Current Information on Sacral Neuromodulation and Botulinum Toxin Treatment for Refractory Idiopathic Overactive Bladder Syndrome: A Review

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Key Words
Sacral neuromodulation · Botulinum toxin · Overactive bladder syndrome

Abstract
The overactive bladder syndrome (OAB) negatively affects the daily life of many people. Conservative treatments, such as antimuscarinics, do not always lead to sufficient improvement of the complaints and/or are often associated with considerable side effects resulting in treatment failure. In the case of failure or intolerable side effects, sacral neuromodulation (SNM) and botulinum toxin are minimally invasive and reversible alternatives. Currently, of these alternatives only SNM with InterStim™ therapy has FDA approval for use in OAB patients. This review attempts to provide an update on the current position of SNM and botulinum toxin in the second-line management of adults with idiopathic OAB, based on the available clinical evidence concerning the efficacy and safety.

Introduction
Idiopathic overactive bladder syndrome (I-OAB) is characterized by a combination of bladder filling symptoms: urgency with or without urgency urinary incontinence, usually accompanied by frequency and nocturia [1]. Large-scale surveys in Europe and in the US estimated an OAB prevalence of approximately 16–17%, of which a third (predominantly women) also have complaints of urgency urinary incontinence [2, 3]. Frequency and urgency can be as distressing as urgency incontinence, and OAB syndrome as a whole has a strong negative impact on the quality of life [2, 4].

In 2009, the International Consultation on Incontinence (ICI) published an algorithm intended to serve as a guide for the treatment of patients with I-OAB (fig. 1) [1]. Behavioral and lifestyle interventions are recommended firstly, followed by bladder and pelvic floor muscle training, or pharmacological treatment with antimuscarinics. However, many patients have insufficient improvement with these treatments [4]. When conservative treatments fail after 8–12 weeks, alternative therapies should be considered [1]. These alternatives used to be invasive and irreversible surgical procedures, such as bladder augmentation or urinary diversion. Currently, new and minimally invasive techniques are available such as sacral neuromodulation (SNM; recommended by ICI – level of evidence A), posterior tibial nerve stimulation (not recommended by ICI – insufficient scientific data) and intradetrusor injection of botulinum toxin (BTX; ICI – off label treatment – level of evidence C) [1].

Because both SNM and BTX injections are increasingly being applied in clinical practice, an overview is
Given on the available scientific and clinical evidence on their safety and efficacy. The position of SNM and BTX as second-line treatment options for adults with I-OAB is discussed.

**Botulinum Toxin**

**Introduction**

BTX is a protein that is produced by the anaerobic Gram-positive bacteria *Clostridium botulinum*. Local injection of BTX leads to temporary chemical denervation and loss or reduction of nerve cell activity at the tissue.

Use of BTX as a muscle relaxant is indicated for various neurological disorders, such as torticollis spasmodica or other spastic diseases of the musculoskeletal system, serious primary caudal hyperhydrosis, and for esthetic reasons.

Among urologists, there is a growing popularity of products containing BTX, mostly type A, in particular Botox® (Allergan, USA) and Dysport® (High-Value Bio-tech, France).

**Working Mechanism**

The effect of BTX in I-OAB patients is based on a temporary inhibition of the neuromuscular nerve signals, which leads to relaxation of the smooth muscles in the bladder. Previously, the main effect was considered as temporary blockage of presynaptic vesicle release which decreases acetylcholine to the neuromuscular junction. Recent research shows expanded effects such as inhibited release of other transmitters (neuropeptide substance P, APT) and downregulation of the axonal expression of purinergic P2X3 and capsaicin-TPRV1 receptors of the nerve endings in the (sub)urothelium, contributing to the afferent desensitization [5]. Besides an effect on the afferent bladder signals, it is very likely that efferent nerves are also being affected. BTX decreases detrusor pressure during both the filling and the voiding phase, and may increase the post-void residual volume [5].

**Treatment Protocol**

There is no standard protocol for the application of BTX. In most published trials, 100–300 U Botox or 500 U Dysport are injected at 10–30 different sites of the bladder wall (table 1) [6–11]. Injections can be performed under local or general anesthesia. The possibility of using

<table>
<thead>
<tr>
<th>First author</th>
<th>Patients</th>
<th>Dose, U</th>
<th>Injections</th>
<th>Injection site</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sahai [6]</td>
<td>18</td>
<td>200</td>
<td>20</td>
<td>bladder wall</td>
</tr>
<tr>
<td>Flynn [20]</td>
<td>7</td>
<td>200/300</td>
<td>8–10</td>
<td>detrusor</td>
</tr>
<tr>
<td>Khan [21]</td>
<td>–</td>
<td>200</td>
<td>20</td>
<td>detrusor</td>
</tr>
<tr>
<td>Schmid [22]</td>
<td>–</td>
<td>100</td>
<td>30</td>
<td>suburothelium</td>
</tr>
</tbody>
</table>
no anesthesia at all is also being tested [12]. In terms of injection technique, a comparative study showed a significantly better effect after 9 months when BTX was injected into the detrusor muscle compared to injection into the bladder suburothelium. Both detrusor or suburothelium injection in the bladder body were better compared to suburothelium injection into bladder base [13]. However, injection into the bladder base reduced the urgency episodes significantly, while the other sites did not. In most trials, the trigone is not injected to eliminate risk of iatrogenic vesicoureteral reflux. However, recent studies argue against this postulation [13–15].

Dose-response studies show that low dosages (100 instead of 150–300 U) injected into the detrusor or suburothelium, lead to a significant reduction of the side effects, but also to a reduction in the duration of the therapeutic effect and the quality of life scores [16, 17].

Effectiveness

Currently, four randomized controlled trials (RCTs) have been published. The first one used BTX type B and showed significant improvements; however, the effect was short-term (6 weeks) [18]. The other three trials used BTX type A [6, 19, 20]. Several nonrandomized, prospective open-label studies have investigated the value of BTX treatment in I-OAB patients. Unfortunately, in most studies, the patient numbers are limited (10–30 patients), reducing the reliability of the results. Only three studies cover relatively large groups of patients [8, 21, 22].

Comparison of all of these studies is difficult due to the differences in the methodology and parameters used. All the RCT trials and the open-label studies show promising results (table 2). Generally, around 80% of the patients treated with BTX experience improvement. The number of voids per day decreases on average by 12–53%, urgency episodes per day by 28–70%, and incontinence episodes per day by 35–87%. The maximum cystometric capacity increased on average by 45%. The Impact Questionnaire-Short Form score decreased by an average of 54–57%, and the Urogenital Distress Inventory score decreased by a mean of 38–64%. Almost all parameters used in the RCT trials showed significant improvements compared with placebo.

Long-term follow-up trials show an average recurrence rate of 27–66%, with a mean duration of clinical improvements of 6–14 months and a mean interinjection interval of 14–23 months (table 3). While some patients have a temporary effect, some patients seem to be ‘cured’ after one or two treatments. Khan et al. [21] showed a cure rate of 10% and Schmid et al. [22] of 38% after the first injection, while another 33% showed a ‘permanent’ good effect when combining the treatment with anticholinergics.

A study on the satisfaction of patients who underwent BTX showed that among 38 patients with neurogenic or I-OAB, 93% of the patients would undergo the procedure again [23]. Overall, patients were satisfied giving the treatment an average score of 6.9 on a satisfaction scale between 0 and 10. Furthermore, 90% of the patients reported clear improvement in their voiding situation, and 6.7% had adverse events.

Safety

BTX is generally well tolerated. No major complications were noted in any RCTs or large open-label studies (table 4). The most common adverse events were high post-void residual (19–43% depending on criteria used) requiring clean intermittent self-catheterization (4–43%
depending on the criteria used) and urinary tract infection (10–43%) [6, 22, 24]. However, this incidence seems to be dose dependent. A dose-effect study among 313 I-OAB patients who received either placebo, 50, 100, 150, 200, or 300 U BTX showed an incidence of post-void residual (>200 ml) of 0, 12.5, 14.5, 20.0, 28.8, 27.3%, respectively [17].

Aside from local side effects of BTX, muscular weakness as a result of unintentional dissemination of the toxin outside the target area may also occur. Between 2003 and 2007, four adverse events were reported in a Danish registry after BTX treatment for urological interventions [25]. Although the real incidence cannot be deduced from these data, it is estimated to be at around 10/10,000 interventions. All adverse events involved muscle weakness, two were throughout the whole body, one in the arms and one in the thoracic muscles necessitating artificial respiration. The latter occurred in a patient with neurogenic bladder dysfunction. In general, serious side effects can occur such as problems with speech, swallowing (dysphagia) or breathing. Mortality after BTX treatment has been reported before, although rarely and only in patients with known neurological disease. Because of this, manufacturers of products containing BTX, after consultation with European regulators, issued a warning about the safety in France, Denmark, Spain, Germany and the UK [25–29].

The safety of repeated injections is rarely or not described. Although the impact of repeated injections on the bladder compliance is unknown, no change in compliance has been demonstrated after up to three injections [30]. Although BTX in its present form has a small antigenic potential and some immune resistance has been reported on I-OAB and BTX, an immune response can occur after repeated injection, and ultimately even tachyphylaxis [10, 31]. Schulte-Baukloh et al. [31] reported the presence of BTX antigen among 8 out of 25 patients after two injections. Further analysis showed a possible correlation between the presence of BTX-antigen and the reduction in treatment effect. To minimize the risk of immune resistance and response as much as possible, it is advisable to wait at least 3 months between injections, and to choose the lowest dose that will achieve the desired clinical effects [32].

Table 3. Reinjections

<table>
<thead>
<tr>
<th>First author</th>
<th>Follow-up</th>
<th>Recurrence rate, %</th>
<th>Duration of clinical improvements</th>
<th>Interinjection interval</th>
<th>'Cure', %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sahai [6]</td>
<td>9 months</td>
<td>–</td>
<td>6 months</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Flynn [20]</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Brubaker [19]</td>
<td>13 months</td>
<td>66</td>
<td>307 days</td>
<td>1.9 years</td>
<td>16.7 (&gt;27 months)</td>
</tr>
<tr>
<td>Kalsi [8]</td>
<td>27 months</td>
<td>–</td>
<td>13.86 months</td>
<td>14 months</td>
<td>10 (&gt;14 months)</td>
</tr>
<tr>
<td>Khan [21]</td>
<td>2.8 years</td>
<td>57</td>
<td>–</td>
<td>9 months</td>
<td>38</td>
</tr>
<tr>
<td>Schmid [22]</td>
<td>7 years</td>
<td>26.8</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

UTI = Urinary tract infection; AUR = acute urinary retention; PVR = post-void residual urine; CIC = clean intermittent catheterization.

Table 4. Most common adverse events associated with BTX therapy

<table>
<thead>
<tr>
<th>First author</th>
<th>UTI, %</th>
<th>AUR, %</th>
<th>Mean PVR, ml</th>
<th>De novo PVR, %</th>
<th>CIC, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sahai [6]</td>
<td>20.50</td>
<td>0</td>
<td>44→51</td>
<td>37.5 (&gt;150 ml)</td>
<td>37.5</td>
</tr>
<tr>
<td>Flynn [20]</td>
<td>13</td>
<td>ND</td>
<td>25→107</td>
<td>26.6 (&gt;200 ml)</td>
<td>6.7</td>
</tr>
<tr>
<td>Brubaker [19]</td>
<td>44</td>
<td>ND</td>
<td>ND</td>
<td>43 (&gt;200 ml)</td>
<td>32</td>
</tr>
<tr>
<td>Kalsi [8]</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Khan [21]</td>
<td>15</td>
<td>ND</td>
<td>ND</td>
<td>43 (&gt;100 ml)</td>
<td>43</td>
</tr>
<tr>
<td>Schmid [22]</td>
<td>10</td>
<td>4 (&gt;400 ml)</td>
<td>21→85</td>
<td>19 (&gt;150 ml)</td>
<td>4</td>
</tr>
</tbody>
</table>
Sacral Neurmodulation

Introduction

SNM comprises the stimulation of the sacral nerves that innervate the bladder, urethral sphincter and pelvic floor muscles. Stimulation electrodes are placed at the level of the third sacral nerve (S3) and connected to an electrical stimulator that is implanted. The implantable nerve stimulator (INS) that is being used for SNS therapy uses the InterstimTM technology (Medtronic, Minneapolis, Minn., USA).

The indications for SNM therapy are I-OAB, nonobstructive urinary retention, fecal incontinence and chronic constipation.

Working Mechanism

The precise mechanism of action of SNM is still not entirely clear. It is assumed that SNM affects the ‘neu- roaxis’ at various levels and restores the balance between excitatory and inhibitory regulation at various locations within the peripheral and central nervous system [33]. Furthermore, SNM may also activate the afferent bladder somatosensors which run to the micturation centre in the brain stem, and/or activate the hypogastric sympathetic nerves [34].

Treatment Protocol

Before implanting the INS, a screening test is performed to assess the clinical effect of sacral nerve stimulation. There are two test protocols. The percutaneous nerve evaluation (PNE) test uses a non-anchored test lead placed into the S3 foramen and connected to an external stimulator. The test period extends between 4 and 14 days, after which the test lead is removed. The procedure is usually done in an outpatient setting. The overall response rate for PNE is around 55% [35, 36]. Lead migration is considered the main factor leading to false negative results [37, 38].

The definitive lead electrode has self-anchoring tines that reduce the risk of migration. These leads can also be used for testing. The lead is usually placed into the S3 foramen under general anesthesia (although some centers also use local anesthesia in an outpatient setting), correct positioning is guided with fluoroscopy, the lead is subcutaneously tunneled and connected subcutaneously to a temporary extension lead that exits the skin and is connected to an external pulse generator. This procedure enables test periods of up to 3–4 weeks. If the patient has a good response during the test, the present lead is connected to an internal nerve stimulator. This procedure is done under local or general anesthesia. Because of the decreased risk of migration and the longer test duration, this test has a higher response rate. According to a study of Kessler et al. [39] prolonged screening with the tined lead has a response rate of 67 compared to 43% during PNE testing. The costs for the test protocol with the tined leads are much higher compared to the PNE test. Currently, the use of either one of the two screening options is arbitrary.

Effectiveness

There is convincing evidence for the success of SNM with the Interstim technique for refractory I-OAB. Three RCTs (two on patients with urgency incontinence and one on patients with urgency frequency) [35, 36, 40] and many articles on long-term observational studies have been published [41–45]. Good clinical response is reported between 64 and 88% of all patients. All parameters reported showed significant improvement compared to the placebo group: a 23–46% decrease in the number of voids per day, 44–77% increase in the average voided volume, 56–90% decrease in incontinence episodes per day, 64–100% decrease in pads and 39% increase in maximum cystometric capacity (table 5).

A 5-year follow-up study on 121 patients with refractory I-OAB showed persistence of the clinical success in the long-term: 84% of the patients with urgency incontinence and 71% of the patients with urgency/frequency who had a successful outcome 1 year after implantation continued to have a successfully outcome after 5 years [43]. A study on the tined lead procedure in 21 patients with I-OAB showed clinical success after an average of 15.5 months to be around 90% [45]. In all reported studies, clinical success is defined as a >50% improvement in one of the relevant urinary voiding parameters.

Satisfaction and quality of life scores after SNM have also been studied. Cappellano et al. [46] showed a significant improvement in the quality of life score in patients with urgency incontinence who underwent SNM from a mean score of 34 to 76. At 18 months of follow-up, they were asked whether they would undergo this treatment again. 90% responded yes and 100% would recommend it to a relative or friend. Foster et al. [47] asked 49 patients with urgency incontinence about their satisfaction with SNM treatment. The majority were satisfied (84%) and would ‘do it all over again’ (80%).

Safety

Adverse events are usually related to the implant procedure, the presence of the implant or of undesirable...
The most common adverse event reported is pain at the implant site. The occurrence in most studies varies between 3 and 42% (table 6) [22, 36, 40–45]. Other adverse events reported are lead migration (1–21%), bowel dysfunction (4–7%) and infection (4–10%). Technical improvements throughout the years have decreased the incidence of adverse events significantly. Two important improvements were the introduction of tined leads (leads with hooks) and the gluteal placement of the INS instead of abdominal. Ever since, both the incidence of adverse events and the reoperation rate per implanted patient have decreased (fig. 2) [44].

The majority of adverse events do not require surgical intervention. Decreased efficacy because of electrode migration and undesirable stimulation can easily be solved by reprogramming the INS. A retrospective analysis among 83 implanted patients with a reduced response or complications, such as pain at the INS site, showed that 18% of the cases could be helped conservatively [42]. Furthermore, the incidence of adverse events is lower with

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**Table 5.** Short-term results of treatment with SNM or with placebo among patients with OAB

<table>
<thead>
<tr>
<th>First author</th>
<th>Follow-up, months</th>
<th>General improvement, %</th>
<th>Voids/day, %</th>
<th>Voided vol., %</th>
<th>IE/day, %</th>
<th>Proportion of group with 100% continence, %</th>
<th>Pads/day, %</th>
<th>MCC, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weil [36]</td>
<td>6</td>
<td>–90</td>
<td>56</td>
<td>–92</td>
<td>39</td>
<td></td>
<td></td>
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<tr>
<td>Schmidt [35]</td>
<td>6</td>
<td>–73</td>
<td>47</td>
<td>–82</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hassouna [40]</td>
<td>12</td>
<td>18 (leg)</td>
<td>5</td>
<td>77</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Kerrebroeck [43]</td>
<td>49</td>
<td>–46</td>
<td>77</td>
<td>–56</td>
<td>–64</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Voskuilen [44]</td>
<td>64.2</td>
<td>64</td>
<td>19</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Voskuilen [45]</td>
<td>22</td>
<td>69</td>
<td>19</td>
<td>5</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sutherland [42]</td>
<td>22</td>
<td>–35</td>
<td>88</td>
<td>–88</td>
<td>50</td>
<td>–100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hijaz [41]</td>
<td>16</td>
<td>–38</td>
<td>44</td>
<td>–65</td>
<td></td>
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</tbody>
</table>

**Table 6.** Most frequent adverse events associated with SNM therapy

<table>
<thead>
<tr>
<th>First author</th>
<th>Pain at implant site, %</th>
<th>Lead migration, %</th>
<th>Other pain, %</th>
<th>Bowel function disturbance, %</th>
<th>Infection, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weil [36]</td>
<td>21</td>
<td>18 (leg)</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schmidt [35]</td>
<td>13</td>
<td>7.9 (lead site)</td>
<td>5</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Hassouna [40]</td>
<td>5</td>
<td>43 (pain or discomfort)</td>
<td>7</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>van Kerrebroeck [43]</td>
<td>19</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sutherland [42]</td>
<td>28</td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>van Voskuilen [45]</td>
<td>7</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hijaz [41]</td>
<td>3</td>
<td>1</td>
<td></td>
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</tbody>
</table>

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Fig. 2. Average number of adverse events and surgical revisions per implanted patient [44].
the new tined leads in comparison with non-tined leads (28 and 73%, respectively) [42]. A study among 235 patients confirmed that tined leads migrated less often, which occurred among 5 patients (2.1%) [48]. The available data indicate that the further development and optimization of SNM limits the risk of adverse events.

**Other Considerations, SNM versus BTX**

Both SNM and BTX have similar effectiveness rates and both have relatively small, treatable and nonpermanent side effects. When having to choose between SNM and BTX, urologists may rely on other data such as long-term safety and effect data and cost-effectiveness data.

Recently, three cost-effectiveness studies have been published on SNM versus BTX, all three in the form of an abstract. Arlandis and colleagues compared SNM with BTX from a public health point of view in Spain; Leong’s group compared SNM with BTX from a hospital point of view in the Netherlands, and Leng’s group compared SNM with BTX from a public health point of view in North America. Both Arlandis’ group and Leong’s group concluded that SNM is cost-effective compared with BTX, whereas Leng and coworkers concluded that BTX treatment dominated SNM (more effect at less cost), even after repeated sensitivity analysis. More data on these abstracts is required to explain these contradictory results.

Another way of choosing between SNM and BTX is a patient-specific approach. Patients with comorbidities in the pelvic region may be better off with SNM. Some studies have shown that other urinary voiding disorders such as urinary retention are present in 1 out of 3 I-OAB patients, and that 26% of women with lower urinary tract disorders also have fecal incontinence [49, 50]. SNM is also approved for the treatment of urinary retention, fecal incontinence and chronic constipation [51, 52]. Recent studies have shown that patients can experience relief from both OAB and other pelvic floor disorders at the same time when treated with SNM [53, 54]. On the other hand, patients who need regular MRI scans may be better off with BTX treatment, because so far SNM is not MRI proof.

**Conclusion**

OAB has a significant impact on the quality of life in both men and women. If conservative treatments are not effective, then there are various second-line treatment options available. SNM and BTX therapy are the most commonly used. Both of these treatments have similar effectiveness rates and both have relatively small, treatable and nonpermanent side effects. Cost-effectiveness analyses have shown contradictory results. BTX treatment has not yet been officially approved for urological disorders due to lack of long-term effect and safety data and lack of consensus regarding the proper dosage and the injection method. However, all BTX studies on patients with I-OAB are promising and point to the direction of approval. Until then, SNM is the only minimally invasive option approved for I-OAB patients who are refractory to conservative treatment.

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opathic overactive bladder syndrome refrac-

opathic overactive bladder syndrome refrac-

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rotoxins®, Vistabel®): Riesgo de efectos adver-
sos graves por diseminación de la toxina,
http://www.agmed.es/actividad/alertas/
usoHumano/seguridad/toxinaBotulinica. 

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port®, Neurotoxins®, Vistabel®, Xeomin®, http://www.bfarma.de/clin_043/SharedDocs/ Publicationen/DE/Pharmakovigilanz/2ub-
handBriefe/2007/botulinumtoxin,template
ld=raw,property=publicationFile.pdf/botu-
Sacral Neuromodulation versus Botulinum Toxin Treatment


