to create a pseudodiverticulum. Two case series [90, 91], in adult patients with idiopathic and neurogenic bladder dysfunction demonstrated poor long-term results caused by fibrosis of this pseudodiverticulum. This technique is rarely used nowadays.

As the last alternative, urinary diversion remains a reconstructive option for patients who decline repeated surgery for OAB. However, there are no studies that have specifically examined this technique in the treatment of non-neurogenic OAB [88].

## 8. Future directions

Recently, studies have been conducted to find a biomarker for OAB to broaden the pathophysiological understanding of OAB. The biomarkers studied till today's date are the nerve growth factor [92], the corticotropin-releasing factor [93], the prostaglandins [94] and inflammatory factors such as the C-reactive protein [95]. Another approach is to use high-yield DNA array profiles to identify the expression of specific genes involved in OAB [96]; however, this approach is not directed and may offer too many non-specific candidate biomarkers.

The sensorial or bladder and urethral input markers have also been studied using various methods. It remains unknown whether an ideal sensorial test for the lower urinary tract would have a clinical impact on the evaluation and management of OAB [97–99]. A recent review highlights the importance of the interaction of the bladder urothelium, the sub-urothelium and the interstitial cells with afferent sensorial fibres [100]. The urothelium is defined as a cellular compartment for sensorial transduction with urothelial cells capable of releasing and responding to specific neurotransmitters, and communicating with the afferent nerve endings inside of the urothelium [101]. The compartments of the sub-urothelium and the

detrusor muscle seem to contain pacemaker-like cells, similar to the intestinal interstitial cells of Cajal, that modulate bladder contractility, rhythmicity and overactivity [102].

Both lines of research related with the basic science and translational research, once developed, will provide a greater understanding of the pathophysiological mechanisms of OAB, which would be of great help to find new therapeutic targets for the treatment of OAB syndrome.

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