
Botulinum toxin A versus percutaneous tibial
nerve stimulation in idiopathic overactive
bladder. A randomized trial.

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“Imbuto y’amahirwe yera ku giti cy’umuruho.”

The fruit of luck grows from the tree of effort.

(Proverb)

I want to express my gratitude to the Urology department of Hospital Josep Trueta,

for their warm welcome, patience and dedication.

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GLOSSARY

- BPH: Benign prostate hyperplasia
- BTX-A: Botulinum toxin A
- CISC: Clean intermittent self-catheterization
- HRQL: Health related quality of life
- HSC: Santa Caterina Hospital
- HUDJT: Doctor Josep Trueta Universitary Hospital
- HUGTIP: Germans Trias I Pujol Universitary Hospital
- ICS: International Continence Society
- OAB: Overactive bladder
- PTNS: posterior tibial nerve stimulation
- PVR: Post-voiding residual volume
- SNS: Sacral neuromodulation
- SUI: Stress urinary incontinence
- UTI: Urinary tract infection
- UUI: Urgency urinary incontinence

ABSTRACT

Botulinum toxin A versus percutaneous tibial nerve stimulation in idiopathic overactive bladder. A randomized trial.

The uprising number of people suffering from overactive bladder, has made evident the need of new treatments to tackle the condition in patients refractory to oral therapies. The development of third line therapies for overactive bladder, has given a lot of patients an opportunity to gain quality of life. However, these treatments can associate severe side effects, which compels us to be cautious with its prescription.

This study compares the efficacy of intradetrusor Botox[®] injections and percutaneous tibial nerve stimulation measured in quality of life. In addition, an analysis of the security, convenience and cost-effective is included.

We designed multicenter clinical trial, where sequential sampling will be used to enroll a total of 234 individuals.

By randomization, we will allocate the subjects in a group for botulinum toxin or a group for tibial nerve stimulation. The collaboration of seven hospitals will be required to perform this evaluation.

Our principal endpoint will be the punctuation in a disease-specific questionnaire after 12 months. The follow up will be conducted at 3, 6, 9 and 12 months with urodynamic measures, symptom reports and quality of life questionnaire.

Keywords: overactive bladder, botulinum toxin, overactive detrusor, posterior tibial nerve stimulation, randomized trial, health related quality of life.

INTRODUCTION

What is overactive bladder?

International Continence Society states that urinary incontinence is *"the complaint of any involuntary loss of urine"* (1). It can be classified by its pathophysiology, signs and urodynamic finding in 3 types:

Table 1. Types of urinary incontinence. Adapted(2)

TYPE	PATHOPHYSIOLOGY	SYMPTOMS
URGE	Detrusor overactivity Neurologic disorders Spinal cord injury	Loss of urine accompanied or preceded by strong desire to void; may be accompanied by frequency and nocturia.
STRESS	Increased urethral mobility Intrinsic sphincter dysfunction	Loss of urine with physical exertion or increases in intra-abdominal pressure (e.g., sneezing, coughing, laughing)
MIXED	Mixed etiology	Combination of urge and stress symptoms

Overactive bladder is a syndrome consisting in urgency, often accompanied by nocturia and frequency, with or without incontinence, in the absence of urinary tract infection or other obvious pathology (3). Although it is common to use these terms indifferently, overactive bladder is not the same as overactive detrusor. The second condition is demonstrated on the urodynamic study by the appearance of involuntary detrusor contractions, during the filling phase, or by a single and tonic contraction.

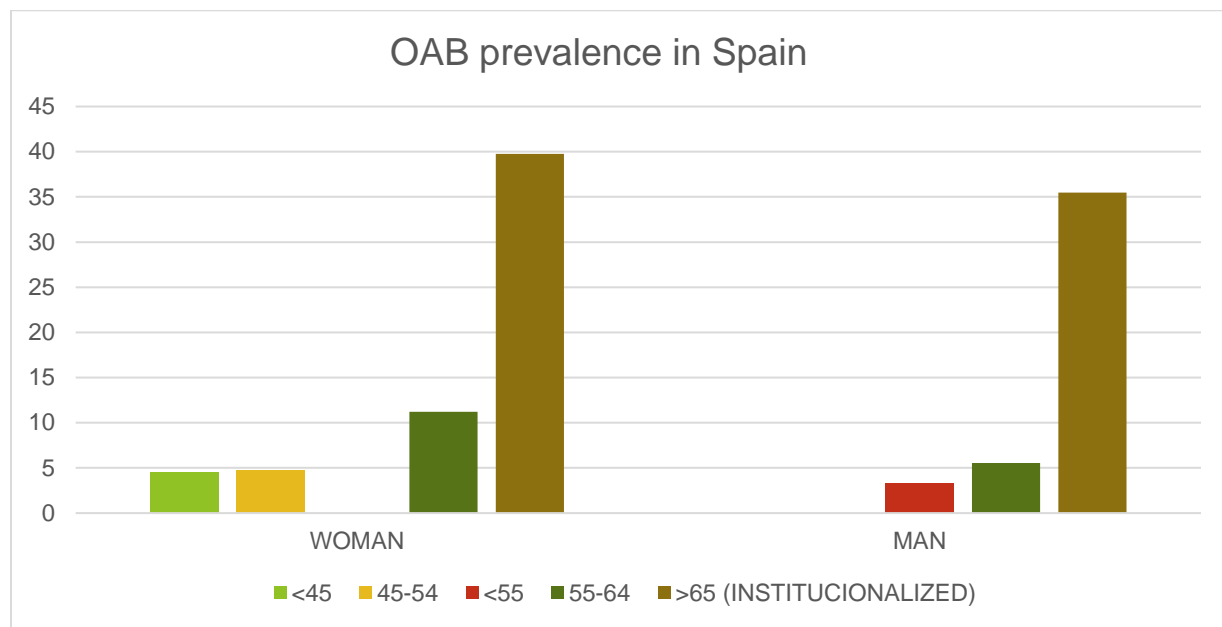
Epidemiology

OAB is a syndrome with a great impact worldwide. Because it is usually underreported, the actual prevalence is probably greater than the one published in most articles. We estimate 400 million people around the world to present symptoms. Most of the reviews report a prevalence between 10% and 20%. In Spain, the EPICC study states that 6% of women aged 25 to 65 suffers from OAB, and this figures rise to 45% in women over 65 years old when they are institutionalized. In

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male population, they observed a prevalence of 4.6% in subjects aged 50-year-old or more, and 35% in patients institutionalized over 65. The disparity observed between men and women is significant only at advanced ages. Women develop urgency symptoms at a younger age, probably because of their anatomic features. Thus, overall, the prevalence is similar between male and female patients(4,5).

Figure 1. OAB Prevalence in Spain. Adapted (5).



Risk factors

There is some controversy over the involvement of the following risk factors in OAB's etiology:

Table 2. Risk factors Adapted. (5,6)

CONSTITUTIVE FACTORS	NON CONSTITUTE FACTORS	
<ul style="list-style-type: none"> • ADVANCED AGE • FEMALE SEX • AFRICAN-AMERICAN ETHNICITY 	<p>REPRODUCTIVE FACTORS</p> <p>Pregnancy, parity and vaginal delivery. Local Estrogens (protective factor)</p>	
	<p>PELVIC SURGERY COMORBIDITIES</p> <p>Oncologic hysterectomy, prolapse and stress incontinence correction BPH, pelvic prolapse, mental disorders, sexual, physical and emotional abuses in the past, diabetes, asthma, hypertension, heart disease, constipation, cystitis, neurologic disorders, osteoporosis, erectile dysfunction...</p>	
	<p>HABITS-LIFE STYLE</p> <p>Carbonated drinks, caffeine, alcohol and tobacco</p>	

Pathophysiology

- Neurophysiologic micturition sequence (Annex 1)

-**Filling phase:** A vesical distention increase generates proprioceptive stimuli that activate the sacral center, which secondarily intensifies vesical contractions. Proprioceptive afferences travel to the pontine nucleus, whose response is modulated by the cortex. When micturition is not appropriate, there is an inhibition of the pontine and sacral nucleus. As a result, the parasympathetic neurons responsible for the bladder contraction are inhibited, and the striate sphincter remains contracted. This mechanism is responsible for continence.

-**Voiding phase:** If the situation is adequate to urinate, by voluntary decision, abdominal pressure rises and pelvic pressure reduces, decreasing the contraction proprioceptive stimuli that were exerting an inhibitory effect over sacral and pontine nuclei.

In parallel, the exiting of urine through the urethra collaborates in the transformation of the reflex tone into active contractions of detrusor. Thus, voiding occurs independently of its fibers lengths reduction.

Simultaneously, the positive activation of both nuclei, sacral and pontine, increases the detrusor contraction and inhibits the thoracic lumbar center (a natural inhibitor of the detrusor muscle and a positive stimulator of the smooth urethral sphincter), which allows the continuous relaxation of the striated sphincter.

Through the combination of these mechanisms, micturition occurs.

-**Transition to continence phase:** There is a voluntary contraction of the pelvic floor that results in two things. Firstly, elongation of the pelvic floor muscles ceases, resulting in a diminution of the reflex tonus of the pontine and sacral nuclei. At the same time, the absence of urine flow in the urethra reduces the detrusor contraction and reactivates the thoracic lumbar center (7).

- Neurotransmitters

The parasympathetic neurotransmission acts through cholinergic muscarinic receptors. The activation of these receptors, induces a detrusor contraction. These receptors can be found all over the bladder, but with less incidence in the trigone

and bladder neck. The sympathetic, by mediation of the noradrenergic system has two opposite functions. Alfa-adrenergic receptors participate in contraction, but due to their preferential location in the trigone and bladder neck, they have a pro-continenence function. Reversely, beta-adrenergic receptors, with a predominance in the detrusor, help to relax the muscle fibers(7).

Table3. Micturition neurologic control(7).

AREA	NEUROTRANSMITTER	NERVES	MEDULAR LEVEL
BLADDER BODY	Muscarinic + β -adrenergic	Pelvic n.	S2-S4 (Parasympathetic nucleus)
TRIGONE +BLADDER NECK	α -adrenergic	Hypogastric n.	T10-L1 (Sympathetic nucleus)
PELVIC FLOOR	Muscarinic	Pudendal n.	S3-S4 (Pudendal nucleus) somatic

- OAB pathophysiology

The whole mechanism causing OAB is still unclear. Three main factors have been proposed:

-**Myogenic factor:** Altered myocytes create an increased and unstable intravesical pressure, which can damage some cells due to ischemia. The resulting tissular changes enhance the excitability and electric coupling between cells.

-**Neurogenic factor:** Alteration on central inhibitory pathways in the brain and sensitization of peripheral afferent terminals in the detrusor release primitive voiding reflexes, triggering detrusor overactivity. I.e.: multiple sclerosis, Parkinson's disease, cerebrovascular events...

-**Urotheliogenic factor:** Functional urothelium sends neurotransmitters to regulate the detrusor activity in presence of thermal, mechanical and chemical stimuli. Dysfunctional urothelium increases de bladder excitability. Vaginal and urothelial mucosa collaborate to the loss of urethral closure, facilitating the incontinence in the presence of uninhibited contractions.

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Metabolic derangement, bladder outlet obstruction and inflammation can increase the excitability of nerve and detrusor muscle and alter the sensory and barrier functions of the urothelium. The true cause of OAB and detrusor overactivity could be diverse in different individuals, including the above and possibly other undescribed mechanisms (5,8).

Idiopathic overactive bladder is by definition not related to any of the following causes of secondary disease (9).

Table 4. Causes of secondary OAB. Adaptation (9,10)

UROLOGIC	PERIPHERIC ORGANS	DISTANT ORGANS	PHARMACOLOGIC
<u>Infectious-irritative:</u> -UTI -Neoplasms -Foreign bodies -Post-radiation changes <u>Bladder outlet obstruction:</u> -Organic: BPH, Urethral stenosis -Functional obstruction	<u>Feminine genitalia</u> -Pelvic inflammatory disease -Endometriosis -Pelvic organ prolapse <u>Intestinal</u> -Diverticulitis -Inflammatory bowel disease -Rectal carcinoma <u>Iatrogenic nerve lesion</u>	<u>Neurologic disease:</u> -Spinal injury -Multiple sclerosis -Parkinson disease -Infectious neuropathy -Diabetic neuropathy -Cerebrovascular diseases <u>Psychosomatic</u>	<u>Parasympathomimetic drugs</u> <u>Other drugs.</u>

Clinical findings

There are four major symptoms defining the syndrome.

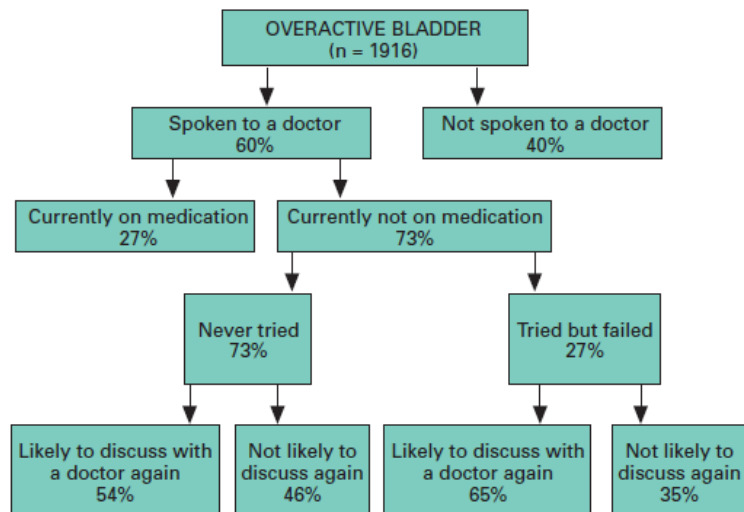
- **Urinary urgency:** Complaint of a sudden desire to urinate which is difficult to defer.
- **Frequency:** More than seven micturition episodes during waking hour.
- **Nocturia:** Sleep interruption because of the need to void.
- **Urgency urinary incontinence:** Involuntary leakage of urine associated with a sudden compelling desire to void.

Urgency with or without UUI must be present for the diagnosis of OAB(10).

It is remarkable, that the only presence of symptoms is not as important as its interference on the patient's life. OAB may be further complicated with infections, erectile dysfunction, UTI, sleep disorders, accidental falls and as a consequence bone fractures(5). Concern about when urgency may appear, prompts the elaboration of coping mechanisms to deal with the condition like toilet mapping, reduce liquid intake or going out of home less often.

Despite the effect of these symptoms, many affected individuals fail to report them. This could be possible explained by self-embarrassment or ignorance of the availability of specific treatments(11). Per the results published by Milsom, only 60% survey participants had notified their physicians. And near 50% of the group had never started a treatment.

Figure 2. Prevalence of medical consultation in OAB(11).



Diagnosis

The diagnosis when OAB is suspected stands over two big pillars: the confirmation of the symptomatology, and the exclusion of possible secondary causes with different prognostic implications.

- Anamnesis

Presence of symptoms is enough to diagnose an OAB, but features like onset, exacerbation and remissions also need to be interrogated. An exhaustive search for contraindications for any of the therapeutic measures available must be performed (10). I.e.: severe coagulation disorders are not always compatible with Botox injections, and anticholinergics have a negative effect over cognitive function in frail and old patients. A case of mixed incontinence should be suspected when the patient relates Valsalva related leakage, complex obstetric history... (5,6)

- **Voiding diaries**

3 days voiding diaries support the diagnosis of OAB, by quantifying the symptom. In addition, they can serve as monitor responses, and raise self-awareness necessary for the behavioural therapy (1,10). (Annex 2)

- **Physical examination**

A close abdominopelvic examination will detect bladder distension, suggestive of urinary retention, and pelvic tenderness or masses, which cause irritating and obstructive symptoms. A rectal-genitourinary exam is needed to exclude prostatic or pelvic floor pathology, atrophic vaginitis or urethral stenosis, and detect perineal skin rash. In order to diagnose stress component in the incontinence episodes, a leakage of urine with Valsalva must be observed in the examination(1). The doctor should also assess perineal sensation and rectal sphincter tone to evaluate pelvic floor tone and potential ability to perform pelvic floor exercises. A quick neurological examination can be considered under suspicion of underlying neurological disorder. Furthermore, a MMSE test determinates the cognitive status, and helps to fix an expectative for the treatment (1,10).

Clinical findings that require a urgent referral to an urologist consult are: associated pain, hematuria, history of recurrent UTI, pelvic surgery or radiotherapy, constant leakage suggesting a fistula, pelvic mass, symptomatic prolapse or grade 3, voiding difficulty or suspected neurological disease (1).

- **Symptom questionnaires**

Validated questionnaires quantify bladder related symptoms, and the resulting degree of disturbance. Numerous instruments have been developed, however, at the moment none of them fulfills all the requirements for assessment(1,5,12). The *Overactive Bladder Questionnaire-Short Form* is a self-administered Patient Related Outcome. It has two scales that evaluate symptom bother and HRQL and have demonstrated good psychometric properties. Although

it was not reported initially by the developers, an internal structure composed by three dimensions (coping, sleep and social) can be identified.

- **Laboratory tests**

A urinalysis with a microscopic study is needed to rule out infection, microhematuria or sterile pyuria. (10,12)

- **Urodynamics**

Most urodynamic parameters show variability within the same session and over time, and all together they have doubtful efficacy predicting outcome after therapy. For this reason, urodynamic is often performed only prior to invasive treatment (6) . A complete urodynamic test must include the following examinations (12):

-**Uroflowmetry:** Uroflowmetry is a flow rate measure of the external urinary stream, expressed as volume per unit time. The report contains, the maximum flow rate (Q_{Max}) and the total volume voided.

-**Post-voiding residual volume:** PVR should be always assessed in patients with obstructive symptoms, history of incontinence, prostatic surgery neurologic diagnoses and other situations, at clinician discretion. When ultrasound scanner is not available, urethral catheterization may be useful instead.

-**Cystometry:** While continuously filling the bladder through a catheter, intravesical pressure(p_{ves}) and abdominal pressure(p_{abd}) will be registered. Detrusor pressure(p_{det}) can be calculated as the difference between p_{ves} and p_{abd} . Cystometry ends with involuntary loss or 'permission to void'. Maximum capacity is when the patient experiences a pain that deters continued filling, normally with values ranging between 400 and 600 ml. The results are considered abnormal when we detect premature desires to void, reduced maximum bladder capacity, pain, urgency or involuntary detrusor contractions are demonstrated. (Any increase on P_{det} greater than $15\text{cmH}_2\text{O}$, or under $15\text{cmH}_2\text{O}$, but associated with urgency). This last situation, is known as hyperactive detrusor, and it can be present in up to 60% of OAB patients (7,14).

In contrast, underactive bladder is characterized by an abnormally low or absent voiding pressure associated with poor urine flow rate(14).

-Pressure-flow study: The intravesical and abdominal pressures are measured, from the moment of 'permission to void' while uroflowmetry is performed with a catheter in place(13,14).

- **Other complementary tests:**

In patients with increased intradetrusor pressures, anatomical bladder changes and urine reflux are common. This reflux can condition upper tract damage. For these situations, a renal ultrasound or a cystoscopy can be recommended. Complications of this kind are more frequent in neurogenic bladder, therefore, imaging won't be determinant for the evaluation of our patients (1,12).

Treatment

Most of the available treatments for OAB can only reduce the symptoms. Treatment failure occurs when the patient does not have the desired change in the symptoms or is unable to tolerate the treatment due to adverse events. To prevent severe irreversible side effects, the patient will be offered first the less invasive measures among the more efficacious. It is critical for patients to have realistic expectations regarding outcomes and adverse events to optimize clinical effectiveness (12).

- **First line: Behavioral therapy**

-Life style modifications: Tobacco and caffeine withdrawal, with a moderate liquid intake reduction and weight loss, are linked with symptoms relief (15).

-Bladder training: Retraining pelvic mechanisms and central nervous system inhibits urge sensation between voids(2).

-Pelvic floor muscle exercises: The contraction of pelvic floor muscles has an inhibitory effect on the detrusor contraction(2,15)

Despite the good results provided by conservative measures, and the absence of notable side effects; their outcomes are very limited by the scarce therapeutic adherence(15).

Such gain is no significantly different from the effect of anticholinergic drugs. However, the addition of behavioral therapy to oral medication has demonstrated a significant decrease of the symptoms(12).

The addition of behavioral therapy to oral medication has demonstrated a significant decrease of the symptoms.

- **Second line: pharmacological treatment**

-**Anticholinergic agents:** These drugs inhibit non-voluntary detrusor contractions through their blockage of the muscarinic receptors. All of them have a similar profile of efficacy, and their differences are a consequence of their range of adverse effects and presentations(1,5). The systemic response to anticholinergic produces dry mouth, constipation, dry eyes, urinary retention, excessive sweating, cognitive disorders and rarely severe events like arrhythmias. Antimuscarinic agents can interfere with drugs commonly consumed by elderly patients if these have anticholinergic effects or the individuals present slow hepatic metabolism(15).

Only short-term rates of cure or improvement of UUI have been reported. The relative risk of curing UI in different trials, was found to rank between 1 and 2, moreover their tolerance can cause up to 50% premature discontinuations and after a year, only 20% of the patients continue the treatment (12,15). Subjects with more severe symptoms, on average, experience greater symptoms reduction(1,12).

-**Mirabegron:** Mirabegron acts stimulating bladder β_3 -adrenoceptors to relax the detrusor. This β -agonist reduces significantly frequency and incontinence, but has not demonstrated higher index of curation than placebo. The most common adverse events were hypertension, nasopharyngitis and UTI. Dry mouth, the most conditioning adverse effect with anticholinergic, had the same incidence than the placebo group. Similarly, their mechanism of action associates less cognitive disorders than antimuscarinics. (1)

- **Third line: Botulinum toxin**

Third line treatments must be prescribed by a specialist in urology, after a deep investigation on possible triggers of OAB.

This is because of their invasiveness, and because their adverse effects are often irreversible (12).

-Mechanism of action: BTX-A blocks the assembly of the presynaptic vesicles, interfering with the release of acetylcholine. This causes a full or partial paralysis that weakens the overactive muscle. Contrary to anticholinergic actions, Botox® has none, or very few system effects. Bladder biopsies demonstrated a downregulation of neuronal sensory receptors(16,17).

-Technique. All the procedure is carried out in an operating room or an endoscopy room. First, to confirm the normality of the bladder, a cystoscopic exploration must be performed. Then, local anesthesia with lidocaine will be administered. 100U BTX-A dissolved in 10 ml of saline are injected in 20 points of the bladder wall. It is recommended to avoid trigone area, as to diminish the risk of vesicoureteral reflux. (Annex 4)

-Efficacy: The relief of the symptoms can be noticed from the third day, with a progressive growth of the effects until the 6th month. Urodynamic measures and QoL follow a similar trend(18). Consecutively, the levels begin to decay, but remaining superior than the baseline at least for the first year. When the clinical benefit wears off, a new injection can be administered if 3 months or more have passed since previous treatment, and moderate-severe symptoms of OAB coexist with low PVR. Repeat injections maintain efficacy without increasing adverse events (19). Some patients develop antibodies against the toxin, that in high titers can condition the response to further injections (12).

Overall, guidelines point out an efficacy of 22.9% versus 6.5% in placebo for continence treatment, and a relative risk of 5.13 for frequency reduction(10,12).

-Side effects Botulinum toxin injections associates frequently the following complications: pain, haematuria and UTI, related to the cystoscopy intervention; increased PVR and urinary retention(10). Urinary retention becomes relevant when requires from CISC, which happens approximately 6-20% of the times (1) being this the main reasons to discontinue successful BTX-A injections. Auto limited systemic side effects like dry mouth, dysphagia, impaired vision, and muscular weakness can appear after treatment(12,20).

BTX-A is contraindicated in the following circumstances: pregnancy, breastfeeding, disease of the motor plaque, antibiotics that increase the toxin effect (aminoglycosids, tetracyclines, lincosamines and polymixine) , severe respiratory disease and botulinum toxin hypersensitivity. If the patient needs anticoagulation or antiaggregation, the indication of the injection will depend on the thrombotic risk(16,18). Furthermore, botulinum toxin must be only counselled in subjects prone to accept clean intermittent self-catheterization(12).

- **Third line: Tibial nerve stimulation**

-**Mechanism of action:** The tibial nerve or sciatic popliteus intern is a sensory-motor nerve, that transports axons passing through the L4–S3 roots.

Mechanism of action is not yet fully understood, but apparently, the peripheric stimulation, travels to the sacral micturition center via the sacral plexus (1)In consequence, the stimuli produces neuromodulator effects, such as increasing inhibitory tone, decreasing awareness of abnormal stimuli, and reorganization of the neuronal system, resulting in restoration of normal reflexes(21). PTNS direct effect over the pontine micturition center may enhance these outcomes.

Repeated short duration stimulation of the tibial nerve induces a persistent therapeutic effect, and this justifies the 12 treatment sessions scheme (22).

-**Technique:** In an office setting, a 34-gauge needle electrode must be inserted near the posterior tibial nerve, that is 5 cm cephalic to the medial malleolus and posterior to the tibia. A second neutral electrode is placed in the surface, medial to calcaneus. An electrical stimulation at 0.5-10 mA, pulse of 200 ms, and 20Hz is performed initially for 30 minutes, one time a week, for a minimum of 12 weeks. (Annex 4)

- **Efficacy:** Its efficacy contrasted to sham procedure has been sufficiently demonstrated in the SUmIT trial. This essay obtained after 12 weeks significant improvements in bladder diaries, patient reported overall symptoms and condition specific scores (OAB-q SF) (23). Sustained efficacy upon the completion of the initial protocol has proved to last between 6 months and 3 years. However, some guidelines disagree with this statement, and consider that PTNS can not sustain

the effect, and therefore does not cure OAB(10,19). In the event of recurrence, maintenance protocols can be applied, usually reducing the interval between sessions until only one session per month is necessary(12,15). Because PTNS and pharmacologic therapy have different mechanisms of action, they can be used concurrently without fear to increase the rate of adverse events (17).

-**Side effects:** Less than a 5% of the patients present adverse effects. Among these, the more common are pain at the puncture site, local bleeding, bruising, transient paresthesia and excoriation. None of these complications however is severe.

PTNS is contraindicated in pregnant women, pacemaker or implanted defibrillator users, and patients with nerve damage that could have impact on tibial nerve or pelvic floor function.

- **Third line: Sacral neuromodulation and other surgical options**

Good long-term results have been demonstrated with SNS, but it requires a permanent surgical implant with up to a 40% complication rate in 5 years (23) as infections, lead migration or transient electrical shock . The use of more complex surgical procedures like enterocystoplasty is uncommon in idiopathic OAB due to its inconsistent long-term results and elevated morbidity(1) .

JUSTIFICATION

Overactive bladder is a condition with high prevalence rate, very common in the elder and/or multi-pathological patients. Its importance relies on the loss of life quality experienced by the individuals. The leaks and the fear to urinate in a social environment, can lead these patients to isolation, depression and anxiety. Economic burden must be taken into account, as cost due to absenteeism, all together with absorbent material and the treatment for complications represent a major issue for families and health systems(5).

Studies have proved that many of the drugs used today fail after short periods of time, or never reach significant rates of remission(11). Considering that the life expectancy is higher every time (24), partly because of the availability of treatments for chronic conditions; the upcoming generations will suffer from more side effects and drug interactions to classic OAB drugs. Furthermore, when PTNS or BTX-A are not suitable or successful, only invasive measures like surgery or SNS can be offered. Hence, a cautious evaluation of the situation must be done in order to achieve the best outcomes possible with third line therapies, and avoid aggressive treatments(1,12).

Our project intends to give an answer to those patients who having tried the available conservative treatments remain symptomatic. We also try to minimize the side effects and the expenses related to unfruitful therapies.

We have at our disposition the equipment and trained personnel to provide these two treatment strategies, but we miss the scientific evidence necessary to recommend one technique over the other, when inclusion criteria are met for both.

The guidelines and other publications reviewed are unanimous in the diagnosis and conservative measures for the disease. However, they have failed to shed light over this problem, leaving the decision for the clinician and the patient based on their preferences. Among the comparisons between PTNS and BTX-A that we found, the only articles that state preference for one of the options, differ in their conclusions. Not only that, many times the source of this recommendations were observational studies.(1,19,25) Because of the absence of quality clinical trials to sustain the recommendations, we decided to perform one ourselves. With this trial, our team aims to start clarifying the decision-

making algorithm for refractory OAB.¹ The outcomes will outline a comparison of the advantages and disadvantages of each technique. Consequently, physicians will be able to take decisions based on scientific evidence, guaranteeing an ideal approach for each patient, regardless of their hospital. This summarizes the justice principle of bioethics.

OBJECTIVE AND HYPOTESIS

Objective

The purpose of this study is to determinate whether intravesical onabotulinumtoxin A injections are more efficacious than posterior tibial nerve stimulation at reducing the symptoms and improving the quality of life. This efficacy is to be assessed in both gender adults with idiopathic overactive bladder refractory to first line drugs after 12 months of the intervention.

Secondary objectives:

- Compare the safety of these techniques, established by the proportion of patients developing side effects.
- Evaluate the adherence to the chosen option after 3, 6, 9 and 12 months.
- Determinate which technique is more cost-effective.

Hypothesis

Individuals under treatment with botulinum toxin A for idiopathic OAB show better HRQL than those undergoing PTNS.

METHODS

Study design

Our team intends to perform a controlled clinical trial. To provide the highest level of evidence, we will randomize our patients into two branches. Blinding is impossible for the patient or the doctor. To minimize the bias, an associate nurse will evaluate the outcomes in QoL, ignoring the treatment administered to each patient. Our biostatistician will be blinded as well. Because we require a great sample, multicentric coordination will be necessary. HUDJT, HSC, Palamós, Figueres,

¹Refractory OAB: Failure of appropriate behavioral therapy of sufficient length and at least one anti-muscarinic administered for 4 to 8 weeks(15).

Olot, Blanes and Germans Trias i Pujol hospitals will be involved in the project. The total length of the study will be of 3 years and 8 months.

Population of study

This trial aims to give an answer for adults suffering from idiopathic OAB who either are refractory or intolerant to pharmacological treatment. Our outcomes would ideally reflect the province response to these strategies.

Table 5 . Inclusion and exclusion criteria

INCLUSION CRITERIA	EXCLUSION CRITERIA
<ul style="list-style-type: none">- >18 y/o- Moderate-severe OAB²- Refractory OAB- >6 months since the diagnosis- Commitment to follow up- Accepting to perform catheterization if necessary	<ul style="list-style-type: none">- Previous treatment with BTX-A, PTNS or SNS- Fragility³- Contraindications for PTNS- Contraindications for BTX-A- Underactive detrusor- Post voiding volume >150 ml.- Botox administration for any indication disease in the last 3 months- Mixed incontinence- Signs of non-idiopathic OAB.

Sample

-**Sample size:** Accepting an alfa risk of 0.05 and a beta risk of 0.2, on the assumption that HRQL score has a standard deviation of 20 units, 180 individuals will be needed to observe a significant difference greater than or equal to 10 points. These calculations were made by using GRANMO calculator. We expect to lose 30% of the sample during the study, therefore, we will enrol a total of 234 patients. With an allocation rate of 1:1, each branch of the trial will be composed by 117 subjects allocated by a computerized random sequence stratified by consumption of oral drugs for OAB.

-**Sampling technique:** Starting on September 2017, the urologists working in our hospitals must elect by order of arrival a total of 234 patients. Considering that every month, an estimate of 15 new refractory cases are diagnosed in our hospital network, if 12 of them meet inclusion criteria, we deduce that 20 months are enough to fulfill our requirements.

² **Moderate-severe:** Urgency level equal or over 4 (“I can’t delay the voiding. I must go to the toilette, otherwise I will have an urine leak”)

³ **Fragility:** age over 65 years plus three or more of the following: unintentional weight loss, self-reported exhaustion, weakness, slow walking speed, low physical activity.

Variables

1.Independent:

Our outcomes are expected to be modified by the independent variable, which is the therapeutic intervention (BTX-A or PTNS) performed on the patient.

2.Dependent:

MAIN VARIABLE: HRQL will be measured using the OAB-q SF sub score. (Annex 5) as it measures the symptoms and disease related QoL in a simple manner. It is composed by two separated scores:

- Symptom severity: Evaluates 6 items, whose scores can range from 1 to 6, being 1 "less degree of discomfort".
- Health related quality of life: Includes 13 items, also punctuated from 1 to 6, where 6 equals "more frequent".

The transformed scores can be obtained by specific formulas. (See Annex 5 for more information)

For us, a full response or success will correspond to a gain of the 50% or more points in the questionnaire.

SECONDARY VARIABLES

- Presence of OAB symptoms (urgency, nocturia, incontinence, frequency.) *Yes/no*
- Bladder diaries outcomes: (Only the arithmetic average of the three days' measures will be recorded in the case report form.)
 - Micturition frequency *Episodes/24^h*
 - Average micturition volume: Voided volume in each episode measured with a measuring cup. *ml*
 - Episodes of urgency *Episodes/day*
 - Urgency severity degree *0,1,2,3 or 4 (Annex 2)*
 - UUI *Episodes/day*
 - SUI *Episodes /day*
 - Change of clothes or absorbent material *Changes /day*
 - Liquids intake: Amount of liquids ingested of any kind during a day *ml/24^h*

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- Diuresis: Total volume voided within 24^h *ml/24^h*
- OAB-q SF symptoms severity score *Transformed score punctuation*
- Reinterventions needed to maintain the results *Number of reinterventions*
- Time until the first reintervention *Months*
- Urodynamic measures:
 - Non-inhibited detrusor contractions during filling phase. Defined as >15 cmH₂O over basal pressure.
Yes/no
 - Post voiding residual volume *ml*
 - Maximum functional bladder capacity *ml*
 - Urine leaks during the cystometry *Yes/no*
- Presence of complications and symptoms associated to OAB despite treatment:
 - accidental falls *Yes/no*
 - sleep disturbances: difficulty falling or staying asleep, excessive daytime somnolence or enuresis *Yes/no*
 - perineal skin infection *Yes/no*
 - UTI: Diagnosed by >5 microscopic visualization of cells per field *Yes/no*
 - sexual dysfunction *Yes/no*
 - depression: Definition given by DSM-5 criteria *Yes/No*
- Side effects: When a symptom can present with different aggressiveness, a visual analogue scale will classify the event in mild (1-3), moderate (4-7) and severe (8-10). These events will be codified as yes/no indicating their presence or absence. Also, we will record as "Others" any side effect not listed below.

Table 6. Secondary variables .Side effects.

MILD	MODERATE	SEVERE
<ul style="list-style-type: none"> ▪ Asymptomatic bacteriuria ▪ Mild macrohematuria: Determined by visual analysis of the sample ▪ Xerostomia ▪ Dysphagia ▪ Transient impaired vision ▪ Mild needle related complications: (bleeding, bruising, pain) ▪ Mild muscular weakness ▪ Paresthesia 	<ul style="list-style-type: none"> ▪ UTI: leucocyturia ▪ Underactive bladder requiring CISC: An asymptomatic residual post voiding volume > 150 cc ▪ Moderate needle related complications: (bleeding, bruising, pain) ▪ Moderate muscular weakness ▪ Moderate hematuria: profuse bleeding without hemodynamic dysfunction ▪ Hypersensitivity reaction 	<ul style="list-style-type: none"> ▪ Urinary sepsis ▪ Acute urinary retention Inability to void that associates hypogastric pain or a residual volume >200ml ▪ Severe hematuria: Accompanied with hemodynamic dysfunction ▪ Anaphylactic shock

- Treatment discontinuation.
 - Due to intolerance: Patients who, despite experiment improvement in their disease, abandon voluntarily the treatment due to unbearable side effects before the end of the trial. *Yes/no*
 - Due to inefficacy: Patients who decide to abandon the study due to lack of improvement in their disease before the end of the trial. *Yes/no*
 - Due to other reasons: Patients who decide to abandon the study for other reasons than intolerance or inefficacy before the end of the trial. *Yes/no*
- Costs:
 - Resources consumption: disease treatment price plus complications' treatment price. *Euros*
 - Work productivity impairment: Evaluated with WPAI GH score. *percentage of work time missed due to health, percentage of impairment while working due to health, percentage overall work impairment due to health, percentage activity impairment due to health (Annex 6)*
 - Cost effectivity: treatment related costs / number of patients who experience a positive response (>50% improvement in the HRQL score) *Euros/ number of responders*

3.Covariates

- Age *Years*
- Sex *Male/Female*
- Marital status: *single/divorced/widow/married/living in couple*
- Education level *Less than high school graduate/high school graduate/Baccalaureate or vocational training/University Degree/More than University Degree*
- Employment status *Employed/Unemployed*
- BMI: Expressed as weight/height² *kg/m²*
- Parity: Expressed as the number of natural births or cesarean assisted births. *Number of births*
- Menopause: *Yes/no*
- Consumption of bladder stimulating agents: One or more units per day of tobacco, caffeine or alcohol. *Yes/no*
- Concomitant treatment with behavioral therapy *Yes/no*
- Concomitant treatment with oral drugs *Yes/no*
- Time since the diagnosis until the first session of 3rd lined treatment *Months*
- Distance from designed hospital: Distance between patient's home and hospital where he/she will receive treatment. More than 30 km to the designated hospital will be considered as "far". *Far/Close*

Procedures

- Recruitment

Eligibility will be evaluated among patients seeking treatment at the urologist practice with a diagnosis of refractory OAB and fulfilling inclusion criteria. Information concerning this study and an invitation to participate must be handled at this moment (Annex 7). The acceptance to participate will be only valid if the individual signs an informed consent (Annex 8). Patients who agree to participate in the trial must fill a form with their demographic details.

- **Evaluation of the disease**

To confirm that the individuals are suitable for the trial, urologists participating in the trial will do themselves an anamnesis, a physical examination, and demand all the complementary test needed to verify the absence of exclusion criteria. Usually a urine analysis is enough, but the study must be broadened in light of the findings. The nurse will now give the indications to fill the bladder diary, and the preparation required to perform the urodynamic study in the next consultation. That includes the temporary suspension of any pharmacological treatment for OAB one week before the test.

We will communicate by telephonic call the admission or exclusion after analyzing the results of the demanded studies.

Each participant hospital will evaluate the OAB's severity of its patients through bladder diaries, OAB-q SF and an urodynamic study. The *Hospital Trueta protocol for urodynamy in OAB*, will be the gold standard (26). Additionally, the presence of comorbidities derived from the disease (skin infection, depression, accidental falls, and sleep disturbances...) must be documented. The results of this second evaluation (elevated post voiding volume, evidence of mixed incontinence) will discard more patients that do not fulfill the eligibility criteria. The remaining participants should now be randomized into two groups. The randomization will contemplate the concomitant treatment with anticholinergic or mirabegron in patients who showed a partial response. Thus, randomization should be stratified according this variable.

- **Intervention**

The interventions will be centralized, so PTNS will be performed only by the Hospital Santa Caterina and Germans Trias, and BTX-A by Hospital Josep Trueta and Germans Trias. Because HUGTIP can offer both options, it will provide service for their regular patients. The rest of the patients will be distributed to Santa Caterina and Hospital Trueta.

-BTX-A Group Patients must start prophylactic antibiotic 1-3 days before the appointment. Anticoagulation and antiaggregation drugs can be suspended prior this intervention if the doctor estimates an important hemorrhagic risk.

Through flexible cystoscopy, the surgeon will evaluate the state of the bladder to detect possible contraindications for the procedure. If the result is normal, after a local dose of lidocaine, he will proceed to inject 100U of botulinum toxin dissolved

in saline. The total amount of drug has to be distributed into 20 injection of 0.5 ml all over the detrusor, avoiding the trigone. The estimated length of the intervention is 20-30 minutes. Patients must wait for 30 minutes in an observation room before being discharged, after doing a spontaneous micturition. There, they will receive information about the findings, or contingency if it is appropriate. The surgeon must inform the patient about the time until response, which is normally 2 weeks; and instruct to seek for medical aid if gross hematuria, acute urine retention or sever UTI appear. Two weeks after the injection, the patient must be seen by the surgeon as to assess the success with anamnesis, and measure post voiding volume with catheterization(16,18,20).

-PTNS group: The intervention will be held at a physiotherapist consult. First encounter is a group session, where various patients will receive the guidelines for the therapy, and discuss their expectations regarding the treatment. It is during the following 12 sessions that therapeutic stimulation will be applied for 30 minutes. The electrical stimulation will be administered with the needle placed 5 cm cephalic to the medial malleolus and posterior to the tibia. A second neutral electrode is placed in the surface, medial to calcaneus. The correct location of the needle can be confirmed by flexion of the toes or a tingling sensation with sufficient simulation. The standard settings are: intensity of 0.5-10 mA , pulse of 200 ms, and 20Hz (17). In each session, the physiotherapist will register the date of the intervention, the technical settings utilized, and the symptoms experienced during the procedure.

- Follow up

Doctors will meet their patients three months after BTX-A injection or PTNS. There are three possible outcomes:

-Full response (>50% improvement in HRQL): They won't be offered concomitant pharmacological treatment. They must program an appointment for a new control after three months.

-Partial response (50-25% improvement in HRQL): Patients who previously showed partial response to anticholinergics or mirabegron, should be proposed to reintroduce these drugs in the doses prescribed in the past. Also, the doctor will offer a reintervention in the same treatment group they had been assigned from the beginning.

-Non-response (< 25% improvement in HRQL): These patients will abandon the study, and continue their treatment as indicated by their reference hospitals.

After this first visit post-intervention, the participants will come every 3 months for a routine consult, where QoL questionnaires, voiding diaries, OAB related symptoms and comorbidities, urodynamic measures and side effects will be collected.

The decision to arrange a reintervention will consider patient's preferences, response, tolerance and clinical judgment.

- **Criteria to stop the trial**

Significant differences in efficacy or security in an interim analysis when 50% of the sample is enrolled, are a clear indication to stop the trial. The same attitude will be adopted when this analysis demonstrates severe adverse events at greater frequencies than published.

STASTICAL ANALYSIS

- **Descriptive analysis**

We will start with an univariate analysis of the sample. With this, the distribution of the patient's characteristics among the two treatment groups will be measured. 95 % confidence intervals built on proportion for nominal variables, and arithmetic mean for numeric variables; will be the tool utilized to determine significance. In this first evaluation, we include a baseline measure of HRQL, and, again with confidence interval, we will try to detect variations between groups.

- **Bivariate analysis**

- The analysis of the numeric discrete variables, and its modification by the treatment will be performed with U-Mann Withney. Accordingly, we will apply this test for the study of micturition frequency, urgency episodes, UUI or SUI episodes, change of clothes or absorbent material, urgency severity and number of reinterventions.

- t-Student allows the analysis of a nominal variable (type of treatment) and a numeric continuous variable. This test will be used to study the arithmetic mean of the following variables: HRQL, symptoms severity score, time until reintervention, micturition volume, liquids intake and total diuresis as recorded in bladder diaries; maximum volume voided in urodynamic study, post voiding residual volume, the direct costs and WPAI score.
- Treatment discontinuation will be studied with 95 % confidence interval with center on the Odds Ratio. A stratification of the analysis by the variable "distance from treatment designated hospital" will be done as well.
- The remaining variables, are dichotomic variables, and its evaluation will be completed with a Chi-square test.

Because ours is a randomized trial, confounding variables should be distributed equally in both arms. Therefore, a multivariate analysis is not required a 'piori'.

This is an intention to treat analysis, thus, individual's data that are incomplete, will be imputed, and their last report will be used as an estimate of the 12th month outcomes.

All the statistical analysis will be executed with IBM Statistical Package for the Social Sciences (SPSS) for Windows®, and alternative hypothesis must be accepted when $p < 0.05$.

WORKPLAN

(Annex 9) We will only launch this project after the approval of the Ethics Committee.

- **STAGE 1. Coordination 1 month**

All the staff involved in this project, this is, nursing staff, urologists, physiotherapist, administrative staff, methodology advisor, and biostatistician must reunite to stablish the activities to conduct, and determine who, when and where will they be completed. Throughout this period, specific training will be given to ensure an homogenous assessment and treatment of the patients and a standardized data recollection. Four future coordination meetings must be timetabled in advance, where provisional outcomes and incidences can be debated. Overactive bladder specialized urologists who decide not to participate in the trial, will be advised on how to refer their patients to the research team.

- **STAGE 2. Data collection 36 months**

A provisional lapse of 2 years is required to gather the number of individuals for the study. An urologist specialized in OAB is responsible for the inclusion of patients in the trial, and the offer of these therapies. A physiotherapist will apply the PTNS , while an specialized urologist will inject the toxin. The outcomes of these therapies and other relevant information must be registered via case report forms as soon as they are obtained. This responsibility will fall on the professional who carried out the evaluation or intervention. Any incidence or deviation from the protocolized directions, must be recorded in the case report forms as "observations".

A quality control will be performed by an external professional who will supervise all the process.

- **STAGE 3. Data analysis 3 months**

The creation of a data base from the case report forms and its analysis is commissioned to a hired statistician.

- **STAGE 4. Interpretation, publication and dissemination of results 4 months.**

The lead investigator must read the analyzed data and drag the conclusions obtained. Then, he will elaborate a scientific paper valid for its consecutive publication in the journal *European Urology*.

FESIABILITY

This study compares two therapies already implemented in our settings. Not all the participant hospitals offer these therapies, so we decided to centralize the treatment to HUDJT, HSC and HUGTIP. Consequently, the participant personnel is by now experienced on the use of the techniques. All the equipment is at our service, but we must consider the supplementary expense for follow up diagnostic tests. We are aware of the magnitude of the expenses for this trial.

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However, the impact of these findings, and the need to provide quality results, will justify them, encouraging the hospital board to approve our budget.

The number of patients required to accomplish a potent study, makes mandatory a multicenter design. The coordination between these hospitals is possible because HUDJT is the reference center for the province, and has always worked closely with HUGTIP. This last institution possesses forefront technology and researchers specialized on this topic.

Last, we must point out the fact that HUDJT participates in numerous and prestigious trials annually. This can guarantee that our research team will have appropriate support, and the trial will be completed with the best methodological advice.

ETHICAL CONSIDERATIONS

The observance of the ethical codes will be guaranteed by the presentation of the study protocol to a Clinical Research Ethics Committee.

In general, the principles enunciated in the *2013 Helsinki declaration* about experimentation on human beings, must be represented in our activity, that should have as gold standard the *ICH guideline for good clinical practice*.

The investigators must be familiarized with, and obey the following laws:

- Real Decreto Legislativo 1/2015, Ley de garantías y uso racional de los medicamentos y productos sanitarios

-RD1090/2015 Regulación de los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos

-Ley 14/2007, Ley de investigación biomédica.

The patient's autonomy must be safeguarded at all cost. For this reason, the team will provide written information regarding the purpose of the study and its implications for the patient. These forms must be accompanied by a verbal explanation of the most important parts. An individual informed and able to decide can freely choose to enrol in the study.

Through a written consent, individuals state their conformity to participate after understanding the all the terms. The

participants have the right to revoke the consent at any moment of the investigation without any penalty or prejudice to future treatments.

In the directions given by *Ley Orgánica 15/1999 Protección de datos de carácter personal*, patient's personal information will remain private, and only personnel participating in the study, will have access to them. The files won't be identified by name or history number, but by an identification number. Additionally, the staff responsible for data collection, will be trained to fill electronic Case Report Form.

The investigators must declare their conflict of interests if this is appropriate, as a proof of transparency. Furthermore, the protocol and results of this trials will be submitted to EudraCT and clinicaltrials.gov, two open data bases created for this purpose.

STUDY LIMITATIONS

Due to the nature of OAB syndrome, we are forced to rely on too many subjective variables. This is indispensable since our main objective is to assess the impact of the condition in patient's quality of life. To minimize the effect of subjectivity, we chose urodynamic variables and specific disease questionnaire. OAB-q is an internationally famous questionnaire, which is also available in Spanish, and validated for a Spanish population. However, we fear that a Catalan version of the same would provide more accurate results. We expect other possible biases inherent to the design of the study. The high rate of withdrawals in this kind of patients comports an attrition bias, thus, a significant part of our data won't come from direct observation.

In our study, triple blinding is impossible, and this adds up to the subjective variations in results discussed above. The blinding of the evaluating nurse and biostatistician is the only measure that we could implement to overcome this limitation.

The reliability of the data from the sample is very conditioned by our non-probabilistic sampling. Furthermore, our strict inclusion and exclusion criteria, make it complicated to extrapolate the findings. On the other hand, the election of a multicentric study, and a big number of participants counterbalance these limitations. The recruitment number is also

calculated as to cover these losses. The abandonment rate, is for us a double-edged sword, since we are also interested in evaluating the adherence to treatment and its causes.

In pursuit of minimal invasiveness, we defer SNS until the patient is declared non-responder to BTX-A or PTNS. Because of the heterogeneity in the published evidence, it is possible to find guidelines where this strategy is indicated prior to our options. As this intervention is not available in most of the hospitals, we believe that the election of BTX-A and PTNS is appropriated to outline the recommendations for our population.

The accomplishment of our secondary objectives can be endangered by the size of the sample. Because we calculated the number of participants to assess the primary objective, we cannot be sure whether this number is enough to detect significance with the statistic power desired.

BUDGET

External collaborators: We require the services of a statistician for 3 months working 10 hours per week, plus 1 month necessary to complete the interim evaluation. The quality control supervisor should endure all the data collection and analysis with a monthly evaluation of 2 hours.

Internal collaborators: The research team will assume all the tasks related with recruitment, interventions, data collection, interpretation and dissemination of results as part of their normal activities.

Meetings and training: The introductory meeting requires the presence of all our hospitals teams. It also associates the costs of the induction day.

Intervention costs: We are giving botulinum toxin and tibial stimulation within their normal indications, therefore, this study will only create expenses related to the follow up.

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Table 7. Budget

CONCEPT	UNITS	PRICE PER UNIT	TOTAL PRICE
Staff			
Statistician	4 months x 10 hours x 4 weeks	30 €/hour	4800 €
Quality control	39 months x 2 hours	30€/hour	2340€
Introductory meeting + formation	1	2000€	2500€
Successive meetings	4	500€	2000€
Material			
Urodynamic study	234 members x 3 studies	126€	88452€
OAB-q SF permission		1862€	1862 €
Publication and dissemination costs			
European Urology			800€
TOTAL			102.754 €

BIBLIOGRAPHY

1. Lucas MG, Bedretdinova D, Bosch JLHR, Burkhard F, Cruz F, Nambiar AK, et al. Guidelines on Urinary Incontinence [Internet]. Stockholm: European Association of Urology; 2015. Available from: <http://www.uroweb.org/guidelines/online-guidelines/>
2. Hersh L, Salzman B. Clinical management of urinary incontinence in women. Am Fam Physician [Internet]. 2013;87(9):634–40. Available from: <https://www.scopus.com/inward/record.uri?eid=2-s2.0-84877095069&partnerID=40&md5=7150c6b8ae79437789ea26ae9022ea15>
3. Milsom I, Coyne KS, Nicholson S, Kvasz M, Chen CI, Wein AJ. Global prevalence and economic burden of urgency urinary incontinence: A systematic review. Eur Urol [Internet]. 2014;65(1):79–95. Available from: <http://dx.doi.org/10.1016/j.eururo.2013.08.031>
4. Ricci A P, Freundlich K O, Solà D V, Pardo S J. Neuromodulación periférica en el tratamiento de la incontinencia de orina: efecto de la estimulación transcutánea del nervio tibial posterior sobre la vejiga hiperactiva. Rev Chil Obstet Ginecol. 2008;73(3):209–13.
5. Adot J, Esteban M, Batista J, Salinas J. Guía vejiga hiperactiva de la AEU. Asoc Española Urol [Internet]. 2014;1–64. Available from: <http://www.aeu.es/UserFiles/files/GuiaVejigaHiperactivaAEU.pdf>
6. Milsom I, D. Altman, R. Cartwright, M.C. Lapitan, R. Nelson, U. Sillén KT. Epidemiology of urinary incontinence (UI) and other lower urinary tract symptoms (LUTS), pelvic organ prolapse (POP) and anal incontinence (AI). In: Abrams, P. Cardozo L, editor. Incontinence [Internet]. 5th ed. Paris: European Association of Urology; 2013. Available from: http://www.ics.org/Publications/ICI_5/INCONTINENCE.pdf
7. Delgado F, Gómez L, Martínez E. Anatomía y fisiología de la continencia urinaria. In: Moreno J, Silmi J, editors. Atlas de incontinencia urinaria y suelo pélvico. Madrid: ENE ediciones; 2006.
8. Meng E, Lin W, Lee W, Chuang Y. The pathophysiology of overactive bladder. Low Urin Tract Symptoms. 2012;4:21–39.

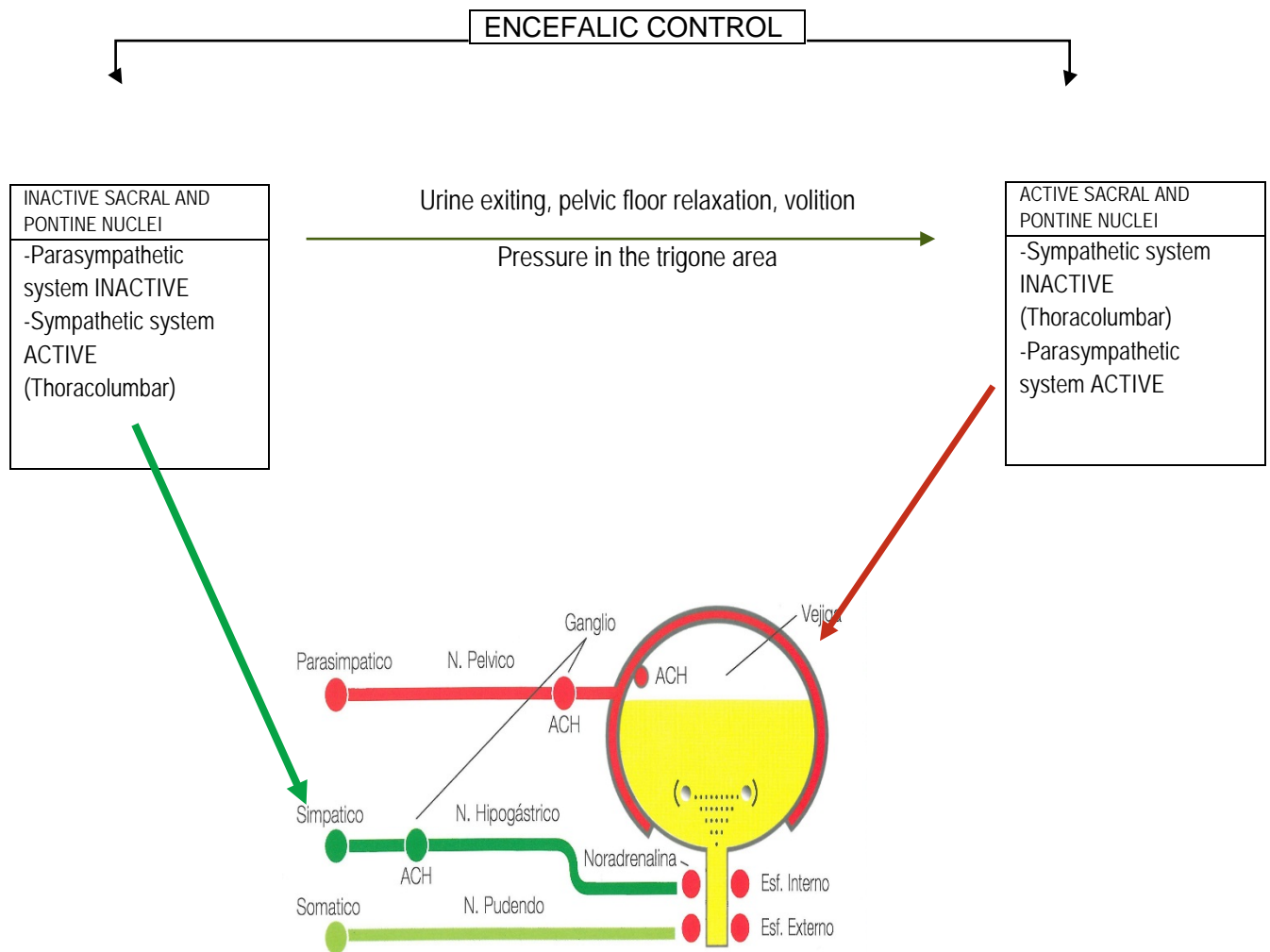
9. Chicharro J, Serrano A, Otero I, Golbano J. Vejiga hiperactiva. In: Moreno J, Silmi A, editors. Atlas de incontinencia urinaria y suelo pélvico. Madrid: ENE ediciones; 2006.
10. Tse V, King J, Dowling C, English S, Gray K, Millard R, et al. Conjoint Urological Society of Australia and New Zealand (USANZ) and Urogynaecological Society of Australasia (UGSA) Guidelines on the management of adult non-neurogenic overactive bladder. *BJU Int.* 2016;117(1):34–47.
11. Milsom I, Abrams P, Cardozo L, Roberts RG, Thüroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int.* 2001;87(9):760–6.
12. Winters JC, Dmochowski RR, Goldman HB, Anthony CD, Kobashi KC, Kraus SR, et al. AUA / SUFU Guideline AUA / SUFU Guideline. 2012;1–30.
13. Rosier PFW., Schaefer W, Lose G, Goldman HB, Guralnick M, Eustice S, et al. International Continence Society Good Urodynamic Practices and Terms 2016: Urodynamics, uroflowmetry, cystometry, and pressure-flow study. *Neurourol Urodyn [Internet]*. 2016;(May):1–18. Available from: <http://doi.wiley.com/10.1002/nau.23124>
14. Gill ABC, Chief MS, Edward E, Kim D. Urodynamic Studies for Urinary Incontinence. 2015;1–14.
15. Truzzi JC, Gomes CM, Bezerra CA, Plata IM, Campos J, Garrido GL, et al. Overactive bladder - 18 years - Parts I and II. *Int Braz J Urol.* 2016;42(2):188–214.
16. Hermieu JF, Ballanger P, Amarenco G, Chartier-Kastler E, Cosson M, Costa P, et al. Guidelines for practical usage of botulinum toxin type A (BoNTA) for refractory idiopathic overactive bladder management: Translation of French recommendations. *Prog en Urol [Internet]*. 2014;24(11):e1–7. Available from: <http://dx.doi.org/10.1016/j.purol.2014.06.005>
17. Ellsworth P. Treatment of overactive bladder symptoms beyond antimuscarinics: current and future therapies. *Postgrad Med.* 2012;124(3):16–27.
18. Arlandis S, Jiménez-Cidre M. Recomendaciones para el uso de Onabotulinumtoxina en vejiga hiperactiva.

- Madrid: Asociación Española de Urología; 2014.
19. Syan R, Brucker BM. Guideline of guidelines: Urinary incontinence. *BJU Int.* 2016;117(1):20–33.
 20. Bótox. Ficha técnica. Madrid: Agencia española del medicamento y productos sanitarios; 2016. p. 1–35.
 21. Marinkovic SP, Rovner ES, Moldwin RM, Stanton SL, Gillen LM, Marinkovic CM. The management of overactive bladder syndrome. *Bmj* [Internet]. 2012;344:e2365–e2365. Available from: <http://www.bmj.com/cgi/doi/10.1136/bmj.e2365>
 22. Staskin DR, Peters KM, MacDiarmid S, Shore N, de Groat WC. Percutaneous tibial nerve stimulation: a clinically and cost effective addition to the overactive bladder algorithm of care. *Curr Urol Rep* [Internet]. 2012;13(5):327–34. Available from: <http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3438389&tool=pmcentrez&rendertype=abstract>
 23. Peters KM, Carrico DJ, Perez-Marrero RA, Khan AU, Wooldridge LS, Davis GL, et al. Randomized Trial of Percutaneous Tibial Nerve Stimulation Versus Sham Efficacy in the Treatment of Overactive Bladder Syndrome: Results From the SUmIT Trial. *J Urol* [Internet]. 2010;183(4):1438–43. Available from: <http://dx.doi.org/10.1016/j.juro.2009.12.036>
 24. INE. Proyección de la Población de España 2014-2064: Notas de prensa [Internet]. Instituto Nacional de Estadística (INE). 2014. p. 1–9. Available from: www.ine.es/prensa/prensa.htm
 25. National Institute for Health and Care Excellence. Urinary incontinence in women: management. 2015;(November). Available from: <https://www.nice.org.uk/guidance/cg171/chapter/1-recommendations#invasive-procedures-for-oab>
 26. Domingo R, Fàbrega J, Callís C, Besalú A. Procediment d'urodinamia. Girona: Hospital Universitari Doctor Josep Trueta; 2013. p. 1–14.

ANNEXES

Annex 1. Pathophysiology

Figure 3. Neurologic control of the micturition reflex. Author.(7)



Annex 3. Urodynamic study

Figure 5. Urodynamic study graphic. Property of the HUDJT Urology department.

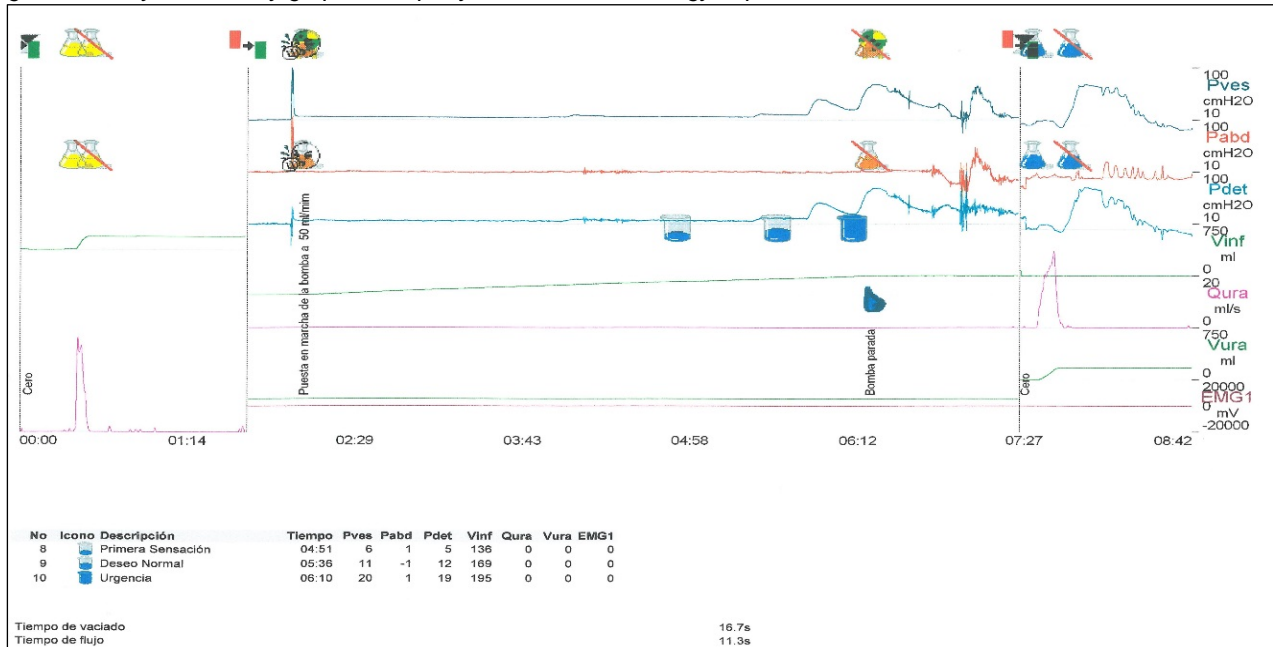


Figure 5. Uroflowmetry, followed by cystometry and pressure-flow study. This cystometry is diagnostic for OAB, as a detrusor pressure of 20 cmH₂O is present. The contraction corresponds with a clinic of urgency, represented by a full recipient in this diagram.

Figure 6: Materials for urodynamic studies. Author.



Figure 6: 1. Commode with measure cup and scale to determine flow rates. 2. Urodynamic system Albyn medical © 3. Examining table with stirrups.

Annex 4. Technical details of the interventions

Botulinum toxin A versus percutaneous tibial nerve stimulation in idiopathic overactive bladder. A randomized trial.

Figure 7: Intradetrusor injection spots (20)

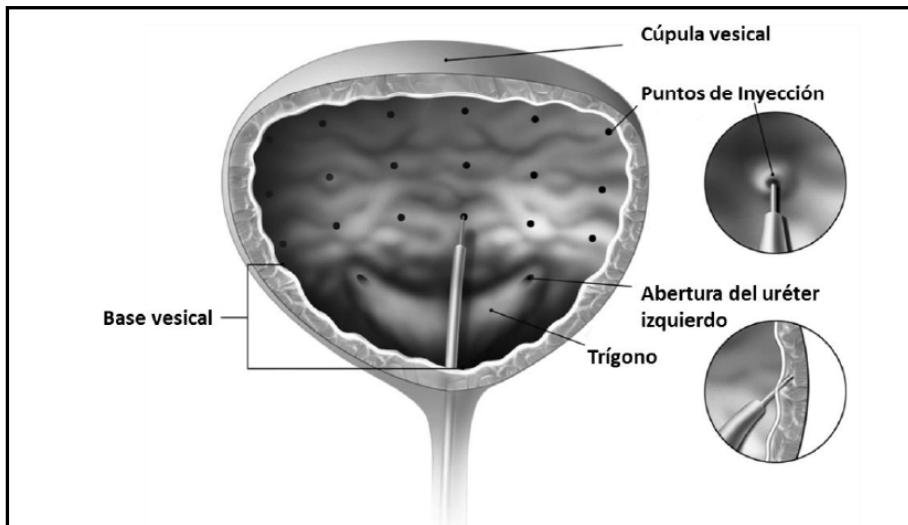
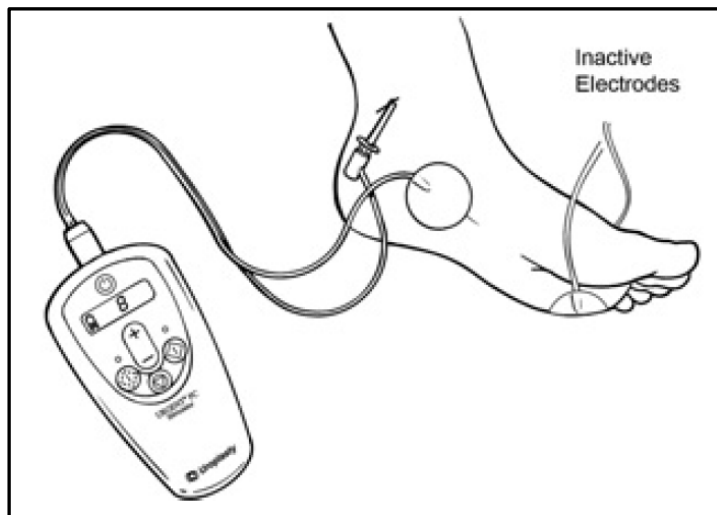


Figure 8: PTNS electrodes situation (23)



Annex 5. OAB-q SF English version

-Symptom bother score: This questionnaire asks about how much you have been bothered by selected bladder symptoms during the past 4 weeks. Please place a + or x in the box that best describes the extent to which you were bothered by each symptom during the past 4 weeks. There are no right or wrong answers. Please be sure to answer every question.

<i>During the past 4 weeks, how bothered were you by. . .</i>	Not at all	A little bit	Somewhat	Quite a bit	A great deal	A very great deal
1. An uncomfortable urge to urinate?						
2. A sudden urge to urinate with little or no warning?						
3. Accidental loss of small amounts of urine?						
4. Nighttime urination?						
5. Waking up at night because you had to urinate?						
6. Urine loss associated with a strong desire to urinate?						

-HRQL score: For the following questions, please think about your overall bladder symptoms in the past 4 weeks and how these symptoms have affected your life. Please answer each question about how often you have felt this way to the best of your ability. Please place a + or x in the box that best answers each question.

<i>During the past 4 weeks, how often have your bladder symptoms . . .</i>	None of the time	A little of the time	Some of the time	A good bit of the time	Most of the time	All of the time
1. Caused you to plan "escape routes" to restrooms in public places?						
2. Made you feel like there is something wrong with you?						
3. Interfered with your ability to get a good night's rest?						
4. Made you frustrated or annoyed about the amount of time you spend in the restroom?						
5. Made you avoid activities away from restrooms (i.e., walks, running, hiking)?						
6. Awakened you during sleep?						
7. Caused you to decrease your physical activities (exercising, sports, etc.)?						
8. Caused you to have problems with your partner or spouse?						
9. Made you uncomfortable while traveling with others because of needing to stop for a restroom?						
10. Affected your relationships with family and friends?						
11. Interfered with getting the amount of sleep you needed?						
12. Caused you embarrassment?						
13. Caused you to locate the closest restroom as soon as you arrive at a place you have never been?						

Botulinum toxin A versus percutaneous tibial nerve stimulation in idiopathic overactive bladder. A randomized trial.

To calculate a symptom severity score, create a summed score from the listed items and use the formula below the table to transform the value. higher score values are indicative of greater symptom severity or bother and lower scores indicate minimal symptom severity.

	Sum Item Values Part A	Lowest and Highest Possible Raw Scores	Possible Raw Score Range	Formula
symptom severity score	1-6	6,36	30	$[(Actual\ raw\ score - lowest\ possible\ raw\ score) : Possible\ raw\ score\ range] \times 100$

For the HRQL subscales (coping, sleep, and social), create summed scores of the listed items for each individual subscale. Use the formula below the table to transform all values. Higher scores will be indicative of better HRQL.

Total HRQL Score	1 through 13	13, 78	65	$[(Highest\ possible\ score - Actual\ raw\ score) : Possible\ raw\ score\ range] \times 100$
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Missing Items: For the subscale analyses, if < 50% of the scale items are missing, the scale should be retained with the mean scale score of the items present used to impute a score for the missing items. If > 50% of the items are missing, no scale score should be calculated, the subscale score should be considered missing.

Annex 6. WPAI:GH

Cuestionario sobre productividad laboral y deterioro de las actividades: Estado general de salud V2.1

Las siguientes preguntas se ocupan del efecto que sus problemas de salud tienen sobre su capacidad para trabajar y realizar actividades cotidianas. Por problemas de salud entendemos cualquier problema o síntoma físico o emocional. *Tenga a bien completar los espacios en blanco o encerrar un número en un círculo, según corresponda.*

1. ¿Está actualmente empleado (trabaja a sueldo)? _____ No _____ Sí
Si la respuesta es NO, marque "NO" y pase a la pregunta 6.

Las siguientes preguntas se refieren a los **últimos siete días**, sin incluir el día de hoy.

2. Durante los últimos siete días, ¿cuántas horas de trabajo perdió debido a problemas de salud? *Incluya las horas que perdió por días de enfermedad, las veces que llegó tarde o se fue temprano, etc., por problemas de salud. No incluya el tiempo que perdió por participar en este estudio.*

_____ HORAS

3. Durante los últimos siete días, ¿cuántas horas de trabajo perdió debido a cualquier otra causa, tal como vacaciones, un día de fiesta o tiempo que se tomó para participar en este estudio?

_____ HORAS

4. Durante los últimos siete días, ¿cuántas horas realmente trabajó?

_____ horas (si la respuesta es "0", pase a la pregunta 6.)

5. Durante los últimos siete días, ¿cuánto afectaron los problemas de salud a su productividad mientras estaba trabajando?

Piense en los días en que estuvo limitado en cuanto a la cantidad o el tipo de trabajo que pudo realizar, los días que hizo menos de lo que hubiera querido o los días en los que no pudo realizar su trabajo con la dedicación habitual. Si los problemas de salud afectaron poco a su trabajo, escoja un número bajo. Escoja un número alto si los problemas de salud afectaron mucho a su trabajo.

Tenga en cuenta únicamente cuánto afectaron los problemas de salud a su productividad mientras estaba trabajando.

Los problemas de salud
no afectaron a mi
trabajo

0 1 2 3 4 5 6 7 8 9 10

Los problemas de salud
me impidieron
completamente trabajar

ENCIERRE EL NÚMERO EN UN CÍRCULO

5. Durante los últimos siete días, ¿cuánto afectaron los problemas de salud a su capacidad para realizar las actividades diarias habituales, excluyendo las de su trabajo a sueldo?

Por actividades habituales, nos referimos a las actividades cotidianas que realiza, tales como tareas hogareñas, compras, cuidado de los niños, deportes, estudios, etc. Piense en las veces en que estuvo limitado en la cantidad o la clase de actividad que pudo realizar y en las veces en las que hizo menos de lo que hubiera querido. Si los problemas de salud afectaron poco a sus actividades, escoja un número bajo. Escoja un número alto si los problemas de salud afectaron mucho a sus actividades.

Tenga en cuenta únicamente cuánto afectaron los problemas de salud a su capacidad de hacer sus actividades diarias habituales, excluyendo las de su trabajo.

Los problemas de salud no afectaron a mis actividades habituales

0 1 2 3 4 5 6 7 8 9 10

Los problemas de salud me impidieron completamente hacer mis actividades habituales

ENCIERRE EL NÚMERO EN UN CÍRCULO

Los resultados del cuestionario WPAI se expresan como porcentaje de incapacitación. Un número mayor indica mayor incapacitación y menor productividad .	
<p>Preguntas:</p> <p>1 = actualmente empleado</p> <p>2 = horas perdidas debido a problemas de salud</p> <p>3 = horas perdidas debido a otras razones</p> <p>4 = horas realmente trabajadas</p> <p>5 = grado en el que la salud afectó a la productividad durante el trabajo</p> <p>6 = grado en el que la salud afectó las actividades regulares</p>	<p>Scores: Multiplique los resultados por 100 para expresarlos en porcentajes.</p> <p>-Porcentaje de tiempo de trabajo debido a la salud $Q2/(Q2+Q4)$</p> <p>-Porcentaje de incapacitación durante el trabajo debido a la salud. $Q5/10$</p> <p>-Porcentaje de incapacitación general en el trabajo debido a la salud: $Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))]x(Q5/10)$</p> <p>-Porcentaje de incapacitación para la actividad debido a la salud. $Q6/10$</p>

Annex 7. Study information sheet

Título: *Botulinum toxin A versus percutaneous tibial nerve stimulation in idiopathic overactive bladder. A randomized trial.*

Estimado/a paciente:

Nos dirigimos a usted para informarle del estudio clínico que se desarrollará en nuestro hospital a partir de septiembre de 2017 y durante los siguientes 3 años. Contará con la colaboración de distintos hospitales de la provincia, como el Hospital Universitario Doctor Josep Trueta, Hospital Santa Caterina, Hospital Comarcal de Blanes, Hospital de Olot y Comarcal de la Garrotxa, Hospital de Figueres y Hospital de Palamós, así como el Hospital Universitario Germans Trias i Pujol de Barcelona.

Finalidad del estudio: El objetivo de este estudio es analizar la mejora en la calidad de vida en pacientes diagnosticados de vejiga hiperactiva con dos tratamientos ya aprobados y utilizados en nuestro entorno. La eficacia de las inyecciones de Botox[®] y estimulación del nervio tibial, han sido demostradas por separado, pero nunca se habían comparado entre sí. Con los resultados de este ensayo, creemos que llegaremos a definir cuál es el tratamiento más indicado para cada paciente según la eficacia y efectos adversos demostrados.

Participación: Los investigadores invitamos a todo aquel que haya sido diagnosticado de vejiga hiperactiva idiopática, esto es, sin ninguna causa conocida; y que, habiendo recibido el tratamiento adecuado, sigue presentando molestias significativas, o no toleró los efectos secundarios del fármaco pautado. Queremos aclarar que su colaboración en el estudio es totalmente voluntaria, y que su decisión no condicionará de ninguna manera la atención que reciba en el futuro. De la misma manera, no se compensará económicamente a los participantes.

Tratamiento: Si usted acepta colaborar con este proyecto, será sometido a una serie de pruebas más específicas que nos permitirán conocer si es candidato a la participación. Las pruebas a realizar, son las mismas que aplicaríamos fuera del estudio, lo que no implicaría riesgos añadidos. A cada paciente se le practicará una entrevista clínica con exploración física, un análisis de orina, y un estudio urodinámico y llenado de cuestionarios de calidad de vida.

La asignación a cada grupo de tratamiento se hará aleatoriamente, y el paciente será conocedor del tratamiento que recibirá desde el principio.

Los pacientes del grupo "Inyección de Botox[®]" serán tratados en el Hospital Universitario Doctor Josep Trueta, o en el Hospital Universitario Germans Trias i Pujol, según les corresponda por su empadronamiento.

Los pacientes del grupo "Estimulación del nervio tibial" recibirán tratamiento en el Hospital Santa Caterina o en el Hospital Universitario Germans Trias i Pujol, también según su domicilio.

Seguimiento: El seguimiento se realizará de manera trimestral en el hospital de procedencia de cada paciente. Para el propósito del estudio, es necesario un seguimiento de un año, en el que se pueden requerir reintervenciones para mantener el efecto. Cada una de estas visitas, constará al igual que la visita inicial de una historia clínica, exploración física, análisis de orina, estudio urodinámico y rellenado de formularios de calidad de vida.

Riesgos: La participación en el estudio conlleva unos riesgos, que usted debe conocer.

-Riesgos derivados del estudio urodinámico:

Durante la exploración, el paciente no experimenta dolor, tan sólo una sensación de llenado. Debido a la manipulación del sistema urinario, es posible la aparición de sangre en la orina, o molestias al orinar el día de la prueba o alta frecuencia de micciones. Si estos síntomas no disminuyen con la ingesta de abundantes líquidos, se recomienda consultar a un médico.

-Riesgos derivados de la electroestimulación del nervio tibial posterior:

Los riesgos que asocia este tratamiento son el dolor en el punto de punción, y hematomas o sangrados, también sobre el lugar de punción.

-Riesgos derivados de la inyección intravesical de toxina botulínica:

La intervención se realiza en quirófano, previa inyección de anestesia local. Esta inyección puede ser dolorosa para el paciente en sí misma. Otro efecto de la punción de la vejiga puede ser la aparición de sangre en la orina.

El efecto farmacológico de la toxina botulínica puede provocar a nivel local: imposibilidad para evacuar al completo la vejiga, o retenciones agudas de orina, e infecciones. Por acción del fármaco en otros órganos, pueden encontrarse debilidad en los miembros o incluso reacciones de hipersensibilidad.

De entre estas, la más frecuente es la infección o infestación del tracto urinario (>10%) y la retención de orina (>1/100), que puede requerir una auto cateterización limpia intermitente para vaciar la vejiga.

Compromiso del paciente con la recogida de datos: El equipo investigador ruega a los participantes que se comprometan a terminar los seguimientos y las sesiones de tratamiento y proporcionar información verídica. Los individuos participantes, son libres de abandonar el estudio en cualquier momento sin repercusiones.

Resultados y beneficio de la participación: Los resultados de esta investigación estarán disponibles para la consulta del paciente. Los beneficios derivados de la investigación, pueden beneficiar al participante como a otras personas, y estos serán adecuadamente utilizados para conseguir los objetivos del estudio y servirán de base para futuras investigaciones en este ámbito.

Confidencialidad de datos: El equipo investigador se compromete a adoptar medidas que aseguren la confidencialidad de sus datos en cumplimiento de la Ley Orgánica 15/1999. Por ello, la información recogida será gestionada de forma anónima y solo se utilizarán en fines de investigación.

Annex 8. Informed Consent

HOJA DE CONSENTIMIENTO INFORMADO PARA LA PARTICIPACIÓN EN UN ENSAYO CLÍNICO

TÍTULO: *Botulinum toxin A versus percutaneous tibial nerve stimulation in idiopathic overactive bladder. A randomized trial.*

Nombre y apellidos: _____

Fecha de nacimiento: ___/___/_____ Teléfono de contacto: _____

La persona aquí firmante declara:

- Haber leído con detenimiento la hoja informativa.
- Haber recibido toda la información considerada oportuna sobre el estudio.
- Haber tenido la oportunidad de discutir esta información con (*Nombre del investigador*) _____, quién le ha respondido con claridad a sus preguntas.
- Entender que la participación en este estudio es totalmente voluntaria, y desinteresada.
- Entender qué se espera de él/ella en el estudio, y estar de acuerdo con las condiciones.
- Entender que puede retirar el consentimiento en cualquier momento, sin dar explicaciones, sin dar justificaciones, y sin que condicione su asistencia sanitaria en el futuro.

Para que así conste, firma este documento en _____ a día _____

El participante:

El investigador:

Annex 9. Chronogramm

		9/2017-10/2017	11/2017-1/2018	2/2018-4/2018	5/2018-7/2018	8/2018-10-2018	11/2018-1/2019	2/2019-4/2019	5/2019-7/2019	8/2019-10/2019	11/2019-1/2020	2/2020-4/2020	5/2020-7/2020	8/2020-10/2020	11/2020-1/2021	2/2021-3/2021	4/2021-7/2021	
COORDINATION Urologists, Nursing staff, Administrative staff, Physiotherapist, Biostatistician, Monitor																		
DATA COLLECTION	RECRUITMENT Urologist																	
	INTERVENTION Urologist, Nursing staff, Physiotherapist																	
	FOLLOW-UP Urologist, nursing staff																	
DATA ANALYSIS Biostatistician																		
INTERPRETATION Urologist, leader of the investigation																		
PUBLICATION Urologist, leader of the investigation																		

